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Editorial

CLOSED LOOP SYSTEMS IN TYPE 1 DIABETES – A DREAM THAT MIGHT SOON COME TRUE?

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Since the discovery of "pancreine" by Prof. NC Paulescu in 1921 [1], major progresses have been recorded in the treatment of type 1 diabetes (T1D) subjects. Starting from the first crude animal pancreatic extracts, a long chain of discoveries led to the current age of modern insulin analogs and inhaled insulin [2]. The last 40 years marked the fast evolution of insulin therapy by continuous subcutaneous insulin infusion (CSII) using insulin pumps [3]. The modern miniaturized insulin pumps have dedicated glucose meters with specific algorithms for the calculation of boluses according to the carbohydrate intake and current blood glucose level. Moreover some pumps have incorporated systems for reading data from continuous glucose monitor (CGM) systems [4]. Despite these progresses, reaching recommended glucose and HbA1c targets by T1D subjects is difficult, the majority of patients, especially children and adolescents, failing to reach these targets [5]. In addition, HbA1c at target may mask glucose variability and frequent hypoglycemic episodes [6]. More frequent are however cases in which despite mean blood glucose levels above targets, hypoglycemia is frequent and represents a real barrier in further lowering HbA1c [7]. A potential tool to improve glycemic control is the use of CGM systems. Thus, a meta-analysis of 4 randomized controlled trials [8] showed that real-time CGM is superior to self monitoring of blood glucose in achieving a lower HbA1c. However, successful use of CGM depends on patient intellectual abilities and motivation and increases the burden of time dedicated to self management of diabetes [9].

All the above clearly show that we need better methods to improve glycemic control of T1D subjects that in the same time improve the quality of life and ideally reduce the risk of emotional burnout. Two major strategies emerged in the last decade and represent important hopes for the future: pancreatic islet transplantation [10] and the use of the automated closed loop control systems of blood glucose in diabetes, also known as "artificial pancreas" [11]. Following the pioneer studies of Camilio Ricordi Edmonton group [12], major progresses have been made in islet transplantation, with increased rates of insulin independence after a couple of years after transplant. However, there are still major hurdles to be overcome, including limited tissue supply and need for life-long immunosuppressive treatment.

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The alternative "technological" approach, artificial pancreas, has also gone a long journey from the biostator of the 1970's [13] to the bionic pancreas of 2014 [14]. In the late 1980's, was developed an implantable artificial pancreas system that combined an insulin pump with intraperitoneal delivery with an intravenous glucose sensing technique [15]. The technology was further developed but its clinical application remained limited because the need of surgical procedures for implantation of sensor and pump [16].

The basic principle of modern "artificial pancreas" systems is to combine an external insulin pump, infusing insulin in the subcutaneous tissue through an infusion set, with a CGM device that provides continuously information regarding blood glucose levels (blood glucose is estimated from the actual interstitial fluid glucose levels measured by the sensor canula inserted in the subcutaneous tissue). Information from the sensor is provided to a command device (personal computer, Smartphone, etc.) that uses a control algorithm in order to determine the rate of insulin infusion from the insulin pump [11]. The modern control algorithms are known as *model-predictive control (MPC)* and use mathematical models of the metabolic system of the subjects, derived from the Richard Bergman's Minimal Model of Glucose Kinetics [17]. These MPC algorithms try to compensate for the major limitations of subcutaneously glucose sensing and insulin infusion, mainly the time lag for insulin absorption and time-to-peak (which even for modern rapid acting analogs is around 1-2 hours) and the time lag of the blood glucose estimate provided by the sensor, which reflects the real blood glucose value from 5-10 minutes before [16].

Starting from the late 2000's, more and more T1D subjects used CGM systems in parallel with an insulin pump in order to improve blood glucose control. This type of therapy, also known as sensor-augmented pump therapy (SAP) is considered by some to be the current gold-standard of insulin therapy in T1D [18,19].

The first step in the development of modern outpatient closed loop systems was to incorporate in a sensor based-insulin pump (the Medtronic Paradigm Revel 2.0 model) the control algorithm for suspension of insulin delivery when blood glucose reaches a critical low threshold. The first study to validate this approach included 247 T1D subjects that were randomized to receive standard SAP therapy (126 patients, control group) or the low threshold suspend feature (121 patients, intervention group) for a total study period of 3 months [20]. The study showed a reduction with 37.5% of the area under the curve for hypoglycemia while nocturnal hypoglycemic events occurred 31.8% less frequently in the intervention group. A subsequent progress of this technology is suspension of insulin infusion before reaching a critical low glucose threshold, using the function of *predictive threshold suspend* [21]. In this study, 45 T1D subjects aged 15-45 years used the pump with this facility for a total of 42 nights, each night being randomly assigned to standard SAP (control night) or predictive *threshold suspend usage* (intervention night). Overall the median hypoglycemia area under the curve was reduced with 81%. Both these two studies are based on commercial available technology.

The next step in the development of the "artificial pancreas" was represented by systems that automatically controlled the rate of insulin infusion during night based on readings from the CGM. The first trial to investigate such a device included 56 T1D adolescents that were followed for a two nights in a diabetes camp [22]. During one night subjects used the artificial pancreas

(AP) while in the other night standard SAP pump therapy. Median values for the individual mean overnight glucose levels were 126.4 mg/dL with AP vs. 140.4 mg per deciliter with SAP, while during AP nights there were significantly shorter episodes of nocturnal hypoglycemia (blood glucose < 63 mg/dL). Two other interesting studies (performed by the group of Prof. Roman Hovorka in Cambridge) analyzed a different AP system in both adolescents [23] and adults [24] in a home use setting. Both had a cross-over design, with 3 weeks of overnight AP and 3 weeks of standard SAP therapy. The artificial pancreas used was the Florence closed-loop system that comprised a MPC algorithm installed in a small laptop linked by cable to the sensor receiver, controlling the study pump via a WiFi communication [25]. The adolescent study included 16 subjects while the adult study 25 subjects. In both studies, the time at blood glucose target was higher for the AP (64% vs. 47% in adolescents, respectively 53% vs. 39% in adults) and mean glucose was reduced from 151 to 137 mg/dL in adolescents, respectively from 162 to 148 mg/dL in adults [23,24].

A major progress in AP technology was represented by the emergence of first prototypes of 24 hours closed-loop glucose control using insulin infusion in outpatients. This represents a cornerstone in the development of AP, exposing the system to the challenges of coping with rapid oscillations of blood glucose following meals and physical exercise. Two randomized controlled trials assessed the efficacy and safety of these AP systems and published their results in 2014. The first one comes from the consortium including the research groups of Prof. Boris Kovatchev from Virginia University, Prof. Eric Renard from Montpelier and Prof. Claudio Cobelli from Padova [26]. The AP system developed by this group includes two Dexcom G4 CGMs, one Tandem t:slim insulin pump and a controller – the Diabetes Assistant (DiAs) consisting of a Smartphone artificial pancreas platform [27]. This outpatient study included 20 T1D adults that each took part in two 40-h crossover study periods: One 40 h treatment with standard SAP insulin pump therapy and the second 40 h treatment with the DiA-AP system. During the study period, subjects took lunch and dinner in a restaurant and a 45 min walk after lunch. Finally, during the AP period, subjects experienced a reduction in the risk for hypoglycemia and a twofold reduction of hypoglycemic episodes requiring CH treatment. The benefit of reduced hypoglycemia was obtained with the price of a slight increase in mean blood glucose (from 151.2 to 160.2 mg/dL) [26].

The second study was performed by the research group of Roman Hovorka and included 17 T1D adults from 3 study centers in the UK, Germany and Austria. Subjects underwent two crossover 8-day periods (with 1 inpatient day in the research center followed by 7 outpatient days at home) consisting of standard SAP pump therapy and automated AP closed-loop insulin delivery [28]. The AP system included a FreeStlye Navigator CGM, a DANA Diabcare insulin pump and a control algorithm included in an ultraportable laptop as previously described [25]. Using this AP system, the percentage of time with blood glucose in target increased significantly (75% vs. 62%) during both daytime and nighttime. No decrease of the hypoglycemia risk was recorded [28].

Finally, maybe the most spectacular AP system completing the clinical trial phase and publishing results in 2014 [29] consists in dual hormone (insulin and glucagon) blood glucose control with the aid of two insulin pumps, one infusing insulin and the other one infusing glucagon when required for the

prevention/treatment of hypoglycemia. This AP system was described by the authors from the Massachusetts General Hospital in Boston, USA as a "*Bionic Pancreas*" [29]. In the seminal paper from NEJM, Russel et al. published the results of two distinct studies, one including 20 T1D adults in a supervised outpatient setting (hotel) and the second including 32 T1D adolescents in a diabetes camp. Both studies had a crossover design, with 5 days of bionic pancreas treatment and 5 days of standard SAP insulin pump therapy. Both studies showed improved mean glycemic levels, with less frequent hypoglycemic episodes. Very recently, the same research group presented during the American Association of Clinical Endocrinologists' (AACE) 2015 Annual Scientific and Clinical Congress in Nashville, Tennessee, the results of two other studies using the "bionic pancreas" and announced plans for a pivotal outpatient trial to include 480 patients as young as 13 years of age, study already proposed to the FDA [30].

I think all the above described progresses in the development of artificial pancreas systems bring this therapeutic alternative from the field of SF closer to reality, with the hope of a better life of T1D subjects, both children and adults. The optimist message that this editorial wanted to transmit was best synthesized already by Dr. Helaine Resnick, the Editor-in-chief of Diabetes Care, in May 2014: "*The Holy Grail of unsupervised, full closed-loop control may be just around the corner*" [31].

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