Telemedical Artificial Pancreas

PARIS (Páncreas Artificial Telemédico Inteligente) research project

Alberto de Leiva, PHD
Maria Elena Hernando, PHD
ON BEHALF OF EDUAB-HSP AND GBT-UPM

DEBATE — The integration of continuous subcutaneous insulin infusion (CSII) (insulin pump therapy) and continuous interstitial glucose monitoring (CGM) appears to be an excellent solution for obtaining the desirable metabolic control for most insulin-treated subjects (1–4). Several studies have suggested that CGM with readings in real-time (CGM-RT) further improves blood glucose control (5–9). The introduction of CGM and CSII into clinical practice has generated an inevitable increase in the amount of data to be managed and interpreted. Telemedicine facilitates data management and preprocessing to optimize therapy. Among other potential benefits, telemedicine improves communication among patients and health care providers, improves quantity and quality of data collection, and eases decision-making and therapy adjustment (10–12). DIABTel, a web-based telemedicine system, is a good example for a solution designed to supply these needs (13).

PARIS (Páncreas Artificial Telemédico Inteligente) is a coordinated research project to develop and validate a telemedical artificial pancreas (TAP), a multi-access telemedicine system that integrates CGM-RT, insulin pump, a smart assistant (SA), and close-loop control algorithms. SA is a personal intelligent assistant based on a handheld digital device to provide both personal and remote loop strategies, using CGM, CSII, and mobile general packet radio service (GPRS) communication with a telemedicine central server (TMCS).

This review summarizes acquired experiences with TAP, integrating these new technologies with the objective to improve glycemic control of type 1 diabetic patients.

RESEARCH DESIGN AND METHODS

Description of the DIABTel telemedicine system

The telemedicine architecture consists of two components: the medical unit (a telemedical central server) and the patient unit (a smart assistant).

The TMCS at the diabetes center of the hospital continuously runs, receiving and processing patients’ monitoring data, messages, and requests for professional advice. A previous publication already reported the benefits of DIABTel, allowing the implementation of an easy-to-use, user-tailored telemedicine system with a technological platform allowing tight integration between multi-access modalities (web, phone, palmtop) for diabetes management (14).

DIABTel provides the information for patient management and support for decision-making through the facilities of four main services: telemonitoring of main parameters of diabetes care (blood glucose, diet, insulin doses, physical activity, severe hypoglycaemia, ketonuria, sick days), telecare (consultation and supervision), remote information access, and knowledge management tools. In previous experiences, DIABTel was effective, improving patient-doctor interaction, data display, and patient’s confidence in self-management by constant professional supervision (15,16).

The SA supports both personal and remote-control strategies supervised by health care professionals through the TMCS. The transfer of information can be activated by the patient at any time through the mobile patient unit, a GPRS-based SA that supports personal and remote control strategies for patients, supervised by physicians through the telemedicine system. The SA architecture includes functionalities for data management: electronic logbook, rule-based reasoning methodology in decision support (17,18), advice generation by relying on a diabetic patient simulator, e-mail facility, and visualization. The blood glucose measurement edition includes specific time of measurement and time intervals between measurements. Monitoring data stored at the TMCS can be downloaded to the SA database through the synchronization process and vice versa. The multiparametric graphic scenario displays a quick overview of the patient’s metabolic status, providing information of interest and supporting the decision-making process; variables such as blood glucose, diet, and administered doses of insulin can be shown.

SA may also allow communication with different medical devices (glucose sensing, insulin pump) for automatic download.

Operation of TAP

TAP is built in two interlinked loops. The “personal loop” allows wireless communication between the SA, the insulin pump, and the CGM device. The “remote loop” connects the diabetic subject to the health care professional via the SA and its wireless connection to the TMCS. The SA platform consists of several systems (user interface, data access, communication devices, model predictive control, and TCMS modules) (Fig. 1). The model predictive control module calculates the modification of the continuous insulin in-
fusion rate provided by the pump, following the physiological model of Hovorka (19). The platform implies two control modes: 1) the patient decides changes in the insulin pump program by using the information coming from the glucose sensor (free mode), and 2) the patient gets advice, through the SA, on the insulin bolus before each meal (advisory mode). The patient uses the SA to register and transfer data related to timing and pre- and post-prandial glucose levels, amount of ingested carbohydrates, and additional relevant information (e.g., previous physical exercise). From this information, the algorithm computes corresponding insulin dose, which has to be approved by the physician through the Web interface, before it is shown to the patient. The analysis and design is based on the MOSAIK-M (modeling, simulation, and animation of information and communication systems in medicine) system model (20). The patient uses the SA to get results of the proposed insulin bolus and decides to follow it or not.

The TAP has been evaluated by a research consortium funded by the European Commission: The Intelligent Control Assistant for Diabetes (INCA Project), introducing the concept, design, and preliminary evaluation of a mobile close-loop system for diabetes management. A feasibility pilot was carried out in a group of type 1 pump-treated diabetic patients investigated at the Institut für Diabetesforschung (München, Germany), with satisfactory outcomes in ambulatory scenarios (21).

**CLINICAL EVALUATION OF TAP** — Various clinical experiences have been designed to investigate the clinical impact of the telemedical artificial pancreas in “real life.” So far, two randomized crossover ambulatory clinical studies have been carried out. Clinical study 1 focused to evaluate the results of the original web-based telemedicine system. Clinical study 2 evaluated the impact of CGM-RT, together with a telemedicine system.

**Clinical study 1: Evaluation of a telemedicine system that includes an SA**

A comprehensive full description of the trial is available (22).

**Design and methods.** The local ethical committee approved the protocol and patients signed the informed consent. Ten insulin pump–treated (for more than 1 year) type 1 diabetic subjects (five women), mean age 40.6 years (range 21–62 years), diabetes duration 14.7 years (3–52), C-peptide negative, and A1C <10%, were randomized into intervention versus control groups and crossed over to alternate arm after 4 weeks. During the intervention phase, patients were assisted by telemedicine (DIABTel System). All subjects were instructed in the use of the DIABTel web service, the management of the SA (a commercial handheld digital assistant: iPAQHP2210 pocket PC, Palo Alto, CA) provided with wireless communication facilities, such as infrared, Bluetooth, and GPRS. Patients were requested to submit blood glucose levels directly from a conventional glucose monitor (Accu-Chek, Accutrend, and Acculin modem; Roche Diagnostics, Basel, Switzerland) and insulin treatment data at least twice a week. In the control phase, patients only used the conventional glucose monitor plus modem for sending data, without any feedback from the diabetes center. In the intervention phase, patients were assisted by telemedicine (DIABTel System) (Fig. 2). Confidentiality was guaranteed through data encryption, using the Secure Locket Layer protocol; patients’ names were coded when interacting with the website. The system notified doctors with predefined alarm messages for out-of-range glucose values. After analyzing data sent by patients, modifications of insulin basal rate and boluses were advised when necessary by health care professionals; all exchanged messages were automatically registered by the DIABTel System. A1C was measured by ion-exchange high-pressure liquid chromatography (Bio-Rad VARIANT II; Bio-Rad laboratories, Munchen, Germany), with a reference range of 4.2–5.7%. Fructosamine was measured by a colorimetric assay system (nitroblue tetrazolium method), provided by BioSystems (Barcelona, Spain); the ref-
Design and methods. Ten insulin pump–treated (D-tron plus; Disetronic, Burgdorf, Switzerland) type 1 diabetic patients (five women), mean age 41.2 years (range 21–62), duration of diabetes 14.9 years (3–52), were randomized in a crossover study with two phases of 4 weeks' duration each, with an interim washout period of 6 weeks. Interaction between patients and health care professionals was supported by the DIABTel System. Real-time CGM data (Guardian RT, Medtronic) was used 3 days per week during the experimental phase. A 72-h masked CGM registry (CGM System Gold, Medtronic, Northridge, CA) was carried out at the end of the control phase. Monitoring data were retrieved directly from the pump, and the Accutrend glucose monitor (Boehringer Mannheim, Germany) and Acculink modem (Roche Diagnostics, Basel, Switzerland) were available on the web and the patient SA (iPAQ HP2210 pocket PC), which communicates with the DIABTel server (mobile GPRS Wide Area Network) (Fig. 3). Within the 24-h period after data reception, physicians analyzed patients' data and advised treatment changes, when necessary. A1C was measured by ion-exchange high-performance liquid chromatography (VARIANT II, Bio-Rad), with a reference range of 4.2–5.7%. Statistical analyses were performed using SPSS v 14.0. Comparisons were made using nonparametric tests for paired data (Wilcoxon's test). The study had been previously approved by the local ethics.
Telemedical artificial pancreas

showed that identical A1C at different stratified levels produced different and unpredictable diurnal patterns. Although CGM still remains experimental, it permits recognition of the diurnal modal profile in ambulatory observation for extended periods, which may be linked to diabetes complications (39).

CGM is still a clinically experimental, invasive (although minimally), rather cumbersome alternative to SMBG, requiring the periodic change of the indwelling sensor (40). A dynamic picture of the glucose profile is provided by the CGM, as well as the direction and speed of its movement (41). Fasting glucose levels correlate better with A1C, and it is not a good indicator of diurnal glucose changes. In the specific group of women with gestational diabetes, in whom postprandial glucose is critical regarding fetal complications, the experience has suggested advantages of CGM in detecting abnormal postprandial glucose levels (42).

A recently published multicenter clinical trial has shown that CGM is associated with improved glycemic control in adults (25 years of age or older) with type 1 diabetes, being the primary outcome of the change in A1C level at 26 weeks (43). The same trial, as well as a systematic review and meta-analysis, confirmed that CGM is not better than SMBG with regard to improvement of metabolic control among type 1 diabetic children (44). A plausible explanation for these findings may relay in the observation that among the subjects using CGM, those in the 15- to 24-year-old group were less adherent to sensor use than were older or younger patients (43). Rates of hypoglycemia were similar with CGM and SMBG in all age-groups.

Our work strongly suggests that the intermittent use (42% of the time) of GCM, with the support of telemedicine, achieves reduction of A1C and improvement of glucose stability in type 1 diabetic patients. Furthermore, for the first time, real-time CGM, in conjunction with telemedical support, has been successfully assessed. CGM, together with SMBG and insulin pump, generate a tremendous amount of data, which makes processing by patients and physicians quite troublesome; thanks to DIABTel, the analysis is facilitated by data aggregation, statistics, and graphic registries in an easily integrated and user-friendly manner.

Improved accuracy of real-time CGM facilitates the development of close-loop systems, with the greatest potential for the near future and the support of the Juvenile Diabetes Research Artificial Pancreas Project (45).

In conclusion, the PARIS Research Project has shown that a Telemedicine System incorporating an SA improves glucose control in adult type 1 diabetic subjects. The investigation has also proven that the use of real-time CGM in conjunction with telemedical assistance improves glucose control and glucose stability in adult type 1 diabetic patients, treated with an insulin pump. Because of the small size of the recruited samples, these results need to be reproduced in larger groups of type 1 diabetic patients in the coming future. The Telemedical Artificial Pancreas solution, proposed in the PARIS Research Project, integrates a personal loop that allows wireless communication between the SA, insulin pump, and CGM device, with a remote loop that connects the diabetic patient to the health care professional via the SA and its wireless communication with a telemedicine central server. The TAP offers four control strategies, each of them supported by a special function of the smart assistant. In strategy 1, the patient decides changes in the insulin program by using the information provided by the glucose sensor. In strategy 2, the physician prescribes changes in insulin treatment, using the information provided by CGM and CSII, reaching the TMCs from the SA. In strategy 3, the SA is remotely programmed by automatic procedure, under the physician supervision (remote loop control algorithm). Finally, in strategy 4, the SA provides a real-time control of the insulin pump based on the information offered by the CGM (personal loop control algorithm). The selection of a specific strategy or combination of strategies depends on the different circumstances of the patient (for example, an automatic personal loop control algorithm could be active at night and a control mode could be used during the day). Close-loop systems may generate a revolution in diabetes management; nevertheless, their introduction must be gradual and progressive, in parallel to advance of knowledge, increasing experience, accuracy of the systems, and overall, the patient’s safety.
References

1. Hovorka R. Continuous glucose monitoring and closed-loop systems. Diabet Med 2005;23:1–12
2. Baquette BV. A critical assessment of algorithms and challenges in the development of a closed-loop artificial pancreas. Diabetes Technol Ther 2005;7:28–47
3. Owens C, Zisser H, Jovanovic L, Srinivasan B, Bonvin D, Doyle J III. Run-to-run control of blood glucose concentration for people with type 1 diabetes mellitus. IEEE Trans Inf Technol Biomed 2006;6:996–1005
4. Hovorka R, Chassin J, Lujan-Villegas ME, Copelli C, Camp G, de Leiva E, Pretschner P. What can we really expect from telemedicine in intensive diabetes treatment: results from a 3-year study on type 1 pregnant women. Diabetes Technol Ther 2001;3:581–589
5. Bellazzi R, Liria E, Montana S, Riva A, Stefanelli M, D ’ Annunzio G, Lorenzi R, Gómez EJ, Hernando ME. Brugués E, Germeño J, Corcoy R, de Leiva A, Cobelli C, Nucci G, del Prato S, Maran A, Kilki G, Tuominen J. A telemedical support for diabetes management: the T-IDDM project. Comput Meth Prog Biomed 2002;69:147–161
6. Gómez EJ, del Pozo F, Hernando ME. Telemedicine for diabetes care: the DIABTel approach towards diabetes telecare. Med Inform 1996;21:283–295
7. Bellazzi R, Arcelli M, Bensa G, Blankenfeld H, Brugués E, Carston E, Cobelli C, Cramp D, d ’ Annunzio G, de Cata P, de Leiva A, Deutsch T, Fratino P, Gazzaruso C, Garcia A, Gergely T, Gómez E, Harvey F, Ferrari P, Hernando E, Boukou M, Larizza C, Ludekke H, Maran A, Nucci G, Ferranti C, Ramal S, Roudsari A, Riga M, Stefanelli M. Design, methods, and evaluative directions of a telemedical service for the management of diabetes mellitus patients. Diabetes Technol Ther 2003;5:621–629
8. Hernando ME, Gómez EJ, Corcoy R, del Pozo E. Evaluation of DIABNET, a decision support system for therapy planning in gestational diabetes. Comput Methods Prog Biomed 2000;62:235–248
9. Gómez EJ, del Pozo F, Ortiz E, Malpica N, Rahms H. A broad multimedia collaborative system for advanced teleradiology and medical diagnosis. IEEE Trans Inf Technol Biomed 1998;2:146–156
10. Montani S, Bellazzi R, Liria E, Riva A, d ’ Annunzio G, Fiochi S, Lorni R, Stefanelli M. Protocol-based reasoning in diabetic patient management. Int J Med Inf 1999;53:61–77
11. Hovorka R, Svancar S, Carson ER, Wilman S, Franssen PH. A consultation system for insulin therapy. Comput Methods Prog Biomed 1996;32:303–310
12. Hovorka R, Shojae-Moradie F, Carroll PV, Chassin J, Gowrie IJ, Jackson NC, Tudor RS, Umpleby AM, Jones RH. Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT. Am J Physiol Endocrinol Metab 2002,282:E992–E1007
13. Bott OJ, Bergmann J, Hoffmann J, Vering T, Gómez EJ, Hernando ME, Pretschner DP. Analysis and specification of telemedical systems using modelling and simulation: the MOSAIK-M approach.

García-Sa´ez, I. Martínez-Sarriegui, A. Rodríguez-Herrero, C. Pérez-Gandía, and F. del Pozo.

Stud Health Technol Inform 2005;116:503–508
21. Gómez EJ, Hernando ME, Vering T, Rigla M, Bott O, García-Sa´ez G, Pretschner P, Brugués E, Schnell O, Patte C, Bergmann J, Duddle R, de Leiva A. The INCA system: a further step towards a telemedicale medical apparatus. IEEE Trans Inf Technol Biomed 2008;12:470–479
22. Rigla M, Hernando ME, Gómez EJ, Brugués E, García-Sa´ez G, Torralba V, Prados A, Erdozain L, Vilaverde J, de Leiva A. A telemedicine system that includes a personal assistant improves glycomic control in pump-treated patients with type 1 diabetes. J Diabetes Sci Technol 2007;1:505–510
23. Rigla M, Hernando ME, Gómez EJ, Brugués E, García-Sa´ez G, Capel I, Pons B, de Leiva A. Real-time continuous glucose monitoring together with telemedical assistance improves glycomic control and glucose stability in pump-treated patients. Diabetes Technol Ther 2008;10:194–199
24. Kovatchev BP, Clarke WL, Breton M, Brayman K, McCall AL. Quantifying temporal glucose monitoring: mathematical methods and clinical application. Diabetes Technol Ther 2005;7:849–862
25. McCall AL, Dow J, Cen J, Glorster M, Kovatchev BP. A novel analytical method for assessing glucose variability: using CGMS in type 1 diabetes mellitus. Diabetes Technol Ther 2006;8:644–653
26. Kovatchev BP, Otto E, Cox D, Gonder-Frederick L, Clarke W. Evaluation of a new measure of blood glucose variability in diabetes. Diabetes Care 2006;29:2433–2438
27. Bolli GB. Glucose variability and complications. Diabetes Care 2006;29:1707–1709
28. International Diabetes Federation. Global Guidelines for Type 2 Diabetes. Brussels, Belgium, IDF, 2005
29. Schiffin A, Belmonte M. Multiple daily self-glucose monitoring: its essential role in long-term glucose control in insulin-dependent diabetic patients treated with pump and multiple subcutaneous injections. Diabetes Care 1982;5:479–484
30. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
33. Evans JMM, Newton RW, Ruta DA, MacDonald TM, Stevenson RJ, Morris AD. Frequency of blood glucose monitoring in relation to glycaemic control: observational study with diabetes database. BMJ 1999;319:83–86
34. Karter AJ, Ackerson LM, Darbinian JA, D’Agostino RB Jr, Ferrara A, Liu J, Selby JV. Self-monitoring of blood glucose levels and glycemnic control: the Northern California Kaiser Permanent Diabetes Reference

PI 61067/PI 60437, CIBER-BBN), and FUNDACIO DIABEM and also by European Union Grants EU-TIDDM HC 1047 and EU-Corpusuint As INCA (IST-2001-37632).

We thank Medtronic (Madrid, Spain) and Roche-Disetronic Medical System (Burgdorf, Switzerland) for technical and instrumental support.

No potential conflicts of interest relevant to this article were reported.

Other coauthors from EDUAB-HSP include M. Rigla, I. Capel, E. Brugués, B. Pons, L. Erdozain, A. Prados, and R. Corcoy. Other coauthors from GBT-UPM include E.J. Gómez, G. García-Sa´ez, I. Martínez-Sarriegui, A. Rodríguez-Herrero, C. Pérez-Gandía, and F. del Pozo.

 carrodiabetesjournals.org DIABETES CARE, VOLUME 32, SUPPLEMENT 2, NOVEMBER 2009 S215
33. Welschen LM, Bloemendal E, Nijpels G, Dekker JM, Heine RJ, Stalman WA, Bouter LM. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. Diabetes Care 2005;28:1510–1517

34. Sarol JN, Nicodemus NA, Tan KM, Grava MB. Self-monitoring of blood glucose as part of a multi-component therapy among non-insulin-requiring type 2 diabetic patients: a meta-analysis (1966–2004). Curr Med Res Opin 2005;21:173–183

35. Jansen JP. Self-monitoring of blood glucose in type-2 diabetes mellitus: a Bayesian meta-analysis of direct and indirect comparisons. Curr Med Res Opin 2006;22:671–681

36. Palmer AJ, Dinneen S, Gavin JR, Gray A, Herman WH, Karter AJ. Cost-utility analysis in a UK setting of self-monitoring of blood glucose in patients with type 2 diabetes. Curr Med Res Opin 2006;22:861–872

37. McGeoch G, Moore RA. Self-monitoring of blood glucose in type-2 diabetes: what is the evidence? Diabete Metab Res Rev 2007;23:423–440

38. Heinemann L, Koschinsky T. Clinical application and challenges of blood glucose measurement technology for self-monitoring. Diabetes Technol Ther 2008;10 (Suppl. 1):S27–S34

39. Mazze R. The future of self-monitored blood glucose: mean blood glucose versus glycosylated haemoglobin. Diabetes Technol Ther 2008;10 (Suppl. 1):S93–S101

40. Hones J, Müller P, Surridge N. The technology behind glucose meters: test strips. Diabetes Technol Ther 2008;10 (Suppl. 1):S10–S26

41. Laird T, Zisser H, Jovanovic L. Self-monitoring of blood glucose in pregnancy: past to present. Diabetes Technol Ther 2008;10 (Suppl. 1):S82–S87

42. Ben-Haroush A, Yogel Y, Chen R, Rosenn B, Hod M, Langer O. The post-prandial glucose profile in the diabetic pregnancy. Am J Obstet Gynecol 2004;191:576–581

43. Juvenile Diabetes Res Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464–1476

44. Golicki DT, Golicka D, Groeie L, Panikowska E. Continuous glucose monitoring system in children with type 1 diabetes mellitus: a systematic review and meta-analysis. Diabetologia 2008;51:233–240

45. Hovorka R. The future of continuous glucose monitoring: closed loop. Current Diabetes Reviews 2008;4:269–279