A web-based clinical decision support system for gestational diabetes: Automatic diet prescription and detection of insulin needs

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ABSTRACT

Background: The growth of diabetes prevalence is causing an increasing demand in health care services which affects the clinicians' workload as medical resources do not grow at the same rate as the diabetic population. Decision support tools can help clinicians with the inspection of monitoring data, providing a preliminary analysis to ease their interpretation and reduce the evaluation time per patient. This paper presents Sinedie, a clinical decision support system designed to manage the treatment of patients with gestational diabetes. Sinedie aims to improve access to specialized healthcare assistance, to prevent patients from unnecessary displacements, to reduce the evaluation time per patient and to avoid gestational diabetes adverse outcomes.

Methods: A web-based telemedicine platform was designed to remotely evaluate patients allowing them to upload their glycaemia data at home directly from their glucose meter, as well as report other monitoring variables like ketonuria and compliance to dietary treatment. Glycaemia values, not tagged by patients, are automatically labelled with their associated meal by a classifier based on the Expectation Maximization clustering algorithm and a C4.5 decision tree learning algorithm. Two finite automata are combined to determine the patient's metabolic condition, which is analysed by a rule-based knowledge base to generate therapy adjustment recommendations. Diet recommendations are automatically prescribed and notified to the patients, whereas recommendations about insulin requirements are notified also to the physicians, who will decide if insulin needs to be prescribed. The system provides clinicians with a view where patients are prioritized according to their metabolic condition. A randomized controlled clinical trial was designed to evaluate the effectiveness and safety of Sinedie interventions versus standard care and its impact in the professionals' workload in terms of the clinician's time required per patient; number of face-to-face visits; frequency and duration of telematics reviews; patients' compliance to self-monitoring; and patients' satisfaction.

Results: Sinedie was clinically evaluated at "Parc Taulí University Hospital" in Spain during 17 months with the participation of 90 patients with gestational diabetes. Sinedie detected all situations that required a therapy adjustment and all the generated recommendations were safe. The time devoted by clinicians to patients' evaluation was reduced by 27.389% and face-to-face visits per patient were reduced by 88.556%. Patients reported to be highly satisfied with the system, considering it useful and trusting in being well controlled. There was no monitoring loss and, in average, patients measured their glycaemia 3.890 times per day and sent their monitoring data every 3.477 days.

Conclusions: Sinedie generates safe advice about therapy adjustments, reduces the clinicians' workload
1. Introduction

Diabetes prevalence is increasing all over the world due to sociocultural changes. It is becoming a public health problem which is originating an increment in the demand for health services [1]. The most common type of diabetes is type 2 (T2DM), whose risk factors are a poor diet, physical inactivity, advanced age or high blood glucose (BG) during pregnancy, affecting both mother and child [2]. The incidence of Gestational diabetes (GDM) is also increasing, as women tend to delay childbirth to older ages, and if new diagnosis criteria, that has recently proven to be cost-effective [3] are adopted, the prevalence could be doubled. Besides causing perinatal complications such as foetal macrosomia, shoulder dystocia or caesarean section [4], women affected by GDM have a 7-fold increased risk of developing T2DM compared with those who had a normoglycaemic pregnancy [5]. Clinical guidelines for GDM [6–8] establish that pregnant women with GDM should register self-monitoring data (glycaemia, diet, ketonuria) and attend periodic visits to the medical centre every 1 or 2 weeks. It is recommended that patients measure their BG levels at least four times a day: before breakfast (breakfast preprandial) and after the three main meals (breakfast postprandial, lunch postprandial and dinner postprandial). Patients also have to monitor their fasting urine ketones every day using urine strips. During medical visits, clinicians assess if a treatment adjustment is needed based on the patients’ monitoring data.

Telemedicine systems, widely applied to diabetes care, have shown that they are able to improve clinical outcomes and self-care by registering electronically diabetes monitoring data [9–11], and are especially useful in rural areas where, due to a lack of health care professionals, patients have to travel tens of kilometres to reach the specialized assistance [12]. In GDM, telemedicine has proven to reduce face-to-face visits as it allows remote patient monitoring so visits are only scheduled if a change in the therapy is required [13,14]. A recent study [15], reported that telemedicine reviews require less time than face-to-face visits (4.6 min vs. 11.7 min). Some studies conclude that telemedicine, through a more accurate and frequent monitoring, improves glycaemic control and reduces GDM complications [16,17]. But there is still some controversy in the area as other studies [13,18–20] obtained that, although not inferior, telemedicine does not improve glycaemia values or neonatal outcomes compared to traditional care.

Limitations and research gaps identified in telemedicine systems for diabetes include usability, real-time feedback, and decision support capabilities [21]. Although telemedicine saves the patients unnecessary displacements and improves the access to specialized assistance, it might raise the clinicians’ workload to unacceptable levels, as it generates a greater amount of patient data that needs to be evaluated. The use of decision support tools (DSTs) integrated in telemedicine systems, are pointed out as a feasible solution to limited human resources in order to analyze the information generated [22]. Expert systems are computer systems designed to imitate the decision-making ability of a person who has expert knowledge and experience and they usually incorporate a knowledge base containing accumulated experience and an inference or rules engine [23]. An increasing number of expert systems has been proposed to manage diabetes care and to build DSTs, including diabetes diagnosis, therapy adjustment and support to patient self-management [24–27]. The complexity of diabetes care which is affected by multiple variables and the lack of a gold standard affect the formalization of knowledge when building expert systems in diabetes. DSTs are able to prevent clinicians from undertaking the time consuming task of raw data assessment helping to automatically inspect self-monitoring data. Clinicians can interpret the information obtained by the automatic analysis of DSTs, such as recognized glycaemic patterns or weekly statistics, to make a more accurate high level evaluation. DSTs based on expert systems can also suggest treatment changes using protocol-based reasoning [28], automating some of them and asking for medical verification only when a more thorough decision needs to be taken. The validation of advice generated by expert systems and DSTs is a time-consuming task which requires clinical co-operation.

Clinical decision support systems (CDSS) contain DSTs to assist in decision-making tasks. CDSS have been developed in different clinical domains to generate several modes of decision support, including alerts when critical values are detected, reminders and advice for therapy prescription [29], CDSS can help to optimize the clinicians’ time indicating those patients which are more critical and therefore need a deeper examination. CDSS have shown to improve the practitioners’ performance, but the effects on patient outcomes in acute care have been inconsistent [30]. In GDM, the use of CDSS has been very limited. The DIABNET system was designed to be used by physicians during face-to-face visits and proposed qualitative diet modifications and quantitative changes in insulin therapy based on the offline analysis of self-monitoring data [31] and therefore did not aim to reduce them. The MobiGuide system, which is based on computerized clinical guidelines, proposes personalized decision support for GDM patients and their caregivers and is adapted to a mobile environment [32].

This paper presents Sinedie (Smart and educational system for gestational diabetes), a telemedicine and educational health platform for GDM care enhanced by decision support capabilities. The following sections describe the system functionalities and design and present the evaluation results related to the usage of the system during a clinical trial at “Parc Taulí University Hospital“ (PTUH) in Spain.

2. Materials and methods

Sinedie is a web based CDSS that aims to provide a safe and effective platform to manage GDM patients’ care. The main objective is to enhance healthcare processes, by improving the access to specialized healthcare assistance, reducing face-to-face visits to prevent patients from unnecessary displacements and optimizing the clinicians’ time by reducing the clinical evaluation time required per patient.

2.1. Care protocol using the sinedie system

With Sinedie, patients with GDM follow the same self-monitoring guidelines as in standard care, but instead of going to the medical center every week they send their data (glycaemia, ketonuria and diet) to the system every 3 days, being able to do it more frequently if desired. When no data is received during the last
3 days, the system sends a Short Message Service (SMS) message to the patient to remind her about the lack of data transmission. The SMS reminder is repeated every day until the patient performs a new data transmission. After each data reception, the system automatically analyzes them to establish the patient’s metabolic condition (MC) and to verify the patient's compliance with the recommended self-monitoring guidelines. Based on the analysis results, a DST generates patient-specific recommendations to provide advice for therapy planning in the pre-insulinization treatment stage (before insulin therapy is prescribed). The DST determines if the patient needs a treatment change, the type of therapeutic action that needs to be taken, and whether it can be automatically prescribed or requires clinical verification in advance. The DST detects situations that require diet therapy modifications or situations that require the initiation of the insulin therapy. Recommendations about diet adjustments are automatically prescribed by the DST whereas proposals about insulin therapy have to be reviewed and approved by the patient's endocrinologist before any clinical action is performed. Patients receive instant feedback after each data upload. If during the data analysis, an insulin treatment proposal is generated, the system also informs the physician in charge that there is a proposal to evaluate.

The medical team can check the patients’ status in the system at any time. The system shows the MC, the therapeutic recommendation determined by the system and the date of her last data transmission for every patient. When selecting a patient, her detailed monitoring data is shown in an electronic logbook, as well as any treatment proposal pending of evaluation and her endocrinologist and gynecological clinical history. Clinicians can contact any patient by phone in case they need more information to evaluate their MC, or to avoid any evaluation delays if they observe that a patient is not sending data. During telephone calls, clinicians can modify the patients’ dietary treatment, and must enter into the system the therapy change performed. If clinicians consider that a patient should start an insulin therapy, they will contact her to arrange a face-to-face visit. Fig. 1 summarizes the main interactions between patients and physicians through the Sinedie system.

2.2. Architecture

The telemedicine platform is developed under a two layer client-server architecture with a web interface as a front end to provide access to the system functionalities from any computer with a web browser and internet connection, without the need of installing additional software. Fig. 2 shows a wise picture of the process of data analysis and therapy advice generation indicating the interaction between each component involved.

The role of module 1 in Fig. 2 is to manage the patients’ monitoring data introduction. The web graphical user interface (GUI) includes additional modules (not represented in detail in the figure) to manage other patients’ interactions with the system (visualization of monitoring data, history of treatments or notifications received; introduction of other monitoring parameters such as ketonuria, access to educational content, etc.). Module 2 contains an automatic glycaemia classifier whose role is to add the moment of measurement, according to meal intakes, to each incomplete glycaemia datum that lacks that information (explained in Section 2.3.2). Module 3 contains two Moore machines that analyse the monitoring data to obtain the patient’s MC. (explained in Section 2.3.3). The role of module 4 is to generate advice on therapy planning as explained in Section 2.3.4. Module 5 implements the notification of analysis results explained in Section 2.3.5 and module 6 manages the physician’s interaction with the web GUI.

The process to generate therapy advice (described in Fig. 2) is initiated by a patient data upload, sequentially progresses and only needs data related to the patient who invoked the analysis. Different patients uploading data at the same time do not share any data so no synchronization is required and data is never blocked by any thread, being always available for the decision algorithm.

2.3. System functionalities

The main functionalities provided by the system are: Remote patient monitoring, automatic data analysis and advice on therapy planning.

2.3.1. Telemonitoring and educational platform

Patients upload their monitoring data to the system through a web GUI. Decision support systems for diabetes management can be significantly affected by transcription errors [33]. For this reason, glycaemia values can only be introduced into the system by downloading the glucose meter. Patients use the Accu-ChekTM Smart Pix device reader to transfer glycaemia measurements from their glucose meter to their PC which are securely transmitted to Sinedie. The server preprocesses the glycaemia data received to detect incomplete measurements, checking if each BG value includes its associated moment of measurement. An automatic glycaemia classifier completes the measurements when required. To finalize the data upload process, the classified results are sent back to the patient for verification and to request the introduction of other meaningful monitoring data such as ketonuria values and non-compliance about dietary intakes associated with glycaemia data. Patients introduce these values through the web GUI by selecting the appropriate option in the corresponding dropdown lists (see Fig. 3). By the use of dropdown lists we avoid the potential mistakes patients can make with free text introduction. All the monitoring data entered are transmitted to the server for automatic remote evaluation.

Monitoring data are presented in an electronic logbook (Fig. 4) to both clinicians and patients, classified in relation to main meals and enriched with weekly statistics of glycaemia and the gestational week (GW) to help clinicians in the BG level interpretation. The caregiver can access the patient’s MC and the system’s therapeutic recommendation through the web GUI. Patients can edit the electronic logbook to manually register additional information they usually note down in paper logbooks, such as insulin doses (when required) and other events such as physical exercise or illness events, which helps physicians to make better prescriptions. Dropdown lists in the web GUI are also used for the introduction of this additional information.

Maternal weight, blood pressure, foetus percentile, HbA1c or albuminuria results from periodical gynaecological and endocrinological visits can also be introduced by the web GUI (see Fig. 5).

2.3.2. Glycaemia classification

In order to determine if hyperglycaemia in a GDM patient is caused by a specific meal or during fasting conditions, BG values need to be examined together with their moment of measurement according to the corresponding meal intake. The functionality of registering the moment of measurement after the patient measures each BG value is not available in all glucose meters, and even if it is, patients sometimes forget to introduce it. We built an automatic glycaemia classifier to calculate the moment of measurement, an essential input for the automatic data analysis, in case patients do not insert this information in the glucose meter. The glycaemia classifier is designed using the components which achieved the best accuracy results (95.92%) in a previous study [34]. The classification is performed in two steps: 1) The Expectation Maximization clustering algorithm [35] is used to group BG measurements in three sets according to the three main meals (“breakfast”, “lunch” or “din-
Fig. 1. Activity diagram of the Sinedie system. It shows the main interactions between patients (left block in the figure) and physicians (right block in the figure) through the Sinedie system (middle block in the figure). The main actions in each block are highlighted (Patients' data transmission; Sinedies' data analysis and therapy management; and review of patients by physicians).

Fig. 2. Architecture for therapy advice generation in Sinedie. 1) Monitoring data introduction, 2) Glycaemia classification according to meal intakes, 3) Automatic data analysis, 4) Decision support tools for therapy planning, 5) Notification of analysis results, and 6) Results presentation.
A. Monitoring data ordered by descending date. The columns (from left to right) show: Date, Gestational Week (G.W.), Glycaemia data classified in time intervals in pink, *Prep: Preprandial; Post: Postprandial; Break./BRK: Breakfast; NIG: Night exercise or other events. B. Statistics of glycaemia for the last week. C. Patient’s metabolic condition and last system therapeutic recommendation can adopt five different values: “breakfast preprandial”, “breakfast postprandial”, “lunch postprandial”, “dinner postprandial” or “other”. The C4.5 decision tree algorithm [36] is used to sequentially process BG measurements to obtain the specific moment of measurement that can adopt five different values: “breakfast preprandial”, “breakfast postprandial”, “lunch postprandial”, “dinner postprandial” or “other”. The C4.5 decision tree was trained with 6080 BG measurements from 25 GDM patients treated at PTUH, and were labelled by the authors according to the information registered by patients in paper logbooks.

Fig. 3. Moment of measurement verification and diet non-compliance and ketonuria introduction.

Fig. 4. Physician e-Logbook in Sinedie.
A. Monitoring data ordered by descending date. The columns (from left to right) show: Date, Gestational Week (G.W.), Glycaemia data classified in time intervals in pink, insulin in case it is prescribed in blue, Dietary treatment and qualitative modifications by patients (e.g. when eating more carbohydrates than prescribed) in yellow, ketonuria, exercise or other events. B. Statistics of glycaemia for the last week. C. Patient’s metabolic condition and last system therapeutic recommendation

"Prep: Preprandial; Post: Postprandial; Break/BRK: Breakfast; NIG: Night"
2.3.3. Automatic data analysis

In order to determine the patient's MC, Sinedie automatically analyses the raw monitoring data uploaded by the patient looking for situations of deficient metabolic control as specified in the clinical guidelines for GDM [6,7]. The patient's MC results from the combination of the glycaemic and the ketonuria status. Both status are determined by a Moore machine [37], a finite deterministic automaton (DFA) [38], where the output only depends on the state. By using automata we avoid repeating the evaluation of already inspected values, since we need to evaluate the patient's monitoring data under a seven day sliding window. Hence, the states are used for remembering the analysis results of the previous days, so only new data need to be evaluated when moving the window to assess each daily condition. The data analysis is divided into two independent procedures that are described in the following sections: Glycaemia Inspection and Ketonuria Inspection.

Glycaemia inspection

The glycaemia inspection procedure checks the patient's compliance to the recommended monitoring plan and the patient's glycaemic status.

The automaton that calculates the patient's glycaemic status processes the patient's BG measurements sequentially and has 3 inputs: 1) qualitative BG level ("Normal", "Moderate hyperglycaemia" or "Severe hyperglycaemia"), 2) compliance with diet prescription ("Yes" or "No"), and; 3) moment of measurement ("breakfast preprandial", "breakfast postprandial", "lunch postprandial", "dinner postprandial", "other"). The automaton has 24 states (1 initial, 11 intermediate and 12 final) that classify the patient's glycaemic status in three different categories:

- "NORMAL". All BG measurements are within normal ranges. It is the patients' initial state when they are enrolled in the system.
- "ALTERED". Some BG measurements are altered (hyperglycaemia is detected) but the number is still too low to require any action. All the automaton intermediate states belong to this category.
- "SIGNIFICANTLY ALTERED". The number of altered BG levels indicates that the patient's therapy needs to be changed. The automaton final states belong to this category.

We can summarize the 12 weekly patterns recognized by the automaton in two cases: 1) Hyperglycaemia values occur in different meal intervals; and 2) hyperglycaemia values occur in the same meal interval.

The diet compliance information is used to interpret whether a patient presents postprandial hyperglycaemia because her diet needs to be adjusted in a specific meal or because the patient did not follow the prescribed diet. The first time in the week evaluation period, when an anomalous BG value is associated with a diet non-compliance, the system will not consider it to propose a therapy change.

Ketonuria inspection

The automaton that calculates the ketonuria status has 1 input related to the patient daily ketonuria condition and can adopt two values: “positive ketonuria” (+) or “negative ketonuria” (−). We grouped the automaton states into two categories: "POSITIVE" and "NEGATIVE". The two final states correspond to the first category ("POSITIVE") and the rest to the second one ("NEGATIVE"). The patterns recognized by this automaton are the following: a) two consecutive days with positive ketonuria values; and b) three non-consecutive days with positive ketonuria values; in both cases within a week (see Fig. 6).

2.3.4. Decision support tool for therapy planning

The inputs of the DST are the patient's MC obtained in the Automatic data analysis, the patient's history of GDM treatments and previous decision support recommendations generated about the patient. The patient's MC is considered deficient (DMC) if it involves either a "SIGNIFICANTLY ALTERED" glycaemic status or a "POSITIVE" ketonuria status. Only DMCs trigger a recommendation generated by the DST. Previous decision support recommendations are considered in order to determine whether to suggest a different therapy adjustment or not, because metabolic changes related to the previous adjustment may take some time to show their effect. If the previous recommendation is recent (less than three days old), or if the patient has not read the previous treatment or if she has read it recently (in the last three days), a new adjustment is not suggested.
The DST knowledge base was created considering GDM clinical guidelines [6, 7] and expert endocrinologists' therapeutic strategies in clinical practice at PTUH. The knowledge base was modelled with a traditional logic rule set consisting of IF-THEN production rules. An example is shown below:

IF 'DMC due to 2 hyperglycaemias in breakfast postprandial and negative ketonuria state'
AND 'no previous diet adjustments by hyperglycaemia' AND 'treatment reading not recent'
AND 'previous recommendation not recent'
THEN 'reduce carbohydrates at breakfast'

When a patient's specific recommendation is generated, an algorithm analyses it in order to automatically prescribe a new diet therapy, to generate an insulin proposal for clinical verification or to wait before performing any therapy adjustment.

**Automatic diet prescriptions**

When the patient is enrolled in the system the DST considers the patient's height, weight and age to automatically propose the patient's initial diet therapy, suggesting the total calorie intake distributed in carbohydrates (CH) units along the day. To calculate the total calorie intake we used the Harris-Benedict equation [39] as they do at PTUH. We did not use any activity factor or made any calorie restriction for obese women. The endocrinologist can modify the personalized diet prescription for each patient.

When a diet adjustment recommendation is generated, driven by the monitoring data analysis, the DST calculates the carbohydrates (CH) distribution required for the new diet therapy and prescribes it automatically for the patient. There are three types of diet recommendations:

- Increment CH units at night.
- Reduce CH units at a certain meal interval (breakfast, lunch or dinner).
- Reinforce diet compliance.

The system could prescribe a maximum of five automatic treatments per patient: the initial diet, one diet reduction due to hyperglycaemia and three diet increments due to positive ketonuria. In case the patient continues to present DMC after these diet prescriptions, the system recommends the physician's assessment.

The system requires several abnormal values in a certain period of time to perform an automatic treatment, so a mistake in the additional data introduction would not necessarily affect the analysis. Although unlikely, a specific combination of mistakes in data introduction could bring the system to automatically change the patient's diet unnecessarily, or not to modify it when required. For example if a patient introduces several positive ketonuria values instead of negative ones or vice versa. In both cases, the results of a wrong therapy adjustment would be soon reflected in the patient's glycaemic state, which will be detected by the system or by the physician in the next data analysis.

**Insulin proposals**

The system was designed to be very sensitive regarding insulin therapy recommendations, in order to not miss any situation that could require insulin therapy. The design goal is to avoid false negatives regardless the occurrence of false positives. When the DST generates a recommendation about the initiation of the insulin therapy, a proposal of daily insulin prescription is automatically generated, indicating the recommended moment of insulin administrations, the type of insulin and the amount of insulin doses. The proposals are only available for the clinicians through patient's e-logbook (Fig. 4.C), where they can accept, modify (reduce or increase the dose or/and change the moment(s) of administration proposed), reject or postpone them. Whenever an insulin proposal is accepted or modified by the physician, the corresponding treatment is automatically created in the system and can be visualized by the patient in the Web-GUI.

The recommendation to assess the initiation of an insulin therapy is caused by repeated hyperglycaemia and ineffective diet adjustment.

### 2.3.5. Notifications of analysis results

Patients and health professionals receive instant feedback from the automatic notification module via SMS and through the web messaging module available in Sinedle. A maximum of 3 concatenated SMS (460 characters) is used to send a notification. The notification module provides alerts for critical values, reminders, advice to patients about carbohydrate intake, advice to physicians about insulin therapy and congratulations when the patient has a good glycaemic control. Notifications can also be manually generated whenever the clinicians or technical personnel want to communicate with patients or with each other.

Patients receive a notification that contains the automatic analysis results along with the DST recommendation immediately after uploading her monitoring data to the system. The physician in charge of the patient's care is alerted by SMS notification whenever an insulin proposal is generated.

The patient notification is composed by three sections:

a) The *Glycaemia and ketonuria analysis results* section presents a summary of the hyperglycaemia and/or positive ketonuria values found in the analysis, or congratulations when no abnormal values have been found.

b) The *Therapy prescription* section indicates if the therapy should be adjusted. In case of diet changes, the patient is requested to view her new treatment in the web GUI. In case of detecting that the insulin therapy is needed, the patient is informed that clinicians will contact her to gather additional information for a more detailed evaluation of her metabolic condition.
c) The Compliance measuring glycaemia section reminds the patients when they do not perform the expected number of measurements a day or when they do not measure their glycaemia at the recommended moments.

Reminders are sent to patients via SMS message whenever the system detects that there are missing glycaemia or ketonuria data for the last three days. The database is analyzed every day to check the last patients' glycaemia downloads and ketonuria data introduction.

The physician notification includes the identification of the patient; the type of situation detected in the data analysis (e.g. 2 or higher values at dinner); and the therapeutic recommendation advised by the DST (e.g. Evaluate start of insulin therapy).

2.3.6. Results presentation in the web GUI

The analysis results are instantly available for clinical review. Patients are listed in the clinicians' view of the web-GUI, along with the glycaemic state calculated from their last data upload and the DST recommendation if it was generated (see Fig. 7). In case a recommendation is not produced (Patients coded as “SUR1”, “SUR2”, “SUR4” and “SUR7” in Fig. 7), the glycaemic status category (“NORMAL”, “ALTERED” or “SIGNIFICANTLY ALTERED”) is shown instead.

Clinicians can see at a glance which patients have worsened according to their metabolic control and therefore need a more exhaustive examination and which ones are evolving satisfactorily and do not need any therapy adjustment. They can also visualize information about when the last recommendation was generated and when the patient performed the last data upload.

Clinicians can consult the progression of the patients' glycaemic status over time. This functionality provides transparency and helps the clinicians to understand how the patient current condition is calculated by the Automatic data analysis tool, as it shows which glycaemia values are considered to determine each glycaemic status.

2.4. Design and implementation

Sinedie is implemented in Java to allow its deployment in any server operating system. Security and privacy are assured by bidirectional communication data encryption using Hypertext Transfer Protocol Secure (HTTPS). Users' passwords are stored encrypted in the database using the MD5 algorithm. The platform is developed following the Model View Controller (MVC) pattern [40] with the Struts2 framework [41], maintaining a modular design encapsulating each functionality as an independent module to ensure its adaptability and easy maintenance. Apache Tomcat 7.0 web container is used to serve the Java server pages (JSP) developed for the dynamic web content creation. The web user interface is implemented as a rich internet application (RIA) using the ExtJS 2.0 framework [41] to facilitate the use of asynchronous Javascript and XML (AJAX) communication, so data transmission can be done partially when necessary to avoid reloading the whole page. Data are stored in a relational database managed with MySQL.

2.5. Evaluation methodology

The evaluation carried out corresponds to the pre-insulinization period of the GDM treatment and has been performed in two stages: A) a study to validate the system, prior to the use of Sinedie in clinical practice; and B) a clinical trial with patients to evaluate the system in terms of safety and effectiveness. In both studies, the medical personnel anonymized patients' data using the pseudonymization technique, replacing real patients' names, surnames and the identification number of their medical records by fictitious ones.

2.5.1. Validation study

In order to test the correct detection of patients' DMC by the Automatic data analysis and to verify the knowledge base of the Decision support tool for therapy planning we performed a validation study with monitoring data from a set of GDM patients treated at PTUH. Patients' glucose meters were downloaded by the medical personnel at the hospital to obtain the stored glycaemia measurements. We also gathered patients' paper logsbooks, and the diet and insulin prescriptions registered in patients' clinical history. We introduced the monitoring data in Sinedie simulating patients' uploads, and compared the patients' MC determined by the analysis tool on the date of each face-to-face visit, with the therapy adjustments performed by the physicians at each visit. We evaluated the sensitivity and specificity of the analysis tool considering true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN) (see the Appendix A for definitions).

A design criterion of Sinedie was to detect all situations that require a therapy adjustment so the number of false negatives should be zero. We also calculated the percentage of coincidence between the recommendations generated by the DSTs and the therapy adjustments performed by the physicians.

2.5.2. Clinical evaluation

A randomized 2:1 controlled trial was conducted at PTUH to assess the safety and effectiveness of remote patients' monitoring using Sinedie, and to compare the telemedical care process with conventional care. Patients were provided with a glucose meter (either the Accu-check Aviva or the Accu-Check Aviva Nano) for glycaemia self-monitoring. The medical team followed the patients' treatment with the Sinedie system until the insulin therapy was needed or the pregnancy ended. The study was approved by the local ethics board and the patients participating in the study signed an informed consent form. The following parameters were evaluated: Physician-patient interactions, the clinicians' workload, decision support effectiveness, the patients' compliance to self-monitoring and the satisfaction using the system. The statistical analysis was performed with IBM SPSS Statistics 23 using the Mann-Whitney U test.

We studied the physician-patient interaction to assess the system effectiveness in terms of face-to-face visits reduction. We calculated:

- \( V_n \): Number of face-to-face visits required per patient.
- \( V_d \): Face-to-face visit duration in minutes.
- \( C_n \): Number of telephone calls required per patient.
- \( C_d \): Telephone call duration in minutes.

The first visit when patients are diagnosed with GDM and the educational visit that patients attend to when they need to start the insulin therapy are not taken into account as there is no accurate registration of its duration. The number and duration of face-to-face visits as well as the number of telephone calls made in the intervention group were registered in the system by the medical team during the study. Telephone calls duration was not registered from the beginning of the study so their average duration was estimated by the endocrinologists as 5 min per call. No telephone calls were made to contact patients in the control group. The duration of face-to-face visits in the control group was not registered. Endocrinologists estimated that the duration of face-to-face visits was 15 min.
The questionnaire was designed by the authors of this research to evaluate patients' satisfaction. Each question is answered with a 10 point semantic response scale that patients filled in at the end of the gestation.

Telematics time per review (Trev): Average time dedicated to a single patient telematics review (see Eq. (1) in the Appendix). We consider that a review starts when a clinician selects a patient from the list (Fig. 7) and ends when the clinician either returns to the patients' list or logs out of the system. On several occasions, we observed that after clinicians select a patient for review, clinicians neither return to the patient list nor log out, so no activity is registered until their session expires. We considered 3 min as a session expiration time, so once a physician stops logging activity while evaluating a patient, a maximum of 3 min is added to the time of that specific telematics review.

Telematics time per patient (Ttpat): Average time dedicated to a patient along the entire treatment using telematics reviews in Sinedie (see Eq. (2) in the Appendix).

Global time per patient (Tglo): Average time dedicated to a patient along the entire treatment considering face-to-face visits, telephone calls interactions and telematics reviews (see Eq. (3) in the Appendix).

The evaluation of decision support effectiveness during the clinical study is focused on its two functionalities:

- **Automatic diet prescriptions**: including initial therapies: We evaluated the number of automatic diet prescriptions performed by the system, which of them were rectified by the medical personnel and the reason for this rectification, and the number and cause of manual diet prescriptions performed by physicians.

- **Proposis to start insulin therapy**: False negatives and false positives regarding insulin therapy needs and percentage of insulin proposals accepted, modified, postponed and rejected by clinicians.

The patient's compliance was evaluated in terms of compliance to measure BG levels, according to a prescribed frequency of 4 measurements per day in the specific moments of measurement (fasting, breakfast postprandial, lunch postprandial and dinner postprandial) and the compliance to frequently use the system in terms of uploading glycaemia data every 3 days.

The patients' satisfaction was evaluated with a paper questionnaire that patients filled in at the end of the gestation. The questionnaire was designed by the authors of this research paper and contains 30 questions regarding the patient's general impressions of the system, including its usefulness, usability and trustworthiness. Each question is answered with a 10 point semantic differential scale (the higher the better), which represents a score for the different aspects of the system.

### 3. Results

#### 3.1. Validation study

We uploaded to Sinedie the monitoring data from 25 patients who were followed up at the hospital (since diagnostic until either insulinization or delivery) during an average period of 63.761 ± 37.073 (median = 69,000; percentile25 = 17,600; percentile75 = 29,000; percentile95 = 87,000; percentile95 = 125,000) days per patient. The data set contains a total of 6025 BG measurements, 124 ketonuria values, and 226 diet non-compliance. Patients attended a total of 75 face-to-face visits where physicians prescribed 11 insulin treatments and 7 diet adjustments. Patients attended an average of 3,000 ± 2,255 (median = 3,000; percentile25 = 1,000; percentile75 = 4,000; percentile95 = 6,800) visits per patient and 11 (44,000%) of them required insulin therapy at gestational week 32.830 ± 4.744 (median = 33,000; percentile25 = 25,835; percentile75 = 30,275; percentile95 = 35,450; percentile95 = 38,775). Table 1 shows the relationship between the DMC detected by the analysis tool and the therapy adjustments performed by the medical team in face-to-face visits.

<table>
<thead>
<tr>
<th>Therapy adjusted</th>
<th>Therapy unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>No DMC</td>
<td>13 (TP)</td>
</tr>
<tr>
<td>DMC</td>
<td>42 (TN)</td>
</tr>
</tbody>
</table>

In the fifth FN case, the medical team changed the therapy in the presence of fewer number of hyperglycaemias than the number considered enough in our specification to determine DMC. In the fifth FN case, the medical team changed the diet as it is done when the ketonuria state is positive, although the ketonuria values were negative in the previous two weeks.

The clinicians performed a total of 18 therapy adjustments: 7 diet adjustments and 11 insulin therapy initiations. The system’s recommendations matched the clinicians' therapy decisions in 73.333% (55 out of 75) of the cases. The coincidences were 3 diet changes, 10 insulin initiations and 42 unchanged therapies.
There were 4 diet changes made by the medical team that did not match the system recommendation. In two of them, the medical team changed the diet therapy, whereas the system recommended insulin initiation, and the other two correspond to 2 of the 5 FNs in which the system did not generate a recommendation because DMC was not determined. The remaining cases correspond to the FN in which the medical team initiated the insulin therapy due to a gynaecological parameter.

The number of false positives obtained means that in 15 occasions the system detected that the patient required a therapy adjustment according to GDM guidelines but the physician did not prescribe it. Different therapeutic actions can produce similar effects in patients' glycaemic control. Faced with the same situation, different specialists may decide to act on different parameters (diet, insulin, time between meals, exercise, reinforce treatment adherence, etc) to normalize the patient's glycaemia. Sometimes, during face to face visits, patients justify the appearance of hyperglycaemias for failing to accomplish the prescribed diet, so the physician could decide to explain the patient the importance of diet compliance and wait until the next visit to see how the patient evolves.

The objective of the validation study was to check if the system was able to correctly establish patients' DMC according to clinical guidelines and to generate the appropriate therapy adjustment recommended in literature to assist specialists in decision-making. After consulting these results with the endocrinologists at PTUH they considered that the analysis tool correctly detected patients' DMC due to hyperglycaemia or positive ketonuria, so no change was needed in its specification. The medical team also considered the recommendations about therapy changes correctly generated by the DST, so they decided to maintain the knowledge base unchanged for the clinical evaluation.

3.2. Clinical evaluation

Ninety patients participated in the clinical trial over a period of 17 months and were randomized into intervention and control group (60 and 30 patients respectively). Only one patient in the control group dropped out of the study. Thirty seven patients in the intervention group (61.667%) required insulin therapy while 13 patients (43.333%) in the control group required insulin. Table 2 shows the data related to the days of follow up and GW of insulinization of patients in the intervention and the control group.

The distribution observed in Table 2 indicates that both groups were equivalent regarding days of follow up and GW of insulinization.

3.2.1. Physician–patient interaction and clinicians’ workload

Table 3 shows the number (Vn) and duration (Vd) of face-to-face visits in both groups, intervention and control, as well as the telephone calls (Cn) and telematics reviews (R and Ttrev) performed by clinicians to patients in the intervention group. In Table 3 it can also be observed the average time devoted to patients along their entire treatment using Sinedie (Tpat) and the global time (Tglo) devoted to patients considering also face-to-face visits.

The use of the system reduced the number of face-to-face visits required per patient by 88.556% (3.207 ± 2.846 visits in conventional care vs. 0.367 ± 0.901 with Sinedie). Physicians performed a total of 38 phone calls to 18 different patients. The average global time per patient was similar in both groups, presenting high variability, but its median value was 27.389% lower in the intervention group. Fig. 8 shows a graphical comparison of physician-patient interactions and the telematics workload between the intervention and the control group.

3.2.2. Decision support effectiveness

Nutritionists accepted 27 out of the 60 initial diet therapies suggested by the system. Among the 33 changes made by clinicians in the initial diet therapy, the majority (29) were addressed to prescribe a lower amount of calories than the system. The system detected all situations that required a diet therapy adjustment due to hyperglycaemia or positive ketonuria and prescribed the corresponding treatment correctly. The system performed 29 diet adjustments to 15 different patients. The physician rectified three of them so we consider that there were three false positives. The reason for two of the rectifications was that the patient was not following the prescribed intake (diet non-compliance), so an increment was not necessary. The other one
Therefore, when the patient performed the data upload and the system detected the positive ketonuria situation, it did not consider the adjustment was already done and it duplicated it.

was explained because during a telephone call the physician prescribed the diet adjustment related to a ketonuria positive state before the patient transmitted her monitoring data to the system. Therefore, when the patient performed the data upload and the system detected the positive ketonuria situation, it did not consider that the adjustment was already done and it duplicated it.

In addition to the ones automatically performed by the system, clinicians manually prescribed 22 diet treatment changes to 18 different patients that were motivated by diverse situations (see Fig. 9):

The system detected all patients (37 out of 60) that needed insulin and received a prescription of insulin therapy by the physician, so, as desired, there were no false negatives. There were 11 false positives, as the system also recommended starting an insulin therapy to another 11 patients that finally were treated only with diet.

Fig. 10 shows the clinicians’ decisions regarding the 107 system recommendations about the onset of the insulin therapy.

The majority of the proposals generated by the system were rejected or postponed. We observed that in 20 (41.667%) of the postponed proposals and in 13 (59.091%) of the rejected ones the physician decided to start an insulin therapy a few days later. We consider that the system anticipated the need of insulin administration if between the postponed/rejected insulin proposal generated and the accepted/modified one passed a maximum of 14 days. This anticipation occurred in 17 out of 37 patients.

The percentage of modified proposals is similar to the accepted ones, and the majority of the modifications performed by clinicians were to prescribe a lower insulin dose than the one initially proposed. So, we conclude that the system correctly detects the need to start insulin, but the insulin treatment generation could be improved by studying the reasons for proposals’ modification (see Fig. 11).

The reason “different BG values considered” appears if the physician evaluates an insulin proposal when the patient uploaded new monitoring data after the insulin proposal had been generated. A new proposal is not generated because the last one is less than three days old, so when the physician evaluates the proposal she also considers the latest patient data.

3.2.3. Patients’ satisfaction and compliance to self-monitoring using the system

Table 4 shows the total number of measurements transmitted or stored in patients glucose meters, the number of measurements per day performed by patients and the frequency of glycaemia data transmission related to the intervention group.

The self-monitoring data of both groups were similar, measuring their glycaemia $3.830 \pm 0.086$ (average and standard deviation of both groups) times a day. Two of the patients in the intervention group only transmitted their monitoring data once before starting
Fig. 10. Clinicians' acceptance rate of system proposals of start insulin.

FIGURE 11. Reasons for modification and rejection of insulin proposals.

Table 4
Patients' self-monitoring results.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. BG measurements per patient</th>
<th>No. BG measurements per day</th>
<th>No. days between glycaemia transmissions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
</tr>
<tr>
<td>Mean</td>
<td>147.017</td>
<td>141.562</td>
<td>3.890</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>144.485</td>
<td>123.117</td>
<td>0.256</td>
</tr>
<tr>
<td>Median</td>
<td>98.500</td>
<td>112</td>
<td>3.944</td>
</tr>
<tr>
<td>Percentile&lt;sub&gt;25&lt;/sub&gt;</td>
<td>9.000</td>
<td>11</td>
<td>3.317</td>
</tr>
<tr>
<td>Percentile&lt;sub&gt;50&lt;/sub&gt;</td>
<td>44.500</td>
<td>52.750</td>
<td>3.992</td>
</tr>
<tr>
<td>Percentile&lt;sub&gt;75&lt;/sub&gt;</td>
<td>201.250</td>
<td>216.5</td>
<td>4.000</td>
</tr>
<tr>
<td>Percentile&lt;sub&gt;90&lt;/sub&gt;</td>
<td>637.000</td>
<td>31,5000</td>
<td>4.238</td>
</tr>
</tbody>
</table>

* Non statistically significant.

4. Discussion

Our first design goal, of face-to-face visits reduction (88.55%), was successfully achieved as patients treated with Sinedie only have to go to consultation when they are required by the physician to evaluate a therapy adjustment (mainly due to the need to start insulin). The average duration per visit did not increase with
The use of telephone calls has also contributed to face-to-face visits reduction, being a complementary source of data and substituting some face-to-face visits, when more details are needed by the endocrinologist to evaluate metabolic control. Whenever clinicians had to contact the patient to evaluate her health state, the telephone conversation helped them to decide whether the face-to-face visit was needed or not. The number of telephone calls performed was small and its contribution to the total time dedicated to a patient was of 5.382%.

The use of a telemedicine and CDSS system, not only has reduced face-to-face visits by 88.556%, but also has reduced the time spent by clinicians in single patients' reviews from 15,000 min (standard care) to 2,778 ± 0.858 min (telematics time per review). The average number of telematics reviews performed by clinicians per patient was higher than the number of visits programmed in conventional care (16.050 ± 13.936 telematics reviews by clinicians per patient was higher than the number of visits programmed in conventional care (16.050 ± 13.936 telematics reviews vs. 3.207 ± 2.846 visits), which results in a more frequent follow up.

The “global time per patient” devoted by clinicians throughout the patients’ entire treatment was similar in both groups (48.027 ± 45.167 min vs. 48.103 ± 42.686), so the use of the system did not increase clinicians’ workload. In fact, the median value of the time devoted by clinicians per patient was 27.389% lower in the intervention group (32,675 min vs. 45,000 min). So, considering the high variability observed in the “global time per patient” in both groups, and focusing our attention in the median values obtained, we can conclude that the system not only does not imply an increment in clinicians’ workload, but also contributes to reduce it, solving the main criticism that telemedicine systems receive.

The initial diet prescription results could be enhanced by including in the specification a calorie restriction according to patients’ BMI and the maternal weight gain. Nevertheless, the prescription of the initial diet is not a critical feature of the system as it is not used for remote patient monitoring. It is considered as an added functionality that can facilitate nutritionists’ workload.

The study results indicate that Sinedie is a safe platform to manage GDM treatment and to identify insulin needs. The system detected all situations that required a diet therapy adjustment due to hyperglycaemia or positive ketonuria and prescribed the corresponding treatment correctly. Two of the reasons for manual diet treatment adjustments were previously identified in the retrospective study, foetus percentile and diet reduction instead of start an insulin treatment, but clinicians preferred not to include them in the analysis tool specification. The results regarding detection of insulin needs are satisfactory since no patient that needed insulin was overlooked by the system, which was a key design goal. The false positives obtained are not a negative result. The purpose of the system is to indicate when a patient meets the criteria described in clinical guidelines to assess the onset of insulin, but the final decision depends on the endocrinologist in charge. The specialist needs to consider not only the aid offered by the system regarding the patient’s metabolic condition, but also other patient specific characteristics such as gestational week, foetus percentile or familiar context.

The majority of insulin proposals generated by the system were rejected or postponed. The medical team reported that proposals related to starting insulin therapy generated in the first week of follow up tend to be postponed (8) or rejected (7), because they need more time to see how the patient’s glycaemic control evolves. However, they prefer to receive early insulin proposals providing that the defined conditions are matched so that they can decide when to start the insulin treatment. The clinicians also reported that they tend to postpone or to reject the first recommendation to start insulin and react to the second one, but found of a high value the anticipation of the system. When analysing the reasons for insulin proposals’ modification, we identify some of the parameters previously observed in the validation study and in the explanations about manual diet prescriptions which are: maternal BMI, maternal weight gain and foetus percentile. As the system already allows registering these variables, we consider that further refinement of the knowledge base specification could enhance the definition of insulin proposals and allow the generation of diet recommendations driven by these parameters.

Patients were compliant with the self-monitoring protocol prescribed by the physician. They uploaded their monitoring data every 3.477 days and measured their glycaemia 3.890 times a day, as recommended.

5. Conclusion

The use of Sinedie reduced face-to-face visits as well as the time clinicians devote to patients’ evaluation, which enhances clinicians’ efficiency to overcome their growing workload. The system detected all cases that required a therapy adjustment, including all patients that needed an insulin therapy, obtaining no false negatives.

The CDSS presented (Sinedie) improves the access to specialized assistance, allowing patients to send their monitoring data from home, which prevents unnecessary displacements. DSTs integrated
What was already known on the topic?

- A CDSS for GDM is able to modify healthcare processes as it generates automatic therapy changes when the patient’s metabolic state is deficient.

What this study added to our knowledge?

- It demonstrates the feasibility of using a CDSS in clinical practice to provide real-time, safe and accurate therapy recommendations for GDM.
- It presents a CDSS as a solution to the increment of the clinician's workload that telemedicine might cause.
- A CDSS that complements telemedicine for managing GDM treatment reduces face-to-face visits.
- A CDSS for GDM is able to modify healthcare processes as it generates automatic therapy changes when the patient’s metabolic state is deficient.

in the Sinedie platform allow to automatically determining which patients have an adequate glycaemic control and therefore do not need to go to face-to-face visits, which can contribute to medical centres’ waiting list reduction. Patients have reported to be highly satisfied with the system, considering it useful and trusting in being well controlled.

The Sinedie system anticipates treatment adjustments, as diet prescriptions are automatically made as soon as the requirements needed are detected by the decision support tools, and the physicians are informed about the need of starting the insulin therapy in specific patients. The automatic determination of the patient’s glycaemic and ketonuria states optimizes the clinicians’ time, pointing out at patients who need a more exhaustive or urgent evaluation, which can help to prioritize those with the worst metabolic condition. Automatic data analysis tools solve the increasing workload that telemedicine can cause, reducing the evaluation time per patient.

Conflicts of interest

None of the authors of this article have competing financial interests or personal relationships with other people or organizations that could inappropriately influence their work.

Author contributions

E. C.-R., G. G.-S., M.E. H. and M. R contributed to the conception and design of the study, E. C.-R., G. G.-S., B.P., M. V. and M. R acquired the data, E. C.-R., G. G.-S., M.E. H., M. V. and M. R analysed and interpreted the data, E. C.-R., G. G.-S., and M.E. H. drafted the article. All authors critically revised the manuscript for important intellectual content and approved the final version to be submitted.

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Appendix A.

Validity study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>TP/(TP + FN)</td>
</tr>
<tr>
<td>Specificity</td>
<td>TN/(TN + FP)</td>
</tr>
</tbody>
</table>

Considering

- TP: Number of visits in which the medical team adjusted the therapy and the system determined DMC.
- FP: Number of visits in which the medical team did not adjust the therapy and the system determined DMC.
- TN: Number of visits in which the medical team did not adjust the therapy and the system did not determine DMC.
- FN: Number of visits in which the medical team adjusted the therapy and the system did not determine DMC.

Clinical study

Considering the following parameters:

- M: Number of clinicians who used Sinedie.
- Prev_m: Number of patients reviewed by clinician ‘m’.n’.
- R_m: Number of reviews made by the clinician ‘m’ to the patient ‘p’.
- Tr: Time dedicated to the review ‘r’.
- P_m: Number of patients assigned to the clinician ‘m’.
- V: Number of visits
- V_d: Visit duration
- C_n: Number of phone calls
- C_d: Phone call duration
- Ttpat: Telematic time per patient

We calculated the “telematics time per review” as in Eq. (1), the “telematics time per patient” as in Eq. (2) and the “global time per patient” as in Eq. (3)

Equation (1) Telematics time per review

\[ T_{trev} = \frac{1}{M} \sum_{m=1}^{M} \frac{1}{\text{Pr}_{vm}} \sum_{p=1}^{P} \frac{1}{R_{mp}} \sum_{r=1}^{R_{mp}} T_{tr} \]

Equation (2) Telematics time per patient

\[ T_{tpat} = \frac{1}{M} \sum_{m=1}^{M} \frac{1}{P_{m}} \sum_{p=1}^{P} \sum_{r=1}^{R_{mp}} T_{tr} \]

Equation (3) Global time per patient

\[ T_{tglo} = \left( V + V_{d} \right) + \left( C_{n} + C_{d} \right) + T_{tpat} \]

References
