Chapter 4

Current Researches on Telemonitoring in Patients with Diabetes Mellitus: A Narrative Review

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Abstract

Background: This is a narrative review of both the literature and Web pertaining to telemedicine projects within the field of type 1 and type 2 diabetes mellitus, with special attention placed on remote monitoring 2.0 projects and studies.

Material and method: A literature search was performed using the PubMed database of US National Library of Medicine, along with Scholar Google. Textbooks on telemedicine and e-Health, from the American Diabetes Association (ADA) and the European Association for Study the Diabetes (EASD), as well as information from international meetings and commercial sites on the Web were used. After rigorous selection, 29 papers were included in our review and analyzed.

Results: Since the beginning of the 1990's, several telemedicine projects and studies focused on diabetes type 1 and type 2 mellitus have been developed. Mainly, these projects and studies show that telemonitoring diabetic result in: improved blood glucose control; a significant reduction in HbA1c; improved patient ownership of the disease; greater patient adherence to therapeutic and hygiene–dietary measures; positive impact on co-morbidities (hypertension, weight, dyslipidemia); improved quality of life for patients; and at least good patient receptivity and accountability. To date, the magnitude of its effects remains debatable, especially with the variation in patients' characteristics (e.g. background, ability for self–management, medical condition), samples selection and approach for treatment of control groups. Over the last 5 years, numerous telemedicine projects based on connected objects and new information and communication technologies (ICT) (elements defining telemedicine 2.0) have emerged or are still under development. Two examples are the DIABETe and Telesage telemonitoring project which perfectly fits within the telemedicine 2.0 framework, being the firsts to include artificial intelligence with MyPrediTM and DiabeoTM (AI).

Keywords: Telemedicine; telemonitoring; artificial intelligence; information and communication technology; diabetes; heart failure; chronic disease.

1. Introduction

The rising prevalence of chronic diseases, e.g. diabetes mellitus (DM) or chronic heart failure (CHF), represents a real concern for public health [1–3]. A prevalence more than 130 million affected people has been reported in the United States of America (USA), with over 400 million affected people worldwide. In France, more than 10 million people suffer from obesity, metabolic syndrome and DM, with a large majority of adult patients [1]. In this context, the cost of this chronic disease that has recently rocketed is estimated at several billion dollars in developed countries [1–3]. And the management of these chronic diseases proves very challenging for healthcare professionals [3–5].

To date, despite major therapeutic advances made, most chronic diseases remain serious in terms of functional or survival prognosis, with high morbidity and mortality rates [1,3,5]. This applies particularly to DM (type 1 and type 2), where the mortality rate increases by 30 to 50% and where cardiac, vascular, renal, ophthalmological and nervous complications affect the functional prognosis and quality of life of patients, with emergency hospitalization and iterative hospitalizations [2,4,5].

Monitoring patients with chronic diseases, as CHF and DM using telemedicine systems may be of real help to optimize the patient management process and possibly prognosis, particularly by preventing emergency [6–8]. In this setting, the most relevant means are the prevention of DM decompensation and other co–morbidities by anticipating patient symptoms through regular monitoring of vital parameters, while promoting compliance with prescribed lifestyle changes and treatment [2,4]. Therapeutic education and medical adherence are two main actors in the long–term management of DM and in the DM telemonitoring solutions [7,8].

In the present article, we review the literature and Internet in the field of telemonitoring diabetic patients.

2. Search Strategy

A literature search was performed on the PubMed database of the US National Library of Medicine and on Scholar Google. We searched for articles published between January 2010 and October 2018, using the following key words or associations: “diabetes mellitus”, “telemedicine” and “telemedicine in diabetes mellitus”; restrictions included: i) language: “English” or “French”; ii) publications date: “from Jan. 1, 2010”, to September. 30, 2018”; and iii) publication type: “clinical trials”, “review articles” and “guidelines”.

Textbooks on telemedicine and e–Health, books from the American Diabetes Association (ADA) and the European Association for Study the Diabetes (EASD), and information gleaned from international meetings were also used, as information gleaned from commercial sites on the Web.

All English and French abstracts were reviewed by at least two senior researchers from our working group focused on telemedicine in chronic diseases at the Strasbourg University Hospital (Strasbourg, France), which is considered as a referral center. We reviewed 201 references, which yielded 85 potentially relevant papers. After rigorous selection, 29 papers were included in our review and analyzed. Only completed telemedicine trials or studies meeting rigorous clinical evaluation were included in this work. It is to note that this narrative review is limited by its focus on non–invasive DM telemonitoring.

3. Rational for Tele Monitoring in Diabetes

The traditional clinician–led model with regular face–to–face consultations for managing patients with chronic diseases, as DM or CHF, is costly in terms of health care professionals' time, rarely supports self–management by patients, and is often not very effective, particularly because therapeutic inertia may result in reluctance to change treatments [2,3]. In this context, numerous reviews indicate that engaging patients in self–monitoring and management can improve clinical outcomes in some chronic disorders (e.g. asthma, arterial hypertension and CHF), but the evidence that self–monitoring of blood glucose (BG) is beneficial in people with DM is less clear [2–5]. This may be due to poor adherence to both lifestyle advice and prescribed medication, therapeutic inertia, as see below, among people with DM, and the fact that patients become anxious when faced with self–monitored evidence of poor control when feedback from clinicians is infrequent. In this context, therapeutic education has proved its effectiveness, as well as the use of motivational tools [2,4].

To date, 50% of diabetic patients, especially those followed in referral center or in hospital, have cardiovascular complications due to macrovascular disorders [2,4]. These patients have a high mortality rate (20% of deaths occur within 5 years of first cardiovascular manifestation, especially myocardial infarction). To date 30% of coronary patients and patients with CHF have DM [3]. In this context, patients are often hospitalized, with an extended hospital stay, and iteratively hospitalized [2,3]. Thus, DM diminishes the patient quality of life and has a major economic impact on health care costs, primarily due to the high cost of re–hospitalization and recurrent episodes of DM degradation [2].

In practice, the main causes of DM deterioration are: non–therapeutic adherence, bad nutrition, poor adherence to prescribed lifestyle changes and therapy, community–based infections, and decompensation of comorbidities and macrovascular disorders [2,4]. The primary symptoms of diabetic decompensation consist of shortness of breath associated with strain, potentially continuing when at rest, and fatigue that can worsen with disease aggravation [2]. In this context, thirst signs, polyuria, polydipsia arise. Such signs may worsen and eventually threaten patients' lives (coma and consciousness trouble).

In view of these facts, "tele–expertise", "teleconsultation" and "telemonitoring" (**Table 1**) have all their places and potentially useful for the patient and health professionals [7]. In the rest of this article, we will focus our proposals on telemonitoring in diabetic patients.

Table 1: Glossary of terms and definitions in the field of telemedicine.

Telemedicine: Provision of remote patient care and consultation using telecommunication technologies.
Telemonitoring: This telemedicine practice allows a healthcare professional to remotely interpret the data necessary for the patient's medical follow–up in order to make decisions about his / her care. Remote data collection from a patient through a connected device or questionnaires to monitor his/her vital parameters and symptoms at home on a daily basis.
Teleexpertise: This practice of telemedicine consists, for a medical professional, to seek the opinion of one or more medical professional experts regarding elements of the patient's medical file. Remote seeking by a health professional of a second medical opinion via sending of images (scanner, X–ray, eye fundus, etc.) and sometimes exchange by Internet–based videoconference.
Teleconsultation: This telemedicine practice allows a medical professional to hold a consultation with a patient remotely. In the context of a teleconsultation, the patient can have at his/her side a health professional assisting the remote professional as well as a psychologist. Second opinion consultation by specialist.
Telemedicine 2.0: Over the last decade, the Internet has become increasingly popular and is now an important part of our daily life. The use of "Web 2.0" technologies in health/medicine care or in telemedicine is referred to as "Health 2.0" or "Medicine 2.0", and "telemedicine 2.0".
Artificial intelligence: This concept makes it possible for machines to learn from experience, adjust to new inputs and perform human-like tasks. These processes include learning (the acquisition of information and rules for using the information), reasoning (using the rules to reach approximate or definite conclusions) and self–correction. Particular applications of AI include expert systems, speech recognition, and machine vision.

4. Current Causes of Hospitalization of Diabetic Patients

The characteristics of hospitalized diabetic patients and the causes of these hospitalizations are well known. They can be detected using telemedicine solutions. In the reference study from Assogba et al. (n=9 987) [9], nearly one–third (31%) of people with DM (type 1: 45%; type 2: 31%, $p<0.0001$) had at least one hospital stay in the year: 13% in hospital for less than 24 hours (type 1: 23%; type 2: 13%, $p<0.0001$), 24% in full hospitalization (type 1: 31%; type 2: 24%, $p<0.0001$). In this study, people admitted to full hospitalization were older than other patients (median age, 69 years vs. 65 years), more often treated 100% for a long–term condition (91%), and more often reported financial difficulties (59%), "old" diabetic patients (54%) and complications. They had more frequent use of care and insulin treatment (29%). They have had an average of 1.6 stays, or 11 cumulative days of hospitalization per person. In multivariate analysis, high age, financial difficulties, history of microvascular or coronary complications, inadequate glycemic control and insulin alone were independently associated with the use of full hospitalization in type 2 diabetics. In this setting, one reference study determines a readmission rate of 26% for diabetic patients (22% for patients without DM); the most common cause for readmission being directly related to DM itself.

Intensive glycemic control has been shown to delay or prevent the development of DM–

related micro– and macrovascular complications. However, an estimated 43.2–55.6% of adults with DM do not meet the ADA target for glycemic control (hemoglobin A1c [HbA1c] <7.0%) [10]. Factors that may contribute to suboptimal glycemic control include inadequate home glucose monitoring, non–compliance with medications or lifestyle changes, suboptimal patient education about the disease, and limited access to providers for DM management [2,10,11]. In the absence of timely and accurate data on home BG values, providers may be appropriately hesitant to escalate some oral hypoglycemic agents or insulin regimens aggressively, due to fear of hypoglycemia. In this setting telemedicine technologies could provide an effective approach for addressing education, compliance, monitoring and provider access issues [2,5]. Glycemic control could be improved safely by basing medication changes on BG readings obtained at home and transmitted in near real time to providers.

In the larger study including 37,702 adults, the most common cause for readmission in diabetic patients as a secondary diagnosis to the index admission was infection–related in front of the macrovascular complications [11]. During the index hospital stay, only a small proportion of diabetic patients (approximately 12%) received any DM service consult. Those who received a diabetic consult had a higher case mix index compared to those who did not. Despite the higher acuity, there was a lower rate of emergency ED/observation readmission in patients followed by the DM services (6.6% vs. 9.6%, p=0.0012), though no difference in the inpatient readmission rates (17.6% vs. 17.4%, p=0.89) was noted. Monitoring diabetic patients using telemedicine systems is a potential means for optimizing the patient management process. Thus to improve DM care, the most relevant means include preventing DM and other comorbidity decompensation by anticipating patient symptoms via regular monitoring of vital parameters, while promoting adherence to prescribed lifestyle changes and therapy [2,5].

5. First-Generation Telemedicine Projects and Studies in Diabetes

Since the early 1990s to the end of 2010, numerous telemedicine projects and trials have been conceived in the DM area [12-33]. Most of them have investigated "telemonitoring" or "telephone follow–up", as it is also known, with a focus on specific population of poor controlled type 1 and type 2 diabetic patients, as: children and young people (n=3), elderly people (n=2), patients with intensified insulin therapy, patients under insulin pump therapy (n=1); and patients with complicated DM (n=2). To our knowledge, to date, no project has been published on "tele–consultation" and "tele–expertise" in the DM domain, as defined under European and French legislation [34]. Since the early 2010, a number of telemedicine projects have been added to these projects, using innovative technologies or approaches [7], as we will see below.

We have identified more than 20 reports of telemonitoring studies in the area of DM, including type 1 and type 2 diabetic patients, involving the upload and direct transmission of BG data by patients with DM to providers via cellular telephone, telephone land line, or a Web–based program [12-33]. The results of these studies were mixed, perhaps because many studies did not target participants with poor baseline glycemic control, or the interval between glucose transmission and follow–up was delayed or unspecified, or mainly with no therapeutic intervention. None of these reports evaluated the intensity of intervention required to sustain achieved reductions in HbA1c after the implementation of home telemonitoring.

It should be borne in mind that these projects and studies [12-33], and particularly the earlier ones, more closely resembled to "telephone follow–up" with care providers (such as a nurse) traveling to the diabetic patient's home, rather than telemedicine use as we think of it nowadays with nonintrusive, automated, smart telemonitoring employing remote sensors via modern communication technology or even artificial intelligence (AI) (Tab. 1) [7]. Moreover, these projects are often based of no–randomized comparative strategies. (concept of proof studies) Hence, in our opinion, these studies represent the "first generation" of telemedicine projects [7].

Unlike in other chronic diseases, particular CHF, the results of these telemedicine projects differed from study to study, with fairly inconclusive results as for potential clinical benefits in terms of balancing DM and metabolic problems, re–hospitalization and decreased morbidity or mortality, and particularly concerning the results' statistical significance [7,35,36].

As a result, experts presently share widely divergent opinions on the actual utility of telemedicine in type 1 and type 2 diabetic patient management [35,36]. In this setting, it should be emphasized that the first studies on telemedicine for DM were at times conducted with [7,36]:

- Inappropriate methodologies, involving unsuitable patient groups, such as well–balanced diabetic patients without DM complications without any representative control group, of small size from 50 to 1 000 patients, and with short follow–up periods from 3 months to 1 year;

- Not well–structured organization, with non–specialized staff for the centers' responses to alarms, without any association of patients' general practitioners, specialists of DM or endocrinologists nor any optimized management process or algorithm;

- Several alarms arising too late and without therapeutic response;

- No educational programs;

- Absence of human interface or contact.

Moreover, most studies were only based on glycemic control, without including other warning or monitoring parameters related to comorbidities or diabetic complication, with quite often device under–utilization [7,36]. Thus in our opinion as in other chronic diseases, these drawbacks rendered "any clinical benefits demonstrated illusory", in particular in terms of statistical significance for the first generation telemedicine projects and trials in diabetic patients [7]!

Besides these medical considerations, it is worth noting that an economical aspect must be investigated and consolidated to promote the development of telemedicine in DM and legitimize it, especially in regard of the budgetary constraints affecting insurance and mutual health insurance companies. Things are less advanced than in the HF [7]. To our knowledge, only Biermann's study is dedicated to this theme of economical aspect [17].

To date, none of the learned societies (e.g. ADA, ESD) involved in the topic of DM has, to our knowledge, made any formal recommendation as to whether or not telemedicine is of benefit to type 1 or type 2 diabetic patients. This is not the case in the setting of CHF, where factual data and medico-economic studies are more numerous, better documented and consolidated (more mature field) [7]. In fact, the 2016 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF were the first to recommend remote patient monitoring of CHF patients with a recommendation Grade IIb, and level of evidence B [37]. In HF area, telemonitoring is mainly focused on predicting acute HF episodes, usually associated with fluid congestion, which require therapy optimization, such as up–titration of angiotensin–converting enzyme inhibitors and beta–blockers.

6. Second-Generation Telemedicine Projects and Studies in Diabetes

Over the last ten years, "second–generation" telemedicine projects and trials have emerged in the setting of DM management, especially in the setting of telemonitoring [38–44]. These projects and trial have for main objectives to evaluate the use of technology to implement medical and cost–effective health care management on a large scale for DM management (in the setting of comparative. Studies) Most of the "second generation" projects related to DM telemonitoring (for type 1 diabetics patients: n=1; for type 2: n=5) incorporate the following [38–44]:

- Self–administered medical questionnaires or forms on: symptoms, signs of DM decompensation; capillary or serum glycemic levels);

- Tools for medical education, particularly disease self–appropriation, food hygiene, and physical activity;

- Tools for patient motivation;

- Tools for therapeutic and hygiene observance;

- Tools for interaction between the patient and healthcare professionals like telephone support centers, tablets, and Web–sites.

6.1. The DiaTel Study

The DiaTel study compared the short–term efficacy of home telemonitoring coupled with active medication management by a nurse practitioner with a monthly care coordination telephone call on glycemic control in veterans with type 2 DM [38]. The included patients were taking oral hypoglycemic agents and/or insulin for ≥1 year and had HbA1c ≥7.5%). At enrollment, the patients were randomly assigned to either active care management with home telemonitoring (ACM+HT group, n=73) or a monthly care coordination telephone call (CC group, n=77). Both groups received monthly calls for DM education and self–management review. ACM+HT group participants transmitted BG, blood pressure (BP), and weight to a nurse practitioner using the Viterion 100 TeleHealth Monitor; the nurse practitioner adjusted medications for glucose, BP, and lipid control based on established ADA targets.

Baseline characteristics of the patients were similar in both groups, with mean HbA1c of 9.4% (CC group) and 9.6% (ACM+HT group) [38,39]. Compared with the CC group, the ACM+HT group demonstrated significantly larger decreases in HbA1c at 3 months (1.7 vs. 0.7%) and 6 months (1.7 vs. 0.8%; $p<0.001$ for each), with most improvement occurring by 3 months.

6.2. The Utah Remote Monitoring Project

The Utah Remote Monitoring Project was a nonrandomized prospective observational pre–and post–intervention study, using a convenience sample [40]. Patients with uncontrolled type 2 DM and/or arterial hypertension from four rural and two urban primary care clinics and one urban stroke center participated in a telemonitoring program (n=109). The primary clinical outcome measures were changes in HbA1c and BP. Other outcomes included fasting lipids, weight, patient engagement, DM knowledge, arterial hypertension knowledge, medication adherence, and patient perceptions of the usefulness of the telemonitoring program. One of two telemonitoring delivery methods was used. One was the Authentidate Electronic House Call™ (Authentidate Holding Corp., Berkeley Heights, NJ), a remote monitoring device for BP and heart rate. Patients used their own glucose meters to measure BG and were provided with a Taylor™ electronic digital scale (Taylor Precision Products, Inc. Oak Brook, IL) to measure their weight. The device was programmed to sound an alarm at a pre–specified patient–preferred time to prompt the patient to initiate a telemonitoring session. Patients were asked to enter data several times during the week. The device was programmed to ask how patients were feeling that day and whether they had taken their medications and then receive a prompt to take the measures. After, the patient received a series of education messages, focused on teaching patients about their diseases (DM, arterial hypertension) and associated comorbidities. The second telemonitoring delivery method was use of an interactive voice response (IVR) system, available from Authentidate Holding Corp., Berkeley Heights, NJ. Patients were provided with an OmronTM series 7 BP monitor (Omron Healthcare, Lake Forest, IL) and electronic digital scales, but they used their own BG meter. The patients have to use the same process described above, but received a call from the telemonitoring IVR service at a pre–specified. Medical providers were contacted either via a note in the electronic medical record (or immediately if there was a concern, in person or by telephone) if there was an out–of–range value (decided by individual providers or clinics as a value that was high or low).

In this study, the mean HbA1c decreased from 9.73% at baseline to 7.81% at the end of the program ($p<0.0001$) [40]. Systolic BP also declined significantly, from 130.7 mmHg at baseline to 122.9 mmHg at the end ($p=0.0001$). Low–density lipoprotein content decreased significantly, from 103.9 mg/dL at baseline to 93.7 mg/dL at the end ($p=0.0263$). Knowledge of DM and arterial hypertension increased significantly ($p<0.001$ for both). Patient engagement and medication adherence also improved, but not significantly. Per questionnaires at study end, patients felt the telemonitoring program was useful.

6.3. Randomized Trial on Home Telemonitoring for the Management of Metabolic and Cardiovascular Risk in Patients with type 2 Diabetes

This study evaluated whether a home telehealth (HT) system enabling the patient to monitor body weight, BG values, and BP values, associated with remote educational support and feedback to the general practitioner, can improve metabolic control and overall cardiovascular risk in individuals with type 2 DM, compared with usual practice [41]. This study was a randomized, parallel–group (1:1), open–label, multicenter study conducted in general practice (29 general practitioners) including 302 patients. Follow–up was for 12 months.

Use of the HT system ($n=153$) was associated with a statistically significant reduction in HbA1c levels compared with the control group ($n=149$) (estimated mean difference, 0.33 ± 0.1; $p=0.001$). [41]. No difference emerged as for body weight, BP, and lipid profile. The proportion of patients reaching the target of HbA1c <7.0% was higher in the HT group than in the control group after 6 months (33.0% vs. 18.7%; $p=0.009$) and 12 months (28.1% vs. 18.5%; $p=0.07$). As for quality of life (evaluated with the 36–item Short Form health survey), significant differences in favor of the HT group were detected as for physical functioning ($p=0.01$), role limitations due to emotional problems ($p=0.02$), mental health ($p=0.005$), and mental component summary ($p=0.03$) scores. A lower number of specialist visits was reported in the telemedicine group (incidence rate ratio, 0.72; 95% confidence interval, 0.51–1.01; $p=0.06$).

6.4. Study assessed the utility and cost–effectiveness of an automated Diabetes Remote Monitoring and Management System (DRMS)

This study assessed the utility and cost–effectiveness of an automated Diabetes Remote Monitoring and Management System (DRMS) in glycemic control versus usual care [42]. In this randomized, controlled study, patients with uncontrolled DM on insulin were randomized to use of the DRMS or usual care. Participants in both groups were followed up for 6 months and had 3 clinic visits at 0, 3, and 6 months. The DRMS used text messages or phone calls to remind patients to test their BG and to report results via an automated system, with no human interaction unless a patient had severely high or low BG. The DRMS made adjustments to insulin dose(s) based on validated algorithms. Participants reported medication adherence through the Morisky Medication Adherence Scale–8, and DM–specific quality of life through the diabetes Daily Quality of Life questionnaire. A cost–effectiveness analysis was conducted based on the estimated overall costs of DRMS and usual care.

A total of 98 patients were enrolled (59 [60%] female; mean age, 59 years); 87 participants (89%) completed follow–up. HbA1c was similar between the DRMS and control groups at 3 months (7.60% vs. 8.10%) and at 6 months (8.10% vs. 7.90%) [42]. Changes from baseline to 6 months were not statistically significant for self–reported medication adherence and diabetes–specific quality of life, except for the Daily Quality of Life–Social/Vocational Concerns subscale score (p=0.04).

6.5. The Telescot Diabetes Pragmatic Multicenter Randomized Controlled Trial

The Telescot Diabetes is a randomized, parallel, investigator–blind controlled trial with centralized randomization in family practices in four regions of the United Kingdom [43]. This study included 321 patients with type 2 DM, with an HbA1c >58 mmol/mol. 160 people were randomized to the intervention group and 161 to the usual care group. The supported telemonitoring intervention involved self–measurement and transmission to a secure website of twice–weekly morning and evening glucose for review by family practice clinicians who were not blinded to allocation group. The control group received usual care, with at least annual review and more frequent reviews for people with poor glycemic or BP control. HbA1c assessed at 9th month was the primary outcome.

The mean (SD) HbA1c at follow–up was 63.0 (15.5) mmol/mol in the intervention group and 67.8 (14.7) mmol/mol in the usual care group [43]. For primary analysis, adjusted mean HbA1c was 5.60 mmol/mol, 0.51% lower (95% CI 2.38 to 8.81 mmol/mol; 95% CI 0.22% to 0.81%, p=0·0007). For secondary analyses, adjusted mean ambulatory systolic BP was 3.06 mmHg lower (95% CI 0.56–5.56 mmHg, p=0.017) and mean ambulatory diastolic BP was 2.17 mmHg lower (95% CI 0.62–3.72, p=0.006) among people in the intervention group when compared with usual care after adjustment for baseline differences and minimization strata.

No significant differences were identified between groups in weight, treatment pattern, adherence to medication, or quality of life in secondary analyses. There were few adverse events, and these were equally distributed between the intervention and control groups. In secondary analysis, there was a greater number of telephone calls between practice nurses and patients in the intervention compared with control group (rate ratio 7.50 (95% CI 4.45–12.65, $p<0.0001$) but no other significant differences between groups in use of health services were identified between groups.

6.6. Educ@dom

Educ@dom is a multicenter, randomized, controlled, prospective study [44]. The primary objective of this study is to compare the efficacy of telemonitoring to standard monitoring in terms of changes in HbA1c after a 1–year follow–up period. The secondary objectives are clinical (changes in knowledge, physical activity, weight, etc.) and medical–economic. The study included 282 patients, 141 patients in each arm [44]. For patients in the intervention group, the device will be given to them for 1 year and then withdrawn during the second year of follow–up. The anticipated benefits of this research are an improvement in BG management in patients with type 2 DM by improving their lifestyle whilst rationalizing recourse to consultations in order to reduce the incidence of complications and cost in the long term. The results of this study are expected in 2019–2020.

7. New Generation Projects and Studies in Diabetes

Over the last 4 to 5 years, new-generation telemedicine projects and trials have emerged in the setting of chronic diseases setting, especially in the setting of CHF and type 1 and type 2 DM [7,45–48]. They support transmission and remote interpretation of patients' data for follow–up and preventive interventions. These projects and trial have for main objectives to evaluate the use of technology to implement medical and cost–effective health care management on a large scale for DM management. One of these telemedicine projects, the TIM–HF2 study in CHF [49], has recently demonstrated, for the first time, the demonstrated the usefulness of telemedicine in the management of chronic diseases in a prospective randomized study (the "gold–standard" of evidence based medicine [EBM]). In this setting, we believe that, thanks to technological innovations in connected health–monitoring devices, the telemonitoring of type 2 diabetic patients using therapeutic educational tools is likely to help them adapt their treatment and lifestyle habits, and therefore improve BG management [7].

These present projects are often known as "telemedicine 2.0", given that they all utilize new Information and Communication Technologies (ICT) and the Web (tools for the "e-Health 2.0") (Tab. 1) [50]. Most projects and trials rely on the standard connected tools for moni-toring type 1 and type 2 DM, such as glucose meters, BP, heart rate monitors, weighing scales, and pulse oximeters, which relay the collected information via Bluetooth, 3G or 4G

[7,45–48]. Several projects also include continuous glycemic monitoring solution and often a video–call [7]. Several of these telemedicine projects use machine learning (AI) in order to be able to:

- Adjust the BG level to the patient's activity (software DiabeoTM [see below]) [46,47];
- Predict patient risks of DM decompensation [48,51]. In this later situation, the cloud–based software aggregates, cleans, and analyzes patient data to allow for identifying patterns that may indicate potential risks and provide predictive insights on healthcare outcomes, as the software MyPrediTM (see below) [7,48].

In telemedicine projects in the setting of chronic diseases, as in CHD or in DM, several tools have been developed and used, such as Artificial Neural Networks (ANN) algorithms, data mining software, ontology [51,52]. In this context, three clinical datasets are of particular interest: 1) patients' phenotype; 2) patients' electronic medical records containing physicians' notes, laboratory test results, as well as other information on diseases, treatments, and epidemiology that may be of interest for association studies and predictive modeling on prognosis and drug responses; and 3) literature knowledge including rules on DM management [52].

Besides these tools, it must be emphasized that DM telemonitoring may use, as for CHF telemonitoring, implantable invasive devices that send either sporadically or continuously data to the receiving physician (automatic telemonitoring) (outside the scoop of this paper) [53]. In management of DM, implantable telemonitoring devices for multi–parameters including mainly glucose–insulin levels monitoring have recently proven to be an effective approach.

7.1. Telemonitoring and Health Counseling for Self–Management Support of Patients with type 2 Diabetes

The objective of this study was to investigate whether the introduction of a health technology–supported self–management program involving telemonitoring and health counseling had beneficial effects on HbA1c, other clinical variables (height, weight, body mass index, BP, blood lipid profile), and health–related quality of life (HRQoL), as measured using the Short Form Health Survey (SF–36) version 2 in patients with type 2 DM (**Figure 1**) [45]. This was a pragmatic randomized controlled trial of patients with type 2 DM. Both the control (n=79) and intervention groups (n=87) received usual care. The intervention group also participated in additional health promotion activities with the use of the Prescribed Healthcare Web application for self–monitoring of BG and BP. About every second month or when needed, the general practitioner or the DM nurse reviewed the results and the health care activity plan.

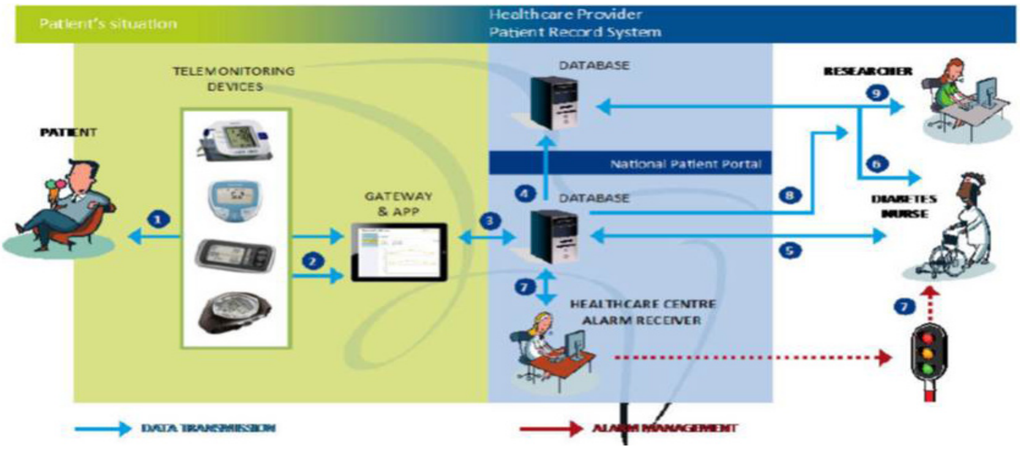

Figure 1: Telemonitoring devices and information flow during the field trial (adapted from [45]).

There were no significant differences between the groups in the primary outcome HbA1c level (p=0.33), and in the secondary outcome HRQoL as measured using SF–36 [45]. A total of 80% (67/87) of the patients in the intervention group at the baseline, and 98% (47/50) of the responders after 19–month intervention were familiar with using a personal computer (p=0.001). After 19 months, no responders (e.g., data from baseline) reported significantly poorer mental health in social functioning and role emotional subscales on the SF–36 (p=0.03, and p=0.01, respectively).

7.2. TELESAGE study

TELESAGE (Suivi A Grande Echelle d'une population de diabétiques de type 1 et de type 2 sous schéma insulinique basal bolus par la TELEmédecine) is a six–month open–label parallel–group, multicenter study, including adult patients (n=180) with type 1 DM (>1 year), on a basal–bolus insulin regimen (>6 months), with HbA1c ≥8%, conducted in approximately 100 centers in France [46,47]. These type 1 diabetic patients were randomized to usual quarterly follow–up (G1), home use of a smartphone recommending insulin doses (DiabeoTM software) with quarterly visits (G2), or use of the smartphone with short teleconsultations every 2 weeks but no visit until point end (G3). The primary objective of Télésage will be to investigate the effect of the DiabeoTM telemedicine system versus usual follow–up, with respect to improvements in the HbA1c levels of approximately 696 diabetic patients with poorly controlled basal–bolus insulin levels. The study will compare a control group (arm 1: usual follow–up) with two DiabeoTM telemedicine systems: (1) physician–assisted telemedicine (arm 2), and (2) nurse–assisted telemonitoring and teleconsultations by a diabetologist's task delegation (arm 3).

Six–month mean HbA1c in G3 (8.41 ± 1.04%) was lower than in G1 (9.10 ± 1.16%; p=0.0019) (**Figure 2**) [46,47]. G2 displayed intermediate results (8.63 ± 1.07%). The DiabeoTM system gave a 0.91% (0.60; 1.21) improvement in HbA1c over controls and a 0.67% (0.35; 0.99) reduction when used without teleconsultation. There was no difference in the frequency of hypoglycemic episodes or in medical time spent for hospital or telephone consultations. However, patients in G1 and G2 spent nearly 5 h more than G3 patients attending hospital visits.

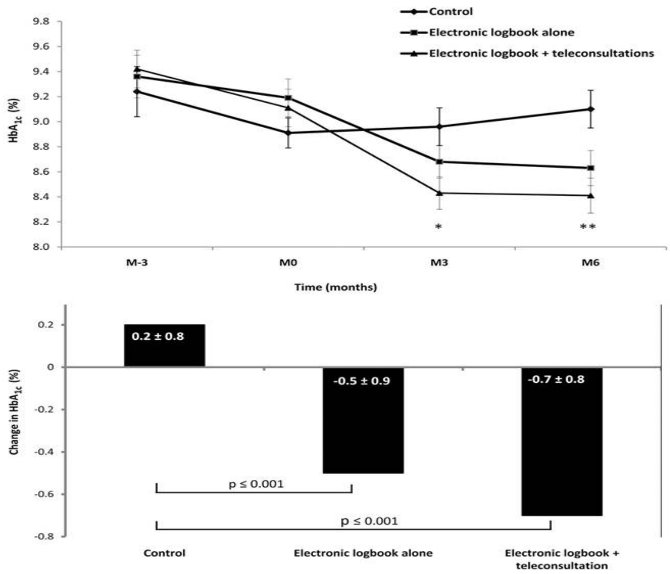

Figure 2: Telemonitoring devices and information flow during the field trial (adapted from [45]).

7.3. DIABETe project

The DIABETe project is based on an intelligent platform that likely assists healthcare professionals by automatically processing the information obtained from nonintrusive medical sensors (BG meter, BP monitor, actimeter, connected scale, etc.) as well as the subjective information provided by the patient himself (questionnaires) and his/her behavior (compliance), enabling it to detect and report, at an early time, these situations at risk of hospitalization [7,48]. Patient– and situation–adapted therapeutic education tools will be made available to the individual, and communication with the subject will likely occur via a touch pad. Alerts indicating a deterioration of the patient's condition will be generated by AI (new software version of MyPrediTM adapted for the management of DM) and transmitted to the health professionals in charge of the patient. The healthcare professional can thus anticipate the decompensation and initiate appropriate measures outside the emergency setting. These innovative and original solutions derived from new technologies should be optimally accepted by the patients. Medical data can likewise be shared among health professionals, being part of a city–hospital network. Ultimately, an improvement in the patients' quality of life is to be expected.

DIABETe is based on a smart system comprising an inference engine and a medical ontology for personalized synchronous or asynchronous analysis of data specific to each patient and, if necessary, the sending of an AI–generated alert (MyPrediTM) [7,48].

Figure 3: DIABETe's connected non–intrusive medical sensors.

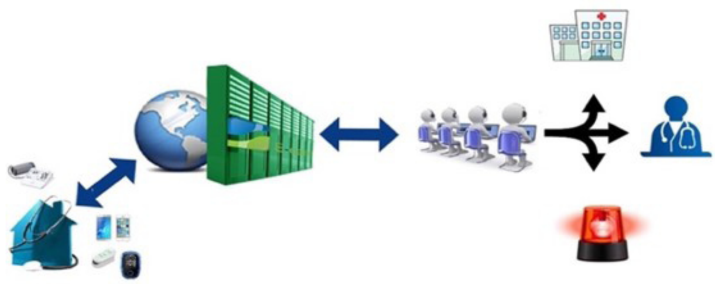

Figure 4: DIABETe's platform.

The system (**Figure 4**) involves a server that hosts the patient's data and a secure internet portal to which the patient and hospital– and non–hospital–based healthcare professionals can connect (**Figure 5**) [7,48].

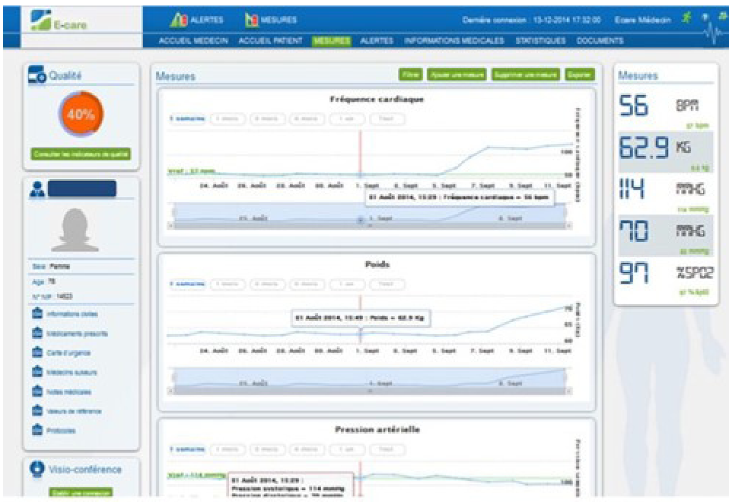

Figure 5: DIABETe's Internet portal

DIABETe is run by a group bringing together the Strasbourg University Hospital (Hôpitaux Universitaires de Strasbourg), East Regional Health Agency (Agence Régionale de Santé du Grand Est), Bas–Rhin branch of France's National Health Insurance (Caisse Primaire d'Assurance du Bas–Rhin), and Predimed Technology start–up [7,48]. This project is likely allowing an in–depth study to be carried out designed to improve diagnosis by machine learning and detect abnormalities in diabetic patients at an early time point.

The telemonitoring platform used in DIABETe was first validated in a monocentric study conducted in the Strasbourg University Hospital, carried out as part of the E–Care project, primarily focused on the problem of CHF [54,55]. Between February 2014 and April

2015, 175 patients were included into the E–care project, some of these patients are diabetic [33]. During this period, the telemonitoring platform was used on a daily basis by patients and healthcare professionals, according to a defined protocol of use specific to each patient.

The mean age of these patients was 72 years, and the ratio of men to women 0.7 [54,55]. The patients suffered from multiple concomitant diseases, with a mean Charlson index of 4.1. The five main diseases were: CHF in more than 60% of subjects, anemia in more than 40%, atrial fibrillation in 30%, type 2 DM in 30%, and chronic obstructive pulmonary disease in 30%. During the study, 1500 measurements were taken in these 175 patients, which resulted in the E–care system (MyPrediTM) generating 700 alerts in 68 patients. Some 107 subjects (61.1%) had no alerts upon follow–up. Follow–up data analysis of these 107 patients revealed that they exhibited no clinically significant events that might eventually have led to hospitalization. Analysis of the warning alerts showed that the platform automatically and non–intrusively detected any worsening of the "patient's HF" (acute HF, criteria 1) and "patient's health" (criteria 2), with a sensitivity, specificity, as well as positive and negative predictive values of:

- For the criteria 1: 100%, 72%, 90% and 100%, respectively;

- For the criteria 2: 100%, 30%, 89% and 100%, respectively. Thus, fir this later criteria, the lack of "alerts" excludes the possibility of a decompensation of the chronic diseases, including DM.

Both the healthcare professionals and patients, even the frailest, used the E–care system without difficulty until the end of the study. For non–autonomous patients, the system was employed by a nurse in addition to her other assigned tasks, such as washing and administering medication, or by close ones and family members.

In this context, we developed an upgraded version of the e–platform and the AI (MyPrediTM, initially designed to follow CHF) in order to follow diabetic patients as part of the DIABETe project [7,48]. It is crucial to note that the system is designed to be a complementary tool to healthcare for detecting situations at risk of DM degradation early on. It renders it possible to anticipate DM degradation occurrence in a timeframe of several days, enabling healthcare professionals to take the right measures to avoid the patient's state of health deteriorating. In emergency cases, however, the patient must still use the appropriate channels, such as calling a doctor, the fire brigade or paramedics.

In this settingThe DIABETe project seeks to detect the risk of hospitalization in type 1 and type 2 diabetic patients at an early time point, with patients classified as: i) "very high cardiovascular risk", when presenting a personal history of myocardial infarction (MI) or stroke, limb amputation or cardiomyopathy; ii) "intensive" insulin therapy, with at least three injections per day or pump administration, while offering them a personalized follow–up and education about their illness and its management [7,48].

This population is particularly interesting, given that it allows for polypathology and polymedication to be targeted, while requiring overall support [9,11]. This population represents about 50% of diabetics hospitalized in departments of diabetology and internal medicine [54]. Apart from cardiovascular complications (myocardial infarction, arteritis obliterans of the lower limbs, etc.), these patients are frequently hospitalized for hypoglycemia, diabetes imbalance, infections, as well as other complications.

DIABETe does not compete with DiabeoTM or other expert systems aimed at optimizing the glycemic balance, which is per se the main objective of DM management [47]. The DIABETe project focuses on the "global" management of diabetic patients through the detection of situations at risk of hospitalization: infection, cardiac decompensation, diabetic foot, as well as hypoglycemia and hyperglycemia episodes, potentially leading to hospitalizations [7,48]. Regarding the remote monitoring platform used in DIABETe, an integration of or interfacing with expert systems such as DiabeoTM appears possible.

8. The First Positive Prospective Randomized Large Study of Tele monitoring in Patients with Chronic Disease: Tim–Hf2 Study

The Telemedical Interventional Management in Heart Failure II (TIM–HF2) is the first positive study in chronic disease, meeting EBM criteria for reference study, i.e., prospective, randomized, multicentric, over a large number of patients [49]. In the context of CHF, TIM–HF2 study clearly shows that remote patient management over 12 months reduced the proportion of days lost due to unplanned cardiovascular hospital admissions, the between–group differences being statistically significant and clinically relevant. This outcome was predominantly driven by a reduction in cardiovascular deaths. Importantly, home telemonitoring triggered several potentially life–saving hospital admissions, although, overall, it slightly reduced the number of days patients were hospitalized due to HF.

Between August 13, 2013, and May 12, 2017, 1 571 patients were randomly assigned to remote patient management (n=796) or standard care (n=775) [49]. Of these patients, 765 in the remote patient management group and 773 in the standard care group actually began their assigned care, being included in the full analysis set. The mean patient age was 70 years, and most were men. At baseline, all patients exhibited a left ventricular ejection fraction of <45% and NYHA Class II or III HF, while receiving treatment with diuretics. About 60% of patients were living in rural areas in Germany. The percentage of days lost due to unplanned cardiovascular hospital admissions and all–cause death was 4.88% (95% CI 4.55–5.23) in the remote patient management group versus 6.64% (6.19–7.13) in the standard care group (ratio 0.80, 95%CI: 0.65–1; p=0.0460). Patients assigned to remote patient management lost a mean of 17.8 days (95% CI: 16.6–19.1) per year compared with 24.2 days (95% CI: 22.6–26) per year for patients assigned to standard care. The all–cause death rate was 7.86 (95% CI: 6.14–10.10) per 100 person–years of follow–up in the remote patient management group versus 11.34 (95% CI: 9.21–13.95) per 100 person–years of follow–up in the standard care group (hazard ratio [HR] 0.70, 95%CI: 0.5–0.96; p=0.0280) (Fig. 6). Cardiovascular mortality did not significantly differ between both groups (HR 0.671, 95%CI: 0.45–1.01; p=0.056).

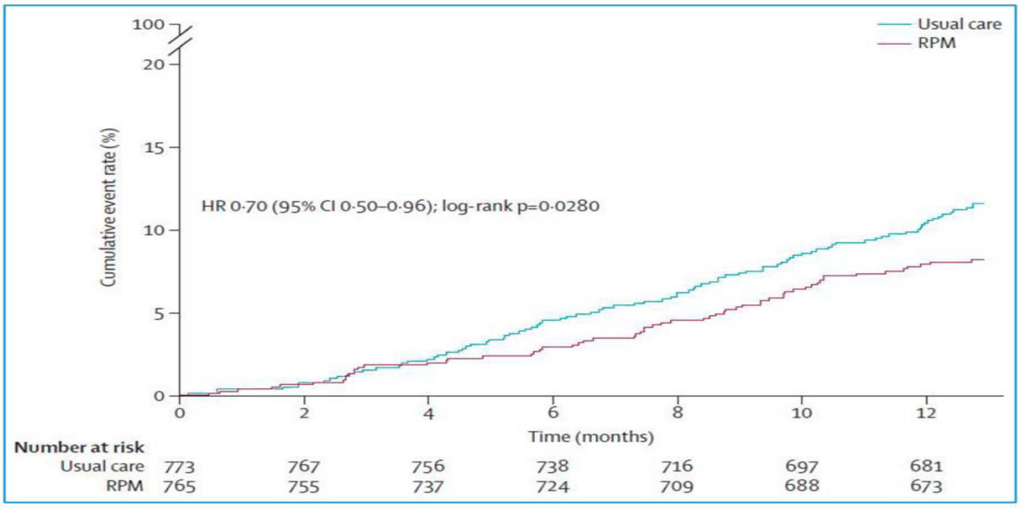

Figure 6: TIM–HF2 trial (n=1 515). Rate of cumulative events in patients randomly assigned to remote patient management (n=796) or usual care (n=775) (adapted from [49])

The study utilized a noninvasive, multi–parameter telemonitoring system installed in the patient's home, comprising a three–channel ECG, BP–monitoring device, and weighing scales, by means of which the information was transferred remotely [49]. Patients received a mobile phone in order to contact the telemedical center in case of emergency. Patients were likewise followed via monthly phone interviews. For this TIM–HF2 care strategy, the key component was a well–structured telemedical center with physicians and HF nurses ("coordination center") available 24 hours a day and every day a week, able to act promptly according to the individual patient risk profile. The actions taken by the telemedical center staff included changes in medication and admission to hospital, as needed, in addition to educational activities.

9. Perspectives Regarding New Developments in Telemedicine

The challenge for "tomorrow" telemedicine is to develop new telemedicine solutions or projects, including and resolving several medical problems and difficulties, such as [7,56]:

- The co-existence of several chronic pathologies (e.g., DM, arterial hypertension, CHF, chronic obstructive pulmonary disease, etc.) and comorbidities (arterial hypertension, renal failure, etc.) in the same individual, while providing comprehensive and "global" care for the individual patient in all its medical and societal dimensions;

- The specificities (no appetite for new technologies and new uses) and problems (e.g., falls, malnutrition, mild cognitive impairment, etc.) of elderly subjects, who are the main subjects affected by chronic diseases;

- The multiplicity of care structures and medical organizations (e.g., with or without human resources, telemedical center, etc.).

- The logistical barriers to implementing tele–health prove to be significant, as many health systems are not yet designed for these technologies to be integrated within existing information systems.

In the context of considering the current problems of access to health professionals, the e–platform must be able to structure the patients' care pathways, a major medical topic that should interest our governments and authorities [56]. Likewise, the E–care and DIABETe projects provide a means for healthcare professionals to exchange with each other, thereby facilitating patient access to medical resources.

Future research must also focus on the accessibility and practicality of telemedicine interventions. Importantly, reimbursement remains a major concern and a barrier ("glass ceiling"), given that much of the care delivered by telehealth is not covered by traditional fee–for–service payment models (e.g., in France, where all diabetic patients benefit from an integral treatment of their health expenses) [7]. The growth of value–based payment models may, however, provide incentives to implement telehealth as a strategy to provide high–quality, cost–effective, and coordinated care [56]. At country levels, variations in practice laws, restrictions on how telehealth can be delivered, and which patients should receive these services limit telemedicine's applicability as well.

Thus, the new telemedicine solution should integrate others objectives like potential targets to meet the needs and requirements of our Societies, as listed in Table 2.

Table 2: Potential parameters to be evaluated in a telemedicine project for chronic disease management.

Overall mortality Specific mortality of the considered chronic disease Number of hospitalization for the considered chronic disease Number of re–hospitalization for the considered chronic disease Number of hospitalization days Health costs Management costs for the considered chronic disease Number of days off work Quality of life	Therapeutic education Hygiene–dietary and therapeutic compliance Optimization of food and sports hygiene Patient self–management Optimization of the care pathway for the considered chronic disease Structuring of the care pathway for the considered chronic disease City–hospital relations Information sharing among health professionals System use by health professionals

10. Conclusions

This narrative review supports the efficacy of telemonitoring diabetic patients with type 1 and type 2. Several studies on DM telemonitoring, using diverse technologies and transmitting different clinical, medical and behavioral data were found. Significant impacts were observed namely at the behavioral, clinical and structural levels. Minimal technical problems and cost–effectiveness analyses were reported.

Close management of type 1 and type 2 DM patients through telemonitoring showed: improvements in control of glycaemia, significant reduction in HbA1c; better appropriation of the disease by patients; greater adherence to therapeutic and hygiene–dietary measures; positive impact on DM comorbidities (arterial hypertension, weight, dyslipidemia); better patient's quality of life; and at least, good receptiveness by patients and patient empowerment. Moreover, a cost–effectiveness analysis found a potential of medical economy. To date, the magnitude of its effects remains debatable, especially with the variation in patients' characteristics (e.g. background, ability for self–management, medical condition), samples selection and approach for treatment of control groups.

To date, relatively few projects and trials in type 1 and type 2 diabetic patients have been run within the "telemedicine 2.0" setting, using AI, ICT and the Web. Nevertheless, this is the case of the project DIABETe. This project, as other projects listed in this review, are perfectly compatible with the care pathways being developed in chronic diseases, particularly DM, CHF, chronic obstructive pulmonary disease, by the authorities of industrialized countries.

Further investigation of telemonitoring efficacy and cost–effectiveness over longer periods of time, and larger samples is needed. Assessment of the attitude of providers is also important considering their heavy workload and issues of reimbursement.

Funding: Grants from the Fondation de l'Avenir, the Agence Régionale de Santé du Grand–Est (ARS) and the Agence Nationale de la Recherche (ANR).

Competing interest: M. Hajjam is the scientific director of Predimed Technology (www.predimed–technology.fr). All other authors have declared that no competing interests exist.

Contributor ship: EA, LM and MH designed the paper and conducted the literature searches. EA, LM, AAZ and MH drafted the results and parts of the discussion. ST, JD, JH, NJ and AEHH provided critical analysis, revised the whole manuscript, and approved the final version for publication. EA is responsible for all revisions and remains in contact with the rest of the review team regarding status reports.

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