Clinical Experience with an Implanted Closed-Loop Insulin Delivery System

ABSTRACT

Aim: To report the first clinical experience with a prototype of implanted artificial beta-cell. **Methods:** The Long-Term Sensor System® project assessed the feasibility of glucose control by the combined implantation of a pump for peritoneal insulin delivery and a central intravenous glucose sensor, connected physically by a subcutaneous lead and functionally by PID algorithms. It was performed in 10 type 1 diabetic patients from 2000 to 2007. **Results:** No harmful complication related to implants occurred. Insulin delivery was affected by iterative but reversible pump slowdowns due to insulin precipitation. Glucose measurement by the intravenous sensors correlated well with meter values (r = 0.83-0.93, with a mean absolute deviation of 16.5%) for an average duration of 9 months. Uploading of pump electronics by PID algorithms designed for closed-loop insulin delivery allowed in-patient 48 hour-trials. **Conclusion:** Although the concept of a fully implantable artificial beta-cell has been shown as feasible, improvements in the sensor structure to increase its longevity and decrease sensor delay that affected closed-loop control at meal-times are expected. **(Arq Bras Endocrinol Metab 2008;52/2:349-354)**

Keywords: Type 1 diabetes mellitus; Glucose control; Artificial pancreas; Glucose sensor; Algorithm

RESUMO

Experiência Clínica com um Sistema de Infusão de Insulina de Alça Fechada Implantável.

Objetivo: Relatar a primeira experiência clínica com um protótipo de célula-beta artificial implantável. **Métodos:** O projeto de Um Sistema Sensor de Longo Prazo avaliou a possibilidade do controle glicêmico através do implante combinado de uma bomba de infusão de insulina peritoneal e um gluco – sensor endovenoso central – conectados fisicamente por um dispositivo subcutâneo e funcionalmente por algoritmos PID (*integral and derivative*). Este projeto envolveu 10 pacientes com diabetes melito tipo 1 de 2000 a 2007. **Resultados**: Complicações significativas relacionadas aos implantes não ocorreram. A liberação de insulina pela bomba sofreu o efeito de períodos de lentificação interativo, mas reversível, devido a precipitação do peptídeo. As medidas da glicose pelo sensor endovenoso mostraram boa correlação com os valores do glicosímetro (r = 0,83-0,93, com desvio médio absoluto de 16,5%) durante período médio de 9 meses. Os dados para construção dos algoritmos PID do sistema de alça fechada de liberação de insulina foram obtidos a partir de 12 pacientes que permaneceram internados com esse sistema durante 48 horas com refeições que continham 40 a 70 g de

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carboidratos. **Conclusão :** Embora o conceito de uma célula-beta artificial totalmente implantável tenha demonstrado ser possível, aperfeiçoamentos são necessários na estrutura do sensor para aumentar a sua longevidade e no sistema de alça fechada de liberação de insulina para diminuir as lentificações que comprometem o controle glicêmico nos períodos relacionados às refeições. **(Arq Bras Endocrinol Metab 2008;52/2:349-354)**

Descritores: Diabetes melito tipo1; Controle glicêmico; Pâncreas artificial; Gluco sensor; Algoritmo

From the consecutive reports of the Diabetes Control and Complications Trial, looking for sustained restoration of close-to-normal glucose control has been consecrated as the ultimate goal of insulin therapy in order to prevent or stabilize long-term complications of type 1 diabetes mellitus (1,2). To face this challenge, the development of an artificial endocrine pancreas has been expected for almost 30 years (3,4). Although considerable improvements have been achieved in insulin formulation and delivery systems, intensification of self blood glucose monitoring, patient education and follow-up, very few patients can only approach normal blood glucose control. Besides, recent advances in pancreatic islet transplantations remain hardly accessible to most diabetic patients and still need some work to increase insulin-independence rate and reduce adverse events associated with this therapy (5,6). Because of these remaining limits of intensive insulin therapy and beta-cell transplantation, the design of an artificial beta-cell nowadays still represents a sound research topic.

To achieve an artificial endocrine pancreas depends on the availability of three crucial components: 1) a safe and reliable device that delivers insulin continuously with a quick reactivity to change, 2) an accurate real-time continuous glucose monitoring system, 3) a control program to adapt insulin delivery according to blood glucose at all times (7,8). Historically, this combination has been made available by the development in the 1970s of the bedside external artificial pancreas, e.g. Biostator® (9). In this model, an IV infusion of insulin from a peristaltic pump is modulated thanks to a continuous blood glucose assessment using glucose-oxidase, by following algorithms that define insulin delivery according to glucose variations. However, the whole system is bulky, and requires an almost constant human assistance. Of note, improvement of the algorithms has requested a large amount of work to allow post-meal glucose control while avoiding hyperinsulinemia that induces secondary hypoglycaemia (10). Although still used for physiological investigations, this system cannot fulfil the objective of replacement of insulin secretion as expected by the diabetic patient for daily life.

Throughtout these last years, more sophisticated insulin delivery systems that better mimic physiology and reasonably accurate glucose sensing devices have been developed that revitalized the feasibility of a closed-loop insulin delivery (11). Short-term trials have been performed using two different approaches: 1) a subcutaneous (SC) insulin infusion combined to a continuous measurement of SC interstitial glucose, 2) an intra-peritoneal (IP) insulin infusion combined to a continuous measurement of venous glucose. Used algorithms followed two main models: 1) one that aims at reproducing the physiological characteristics of insulin secretion, including proportional, integral and derivative (PID) components, 2) and another that is a 'predictive control' model based upon observed relationship between blood glucose and plasma insulin variations. The present paper reports the first clinical experiment with the combination of an implanted pump using IP route for insulin delivery, an implanted intravenous glucose sensor and PID algorithms, representing an original prototype of implantable artificial beta-cell.

BACKGROUND

In order to challenge the kinetic problems of SC insulin delivery and SC sensing, (11) as well as the constraints related to wearable devices, the concept of an implantable system based upon IP insulin delivery and direct IV glucose sensing in view of building an artificial beta-cell has emerged. It has been materialized by the design of the Long-Term Sensor System® (LTSS) by Medical Research Group (MRG), a sister company of MiniMed Technologies (Sylmar, CA, USA), both of which merged into MiniMed-Medtronic (Northridge, CA, USA) in 2002. The LTSS combines an implantable pump for IP insulin delivery and a central IV enzymatic sensor, connected via a SC lead that allows the transfer of sensor signal to the pumping unit (Figure 1). The software that manages the algorithms can be uploaded in the pump

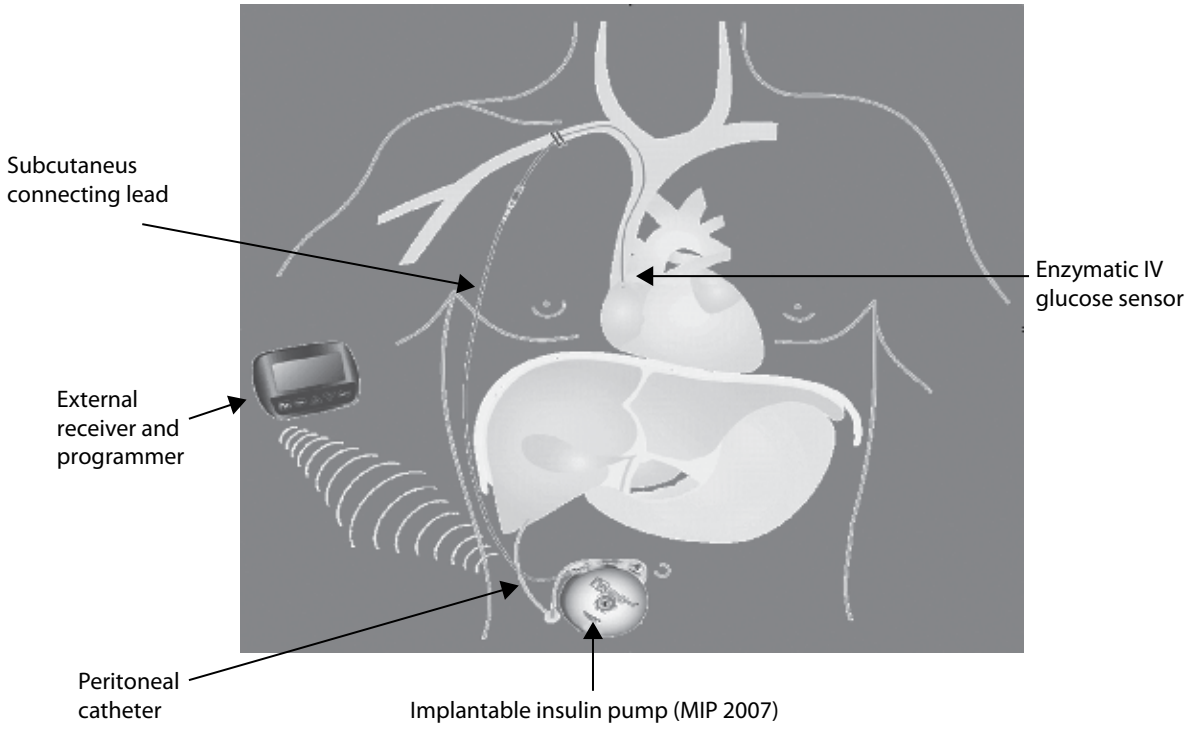

Figure 1. Scheme of human implantation of the Long-Term Sensor System® (LTSS, Medtronic-MiniMed), a prototype of implantable artificial beta-cell.

electronics to allow automated insulin infusion according to measured blood glucose. This first model of implantable artificial beta-cell has been investigated in diabetic dogs and then in diabetic patients from 2000 on, when the first of a series of ten LTSS was implanted at Montpellier University Hospital (12).

FEASIBILITY AND PERFORMANCE OF IP INSULIN DELIVERY

The use of IP insulin delivery aims at reducing and stabilizing the time spent between insulin delivery and insulin action by bypassing the lag and the variability related to SC insulin absorption. Some of our recent investigations showed that the average time to peak of plasma insulin after an IP insulin bolus was 25 minutes, i.e. almost half the time measured after a SC insulin bolus (13). Moreover, pre-hepatic insulin delivery restores physiological positive porto-systemic plasma insulin gradient, with a lower peripheral insulinemia than with SC delivery (14). This unique insulin distribution is likely responsible for the lower incidence of hypoglycaemia associated with IP insulin infusion. The feasibility of IP insulin delivery from implanted devices has been demonstrated in clinical trials since the late 1980s (15-17). Initial trials also investigated the feasibility of central IV insulin delivery from similar systems, but were suspended because of the occurrence of venous thromboses and frequent catheter obstructions (17). These latter events were likely promoted by the pulsatile output of insulin from these pump models. Long-term use of implantable pumps for IP insulin infusion, mainly investigated by the French EVADIAC group, has been shown as safe and reliable (18,19). Improvements of implantation procedures and of catheter components have allowed a dramatic reduction of complications at implantation site as well as of catheter obstructions which were respectively reported in early experiments (20). However, gradual slowdowns of insulin infusion remain a current, although reversible, issue concerning these devices. The limited physical stability of the specific U-400 insulin preparation used in these pumps determinates these slowdowns by gradual insulin ag-

gregation in the pumping mechanism. Periodic (mostly in 9-month intervals) rinsing by NaOH of the insulin pathway inside the pump can both prevent and fix this aggregation problem (21). In spite of this remaining issue, IP insulin infusion from implantable pumps provides lower average HbA1c levels, a significantly improved blood glucose stability and a dramatic decrease of severe hypoglycemic events when compared to SC insulin infusion (18,22,23). Implantable insulin pumps have been approved for clinical use in European Union since 1995. Because of the more reproducible and physiological kinetics of IP insulin delivery, and of the benefits of being implantable and programmable, these devices represent a robust platform toward an artificial beta-cell.

EXPERIENCE WITH IV GLUCOSE SENSORS

IV continuous glucose sensing has been considered as potentially harmful and impractical for long-term in humans because of expected clotting issues (7). However, Armour *et al* (24) reported preliminary studies in dogs using an implanted intravenous enzymatic sensor in the early 1990s that was highly encouraging regarding safety and accuracy. Some of these free-floating sensors in superior vena cava were able to provide very accurate real-time blood glucose data during several months with no sign of venous thrombosis or lung embolia. Besides the intravascular approach, these sensors were using glucose-oxidase coupled with a potentiostatic oxygen sensor. Thus, sensor signal was generated from the discrepancy between oxygen concentration at the site of glucose oxidation and at a nearby reference oxygen sensor with no glucose-oxidase. Because they use a confluent nonporous hydrophobic membrane between the enzymatic layer and the electrode surface, oxygen-based glucose-oxidase sensors allow a significant reduction in chemical interferences, issues of oxygen deficit and enzyme inactivation, and if catalase is included, it is known that all of which are limitations of H_2O_2-based enzymatic sensors (25).

From these initial investigations and in view of developing a fully implantable closed-loop system, the Long Term Glucose Sensor® (LTGS, MiniMed-Medtronic, Northridge, CA, USA) has been designed and firstly tested in diabetic dogs. This sensor is implanted by jugular or subclavian access so that the glucose sensing element is located in the central venous blood flow at the junction of the vena cava superior and the right atrium (12). LTGS is an enzymatic sensor using glucose-oxidase, but its signal is generated by the oxygen consumption related to enzymatic activity in proportion to blood glucose level. Oxygen pressure at a nearby site with no glucose-oxidase is used as a reference to assess how much oxygen is consumed at the enzymatic site according to blood glucose level. The resulting signal intensity is proportional to current blood glucose level, and it can be transmitted via a SC lead to the pump electronics. The initial calibration of LTGS is performed against SMBG measurements during the first days following the IV implantation. Then sensor accuracy is checked once a week against a random SMBG value, and calibration may be renewed if needed. Analysis of LTGS accuracy against multiple daily SMBG values have shown an average mean absolute deviation of 16.5% and a correlation factor of 0.83 to 0.93 that can be sustained for many months with no need for recalibration (8). Average longevity of sensor function has been found to reach about 9 months, with an extreme of 14 months. Sensor longevity appeared to be mainly depending on the mechanical resistance of sensor structure to shearing forces of venous blood flow. No thrombosis has been ever observed although some sensors have been implanted for almost two years. Low-dose aspirin that was taken by the patients may have prevented this eventuality. A drawback of the large glucose-oxidase pad at the sensing site to resist shearing forces created by the blood flow is an internal delay close to 3 minutes (10,13). Moreover, an average delay close to 20 minutes has been observed between blood glucose measurements and sensor values dispatched to the pumping unit (13). This long delay may be explained by the difficult tuning of signal filters when using a sensor with significant transport lag (10).

CLOSED-LOOP TRIALS USING LTSS

A dozen of closed-loop trials have been performed at Montpellier University Hospital using the LTSS for periods of 48 hours including three daily meals with 40 to 70g of carbohydrates. Initial algorithm included basal, proportional and derivative components (26). An integral component was added in the algorithm for the last four trials (27). In some trials, insulin delivery before meals was programmed according to pre-meal blood glucose level and carbohydrate content of the meal (28). Algorithm parameters were finally modulated during the last four trials to allow more aggressive insu-

lin delivery at meal times (13,27). Glucose control data during various trials are summarized in Table 1. The positive results obtained during these trials include a demonstration of the feasibility of closed-loop insulin delivery by using a fully implantable system using IP insulin delivery and IV glucose sensing, a close to normal glucose control at night-time and between meals, and a tighter glucose control while using sensor signal to modulate insulin delivery than when adapting pump bolus and basal rates from SMBG data. However glucose control limitations were observed at meal times that could be related to the too slow increase of plasma insulin levels when blood glucose peaks after food absorption. The sensor delays appeared as the main reason for this failure in maintaining blood glucose levels in near-normal range in meal intakes (10,13). These post-meal glucose peaks could though be prevented by handheld pre-meal insulin bolus or smoothened by algorithm changes to cover meal times (27,28). Of note, high levels of anti-insulin antibodies, which may be promoted by IP insulin delivery in some patients (19,29), significantly impair the feasibility of glucose control because of a 'trapping effect' on insulin when plasma insulin rises and a 'launching effect' of insulin when plasma insulin concentration decreases (30). These undesired and uncontrollable variations of insulin availability make the algorithms poorly effective in glucose control with unexpected glucose ups and downs.

PROSPECTIVE VIEWS ABOUT IMPLANTABLE SYSTEMS FOR CLOSED-LOOP INSULIN DELIVERY

When analyzing data obtained from the implantable artificial beta-cell approach so far, the IP route of insulin delivery from implantable devices has some advantages. The first one is the kinetics of IP insulin that allows a lower variability and a quicker insulin action than SC infusion. The second benefit is the implantable nature of the infusing system that provides a better satisfaction in terms of quality of life than wearable pumps connected to SC catheters (31). Although initially dreaded, the IV sensor approach has resulted in no significant complication. However, the structure of IV sensors has failed in maintaining its integrity, and subsequently, in allowing accurate glucose sensing for more than 12 months in most cases. So, the invasiveness related to IV sensors would result more from the yearly replacement than from the IV implantation itself. Besides, IV sensing has shown unexpected limitations due to sensor delay that prevented timely insulin delivery at meal times. Hence closed-loop trials using IP insulin delivery and IV glucose sensing achieved almost similar glucose control as those using the SC-SC combination (32).

From the pilot experience with LTSS, two investigating conclusions can be drawn: 1) since a combination of IP insulin delivery and IV sensing is feasible, the concept of an implantable artificial beta-cell is valid, 2) because efforts in improving sensor structure and longevity are needed, further clinical studies should wait for improvements.

From the patient point of view, until infusion and sensing systems using the SC approach will be further miniaturized and made more user-friendly (e.g., calibration process), an 'intelligent' implantable insulin pump would have a better long-term acceptance. However, yearly replacement of IV sensors would not be acceptable.

A straightforward strategy at present time could be the consideration of the feasibility of a combined model that would use the kinetic advantage of IP insulin delivery and the shorter response time of SC sensors. This intellectually-stimulating compromise looks like a feasible intermediate step toward an ultimate fully implantable artificial beta-cell.

Table 1. Trials of closed-loop insulin delivery using intravenous glucose sensing and intra-peritoneal insulin delivery (8,27,28).

Number of cases	Duration (hours)	Number of meals	Algorithm	Glucose control (mmol/l)			
				<4.4	4.4-6.6	6.6-13.3	>13.3
2	48	6	Basal + proportional + derivative	6.4%	42.1%	49.6%	1.9%
1	24	3	Basal + proportional + derivative + empirical meal bolus	0.0%	35.4%	64.6%	0.0%
4	48	6	Proportional + integral + derivative + meal tuning	5.2%	22.5%	61.6%	10.7%

REFERENCES

1. The 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;329:977-86.
2. Nathan DM, Cleary PA, Backlund JYC, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353:2643-53.
3. Albisser AM, Leibel BS, Ewart TF, et al. Clinical control of diabetes by the artificial pancreas. Diabetes. 1974;23:297-404.
4. Mirouze J, Selam JL, Pham TC, Cavadore D. Evaluation of exogenous insulin homeostasis by the artificial pancreas in insulin-dependent diabetes. Diabetologia. 1977;13:273-8.
5. Ryan EA, Paty BW, Senior PA, Bigam D, Alfadhli E, Kneteman NM et al. Five-Year Follow-Up After Clinical Islet Transplantation. Diabetes. 2005;54:2060-9.
6. Badet L, Benhamou PY, Wojtusciszyn A, Baertschiger R, Milliat-Guittard L, Kessler L et al. Expectations and Strategies Regarding Islet Transplantation: Metabolic Data From the GRAGIL 2 Trial. Transplantation. 2007;84:89-96.
7. Jaremko J, Rorstad O. Advances toward the implantable artificial pancreas for treatment of diabetes. Diabetes Care 1998;21:444-50.
8. Renard E. Implantable closed loop glucose-sensing and insulin delivery: the future for insulin pump therapy. Curr Opin Pharmacol. 2002;2:708-16.
9. Clemens AH, Chang PH, Myers MW. The development of BIOSTATOR, a glucose controlled insulin infusion system (GCIIS). Horm Metab Res. 1977;Suppl 8:23-33.
10. Steil GM, Panteleon AE, Rebrin K. Closed-loop insulin delivery - the path to physiological glucose control. Adv Drug Deliv Rev. 2004;56:125-44.
11. Hovorka R. Continuous glucose monitoring and closed-loop systems. Diabetic Med. 2006;23:1-12.
12. Renard E, Costalat G, Bringer J. De la pompe externe à la pompe implantable, la fermeture de la boucle est-elle possible ? Diabetes Metab. 2002;28(part 2):2S19-2S25.
13. Renard E, Panteleon AE, Kolopp M, Rebrin K, Steil GM. Efficacy of closed-loop control of blood glucose and characterization of delays based on an implantable IV sensor and intraperitoneal insulin pump. Diabetologia. 2004;47(suppl 1):A92[Abstract].
14. Nelson JA, Stephen R, Landau ST, Wilson DE, Tyler FH. Intraperitoneal insulin administration produces a positive portal-systemic blood insulin gradient in unanesthetized, unrestrained swine. Metabolism. 1982;31:969-72.
15. Point Study Group. One-year trial of a remote-controlled implantable insulin infusion system in type I diabetic patients. Lancet. 1988;i:864-9.
16. Saudek CD, Selam JL, Pitt HA, et al. A preliminary trial of the programmable implantable medication system for insulin delivery. N Engl J Med. 1989;321:574-9.
17. Selam JL, Micossi P, Dunn FL, Nathan DM. Clinical trial of programmable implantable insulin pumps for type 1 diabetes. Diabetes Care 1992;15:877-85.
18. Hanaire-Broutin H, Broussolle C, Jeandidier N, et al. Feasibility of intraperitoneal insulin therapy with programmable implantable pumps in IDDM: A multicenter study. Diabetes Care 1995;18:388-92.
19. Renard E, Schaepelynck-Belicar P, on behalf of the EVADIAC group. Implantable insulin pumps. A position statement about their clinical use. Diabetes Metab. 2007;33:158-66.
20. Gin H, Renard E, Melki V, et al. Combined improvements in implantable pump technology and insulin stability allow safe and effective long term intraperitoneal insulin delivery in type 1 diabetic patients: the EVADIAC experience. Diabetes Metab. 2003;29:602-7.
21. Renard E, Bouteleau S, Jacques-Apostol D, et al. Insulin underdelivery from implanted pumps using peritoneal route: determinant role of insulin-pump compatibility. Diabetes Care. 1996;19:812-7.
22. Broussolle C, Jeandidier N, Hanaire-Broutin H for The Evadiac Study Group. French multicentre experience with implantable insulin pumps. Lancet. 1994;343:514-5.
23. Catargi B, Meyer L, Melki V, Renard E, Jeandidier N, for the EVADIAC Study Group. Comparison of blood glucose stability and HbA1c between implantable insulin pumps using U400 HOE 21Ph insulin and external pumps using lispro in type 1 diabetic patients: a pilot study. Diabetes Metab. 2002;28:133-7.
24. Armour JC, Lucisano JY, McKean BD, Gough DA. Application of chronic intravascular glucose sensor in dogs. Diabetes. 1990;39:1519-26.
25. Gough DA, Armour JC, Baker DA. Advances and prospects in glucose assay technology. Diabetologia. 1997;40(Suppl 2):S102-7.
26. Renard E, Shah R, Miller M, et al. Accuracy of real-time blood glucose measurement by long-term sensor system allows automated insulin delivery in diabetic patients. Diabetes. 2002;51(suppl 2):A126 [Abstract].
27. Renard E, Costalat G, Chevassus H, Bringer J. Closed loop insulin delivery using implanted insulin pumps and sensors in type 1 diabetic patients. Diabetes Res Clin Pract. 2006;74(Suppl 2):S173-7.
28. Renard E, Shah R, Miller M, Kolopp M, Costalat G, Bringer J. Sustained safety and accuracy of central IV glucose sensors connected to implanted insulin pumps and short-term closed-loop trials in diabetic patients. Diabetes. 2003;52(suppl 2):A36[Abstract].
29. Olsen CL, Chan E, Turner DS, et al. Insulin antibody responses after long-term intraperitoneal insulin administration via implantable programmable insulin delivery systems. Diabetes Care. 1994;17:169-76.
30. Sodoyez JC, Koch M, Sodoyez-Goffaux F. Anticorps anti-insuline: méthodologie et implications cliniques. Diabete Metab. 1991;17:255-69.
31. Renard E, Apostol D, Lauton D, Boulet F, Bringer J. Quality of life in diabetic patients treated by insulin pumps. QoL Newsletter. 2002;28:11-3.
32. Renard E, Costalat G, Chevassus H, Bringer J. Artificial beta cell: clinical experience toward an implantable closed-loop insulin delivery system. Diabetes Metab. 2006;32:497-502.

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