

Progress Report

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1. Inter-individual and intra-individual variability of insulin sensitivity in children with type 1 diabetes on Sensor Augmented Pump: a new index for clinical use

Supervisor: Drs. Eda Cengiz and William Tamborlane

Aims: 1. To validate a new insulin sensitivity index (S_I) for estimation of individual insulin sensitivity from continuous glucose monitoring (CGM) in a cohort of adolescents with type 1 diabetes; 2. To adopt the S_I estimation for improving the glucose control in patients on sensor-augmented-pump (SAP)

Introduction

Patient-specific parameters, such as insulin sensitivity (IS) and insulin-to-carbohydrate ratio (CR), may exhibit a wide inter-individual variability as well as intra-individual changes, varying over time, due to several factors (e.g. changes in patient habits, growth, activities).

The recognition of these changes using continuous glucose monitoring systems (CGM) and data records from insulin pumps, and the ability to effect insulin therapy based on these patterns remain a challenge for pediatric diabetologists. To date, the correct estimation of individual insulin sensitivity, in terms of ability of insulin to stimulate glucose utilization and inhibit glucose production, remains chained to invasive methods, unadapt to daily clinical practice.

Only recently has the use of a new insulin sensitivity index (S_I) been proposed, in adults, based on data from sensor augmented pump therapy (SAP). [1]

We have designed a two steps study consisting of:

Phase 1: Validation phase of insulin sensitivity index in adolescents with T1D

Phase 2: Testing the new S_I in-silico and, then, in real life, using a run-to-run (R2R) approach, for periodic adaption of insulin therapy parameters in adolescents on SAP

Phase 1

The new insulin sensitivity (IS) index is calculated assuming fixed parameters from the general population like the glucose volume distribution (V_G) and the glucose effectiveness at zero insulin (GEZI, dl/kg/min), this latter indicating the glucose disappearance resulting from peripheral use and

hepatic glucose output that was estimated in adult cohorts. [1]

To investigate if such parameters differ remarkably in adolescents respect to the adult population this index was initially tested in, we estimated such parameters from a cohort of 12 adolescents with type 1 diabetes followed at Yale Pediatric Diabetes center (age = 15 ± 2 y; BW = 51 ± 10 kg; BMI = 21 ± 3 kg/m²), who consented to undergo a euglycemic clamp. (**Table 1**). This method can be considered the gold standard for assessing the insulin sensitivity of subjects with type 1 diabetes.

	ESTIMATED (MEAN \pm SD)						DERIVED
	S_G (min ⁻¹)	p_2 (min ⁻¹)	S_I (min ⁻¹ per uU/mL)	V (dL/kg)	dG_0 (mg/dL/min)	X_0 (min ⁻¹)	GEZI (dL/kg/min)
Adult cohort	0.02	0.013	0.0005	1.75	0	0	0.01
Adolescent cohort	0.037 \pm 0.020	0.034 \pm 0.016	0.0019 \pm 0.0021	3.58 \pm 1.16	-1.3 \pm 1.2	0.001 \pm 0.003	0.108 \pm 0.006

Table 1. S_G , glucose clearance; p_2 , speed of raise/decay of insulin action; S_I insulin sensitivity; dG_0 , rate plasma glucose variation; X_0 , insulin action at time 0; GEZI, glucose effectiveness at zero insulin

These results show a higher body insulin sensitivity of adolescents as compared to the adult cohort. This observation, although surprising, could be consistent with an effect of disease duration on individual insulin sensitivity that would make subjects with longer disease duration less sensitive to insulin action. However, these data are affected by multiple factors, including the different insulin doses used for the clamp procedure in the two groups, the limited numerosity of the samples, and will have to be confirmed in larger patient population using prospective studies, which can then plan to attempt to account for potential confounding factors. Our purpose was strictly related to the tuning of the model-algorithm, that takes into account other individual parameters, not derived from the general population.

Once tuned the S_I index in adolescents, we have conceived a perspective trial aimed (Phase 2) to test the new S_I in-silico and, then, in real life, using a run-to-run approach, for periodic adaption of insulin therapy parameters in adolescents on SAP in order to improve the post-prandial glucose control.

The periodic adaption of insulin therapy will adopt a Run-to-run (R2R) algorithm developed by our collaborators at University of Padova (Dr.Cobelli) for periodic adaption of both basal rates and insulin-to-carbohydrate ratio (CR).

The algorithm has preliminary been tested *in-silico* using the UVA/Padova T1D simulator.

In-silico test of R2R algorithm for CR adaption

A CR optimization algorithm is here used in a context of automatic adaptation based on a R2R approach [1] and can be used in free-living conditions by T1D patients in sensor-augmented pump (SAP) therapy. The method uses retrospective glucose sensor (CGM), insulin pump (CSII) and meal data, to calculate an index of insulin sensitivity relative to each meal as described [1] and,

based on this information, proposes a recommendation to the current CR profile. It is worth noting that adaptation in CR profile is allowed only if large hypo/hyperglycemic excursions occurred in the historical data (last seven days) and contingent on all information necessary for the calculation being available. Moreover, for safety reason, each CR value provided by the algorithm is constrained to lie within the range 4-40 g/U, with a 0.5 g/U resolution and the final recommendation is ensured to deviate from previous CR profile by no more than 20.

The performance of the proposed method was tested *in silico* using the 100 virtual subjects of the UVA/Padova T1D Simulator [3] including a feature able to recreate the circadian variability of insulin sensitivity [4] reported in the literature.

The simulation scenario was made up of 35 days (7 days of run-in with 28 days of R2R), composed by 3 meals per day at 7am, 1pm and 7pm with containing 40 g, 80 g and 60 g of carbohydrates for breakfast, lunch and dinner, respectively. After one week of run-in phase, since 7 days of CGM and CSII data are needed to propose an update of the CR daily pattern, CR was adapted every 2 days based on data from the last 7 days. To test the goodness of the CR adaptation algorithm, the simulation scenario was performed three times, each starting with a different CR: nominal CR, nominal CR reduced by 20% and nominal CR increased by 20%.

Results.

The use of the R2R algorithm for CR adaptation is able to improve the overall glycemic control in a significant percentage of subjects, by reducing the number of hypo/hyperglycemic events (Figure 1). The more individual CR, at entry, is far from the optimal CR, the higher is the expected improvement of glycemic control after adaptation using R2R algorithm.

The average simulated glucose profiles of the last day of simulation show the improvement in glucose control, with respect to the non-adapted CR (blue line), by reducing the hypoglycemic events, especially when case starting with the nominal CR reduced by 20%, and the hyperglycemic events, especially when starting with the nominal CR increased by 20%.

In Table 1, the improvements during the day, defined as 07:00-00:00 period, are represented following week by week CR adaptation using the R2R algorithm. In all cases, the percentage of time in target (defined as sensor glucose values between 70-180 mg/dL) is increased while reducing the time below 70 mg/dL.

These preliminary *in-silico* results are promising, showing an improvement in glucose control during meal time by adapting CR.

Additional *in-silico* scenarios will test the improvement in glucose control by using a R2R algorithm for basal insulin delivery adaptation during night time and its combination with the CR adaptation, with a major expected benefit on both the post-prandial percentage of time-in-target range and the overall time-in-target.

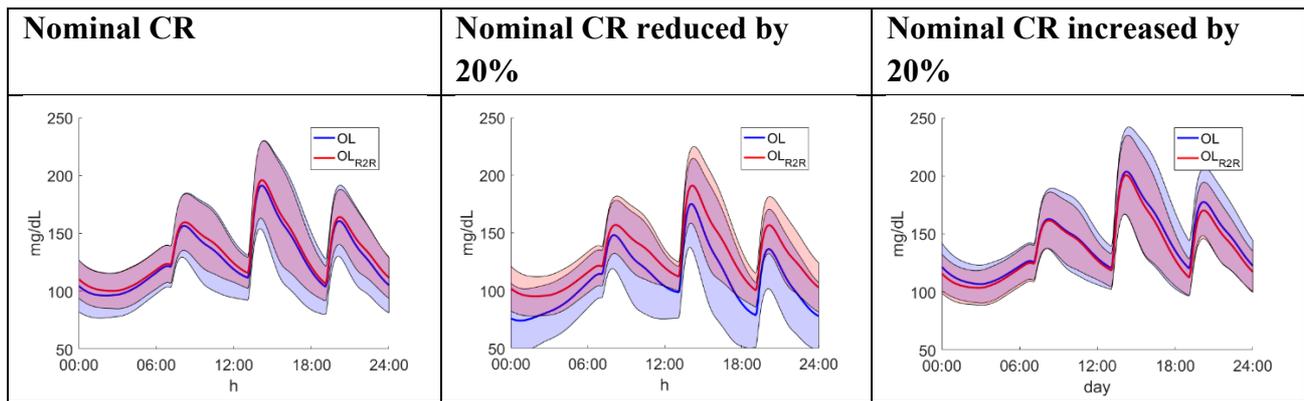


Figure 1: Comparison of average glucose time course in open loop without (OL, blue line) vs. with CR adaptation (OL_{R2R}, red line) during the last day (35th) of simulation. Shaded areas represent \pm SD.

		Week 1	Week 2	Week 3	Week 4	Week 5
Nominal CR	T_b (%)	2.0	1.4	0.8	0.3	0.4
	T_t (%)	80.8	81.1	81.0	82.2	82.3
	T_a (%)	18.2	18.5	18.2	17.5	17.3
Nominal CR reduced by 20%	T_b (%)	12.9	8.7	4.3	2.4	1.5
	T_t (%)	75.9	79.3	82.1	83.8	84.3
	T_a (%)	11.2	12.0	13.6	13.8	14.2
Nominal CR increased by 20%	T_b (%)	0.3	0.2	0.2	0.1	0.1
	T_t (%)	73.7	76.2	77.1	78.7	79.6
	T_a (%)	25.9	23.6	22.7	21.1	20.3

Table 1: Average percentage of improvements during day time [7:00-0:00pm] using the R2R algorithm for CR adaptation. T_b is the percentage of time <70 mg/dL, T_t of time in target (within 70-180 mg/dL) and T_a is the percentage of time >180 mg/dL.

References.

- [1] Schiavon M., Dalla Man C., Kudva Y.C., Basu A., Cobelli C., *Quantitative estimation of insulin sensitivity in type 1 diabetic subjects wearing a sensor-augmented insulin pump*, Diabetes Care 2014, 37(5): 1216-1223.
- [2] Wang Y., Gao F., Doyle III F.J., *Survey on iterative learning control, repetitive control, and run-to-run control*, Journal of Process Control 2009, 19(10): 1589-1600.
- [3] Dalla Man C., Micheletto F., Lv D., Breton M., Kovatchev B.P., Cobelli C., *The UVA/Padova type 1 diabetes simulator: new features*, J Diabetes Sci Technol 2014, 8(1): 26-34.
- [4] Visentin R., Dalla Man C., Kudva Y.C., Basu A., Cobelli C., *Circadian variability of insulin sensitivity: physiological input for in silico artificial pancreas*, Diabetes Technol Ther 2015, 17(1): 1-7.

Timeline and current status: the Phase 2 of this proposal has been approved by Pediatric Protocol Review Committee of Yale University on 12.09.16 (HIC#: **1611018615**), it is currently under review by the Human Investigation Committee of Yale University (expected decision within 2 weeks).

Timeline: 02.2017 start of enrolment; 12.2017 end of enrolment; 12.2017-01-2018 data analysis

Founding: The preliminary tests and the analysis of the Phase 1 of this protocol have been supported by the ISPAD Research fellowship (to Dr Galderisi), the development and implementation of the Phase 2 of this trial (study-related costs) will be supported from mentoring grant of Dr. Cengiz.

Publication plan: the results of this trial will be submitted for the next ATTD meetings and considered for publication in a scientific journal in 2018. ISPAD support will be acknowledged.

Phase 2

Following we report the study design for the second part of the trial.

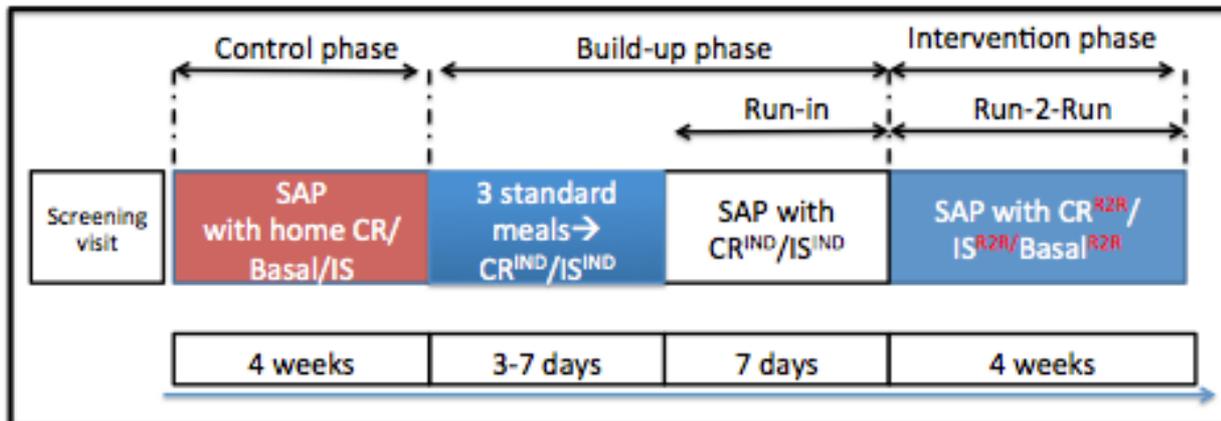


Figure 1 Study design

In details, the new insulin sensitivity index, developed from CGM (IS^{IND}) will be tested in a prospective study using Sensor Augmented pump (SAP), consisting of three phases:

- control phase, with subjects at home using their sensor augmented pump (SAP), with usual IS/Insulin-to-carbohydrate ratio (CR) and basal rate)
- build-up phase: it will consist of 3 standard meals with different insulin-to-carbohydrate ratio, that will allow us to verify the CR/IS in a controlled environment and a Run-in phase with subjects using the new CR and IS calculated previously.
- intervention phase: the subjects will adapt periodically, according to a run-to-run mode, their CR, IS and basal rate over a 4 weeks period.

This approach will allow us to test in real life the efficacy of the IS derived from CGM, along with the effect of a run-to-run adaptive algorithm on glycemic control in patients using SAP.

The potential benefits of this approach are represented by:

- the availability of a CGM based IS and its validation in adolescents
- the use of a run-to-run adaptive algorithm in SAP for adjusting insulin therapy, that could be transferred, in the future, on dedicated interfaces or apps.

Publication plan: the interim and final results will be submitted for presentation at a scientific meeting (such as ISPAD 2017, ATTD 2018, and/or ADA 2018) and a manuscript detailing the findings for the study will be prepared for publication. ISPAD support will be acknowledged whenever the findings are disseminated.

2. Effect of pramlintide and liraglutide on glucagon and glucose after a mixed meal tolerance test in type 1 diabetes

Supervisor: Drs. Jennifer L. Sherr and William Tamborlane

Content: While postprandial hyperglycemia remains a problem in type 1 diabetes, results of acute studies suggest that pramlintide and liraglutide may blunt post-meal glucose excursions by delaying gastric emptying and suppressing dysregulated increases in plasma glucagon. To examine these

questions, mixed meal tolerance tests (MMTT) have been performed before and after 3-4 weeks of treatment of pramlintide and liraglutide.

We have analyzed two MMTTs from 8 patients on pramlintide and 11 on liraglutide.

Publication plan: the results of this trial have been submitted to the next American Diabetes Association meeting (San Diego, June 2017; not disclosed due to ADA policy). Indeed preliminary results only focusing on the liraglutide data have been accepted as poster at the next Advanced Diabetes Technologies and Therapeutics Meeting (Paris, 2017). Currently, a manuscript detailing the findings of this study has been drafted and will be submitted for publication to *Diabetes Care*. ISPAD support will be acknowledged both on presentations at academic meetings and in the final publication.

3. Menstrual cycle and insulin sensitivity changes.

Supervisor: Dr. Eda Cengiz

Aim: the study is aimed to assess, through euglycemic clamp, the individual insulin sensitivity during the follicular and luteal phase of menstrual cycle in young woman with type 1 diabetes. Additionally, data collected through CGM and insulin pump downloads will allow for analysis of glucose control during different phases of the menstrual cycle. The recruitment is currently ongoing.

Publication plan: the preliminary results have been submitted to the next ADA meeting (San Diego, 2017).

4. Development of a new algorithm for fault detection of infusion set in hybrid closed loop systems

Supervisors: Dr. Jennifer Sherr, Dr. Claudio Cobelli, Dr. William Tamborlane

Content: Following an initial letter of intent, a full application for JDRF funding is being prepared. This multicenter clinical trial will include both pediatric and adult subjects with type 1 diabetes. The primary aim of the study is to develop and test a detection algorithm for infusion set faults in hybrid closed loop systems. This study will perform various inpatient studies to mimic infusion set failures (no bolus at meals, suspension of basal insulin delivery, etc) and through data collected during these inpatient studies, an algorithm to determine infusion set failure will be constructed. Following development of the algorithm, outpatient testing will be completed by having participants using the algorithm at home and encouraged to wear infusion set up to 7 days, in hopes of having an increased rate of infusion set failures due to prolonged wear. The centers involved are Yale University (Pediatrics), University of Virginia (Pediatrics), University of Montpellier (Adult), University of Amsterdam (Adult). The role of Dr. Galderisi has been to write the grant proposal along with Dr. Sherr, Dr. Cobelli and Dr Tamborlane, to create the protocol and the study plan.

Timeline: expected start 06.2017

5. Learning of specific techniques:

- Euglycemic, hypoglycemic and hyperglycemic clamp: these procedures are routinely conducted on the Hospital Research Unit at Yale in pediatric patients and young adults by the Investigators of our research group (Dr.Cengiz, Dr.Sherr, Dr.Caprio). Dr. Galderisi is currently being trained by the involved investigators during the procedures.

-Arginine Stimulation studies: these procedures are conducted on the Hospital Research Unit at Yale in adults and Dr. Galderisi has been trained by the investigators during the procedures.

- training sessions for insulin pumps, CGM devices, and hybrid closed loop systems are routinely held in our section.