

## *Progress report*

# **ROLE OF TASTE IN METABOLIC CONTROL OF TYPE 1 DIABETES MELLITUS**

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## **Background**

The sense of taste is one of the main factors that determine the choice of food and feeding behavior with important implications on health status.

In the last years, studies have highlighted the existence of taste receptors also in the gastrointestinal tract, where they seem involved in digestion and in food refusal. It is known that activation of sweet taste receptors in the bowel can trigger the release of the incretin hormones, that control blood glucose level, through an increase of insulin secretion, a reduction of glucagon secretion and consequent slowing of gastric emptying and intestinal motility.

An impact of taste perception and genes coding for taste receptors on type 2 diabetes (T2D) as well as on glucose homeostasis has been reported, but there are few data on the perception of taste in patients with type 1 diabetes (T1D).

Moreover, the expression in the gut of the receptors responsible for the sweet taste perception has been related to the glucose concentration in the blood in patients with type 2 diabetes.

Finally, studies have reported that GLP-1 possesses beneficial effects in protecting progressive impairment of pancreatic  $\beta$ -cell function and preservation of  $\beta$ -cell mass.

To date, although many predisposing gene variants have been discovered for both T1D and T2D, little attention has been paid to the possible impact of genes that affect taste perception and preferences. Furthermore, differences in metabolic control among patients treated for diabetes are well known; however, there are no studies that evaluate whether these differences have a genetic basis or not.

Therefore, considering the emerging implication of taste receptors in incretin secretion and glucose homeostasis, the present project aimed to evaluate whether taste perception and genetic variants in taste receptors genes and pathways (TAS1Rs, TAS2Rs, GLUTs, GLP-1, GIP, etc...) can have a role in predisposition or protection to T1D and in its metabolic control.

Specifically, the project aimed to analyze:

- differences in taste perception and related genes among patients with type 1 diabetes (T1D) and healthy subjects as controls;
- differences in taste perception and related genes among patients with T1D in good and poor metabolic control.

Moreover, thanks to the availability of whole-genome-wide data, this project could identify new genes influencing T1D metabolic control.

## **Note**

Since the Executive Committee of the ISPAD in its meeting held in Berlin decided that doctors awarded with ISPAD-JDRF grant can run the study at their home university/hospital, and is not needed to go in another center of excellence, the project has been held in Institute where I work.

### Study population

Patients with T1D, with at least 1 year of disease duration, aged between 6 and 22 years and control subjects, matched for sex and age, after acceptance and signature of informed consent. For patients aged <18 years, informed consent was signed by parents.

### Exclusion criteria

- Patients who were unable to express a valid informed consent or whose parents are unable to express a valid informed consent.
- Patients <6 years or ≥22 years

#### Cases:

- Patients with onset <12 months before
- Patients for whom information about medical history (starting from the onset of diabetes) was unavailable
- Patients with other types of diabetes mellitus (type 2, monogenic diabetes, cystic fibrosis related diabetes...)

#### Controls:

- Subjects with diabetes or a family history of diabetes
- Subjects with obesity, metabolic disorders, bowel diseases, allergies, food avoidance
- Subjects with HbA1c >6%
- Patients who were unable to express a valid informed consent or whose parents are unable to express a valid informed consent.

### Collected data

#### *For T1D patients:*

- medical history
- clinical history of the disease (age at onset, DKA at onset, length of remission period, duration of disease)
- auxological parameters (height, weight, BMI)
- laboratory values (lipids, microalbuminuria, creatinine)
- median A1c over last year (if ≤7.5% it was defined as “good control”, otherwise as “poor control”)

#### *For controls:*

- medical history
- family history of diabetes, obesity or metabolic diseases (exclusion criteria)
- auxological parameters (height, weight, BMI)
- A1c (determined by DCA)

### Data sample

*T1D patients:* 93 subjects (43 F - 50 M) - mean age 14.2 years (SD 3.5)

- poor control (A1c >7.5%): 47 subjects (22 F - 25 M) - mean age 14.0 years (SD 3.7)
- good control (A1c ≤7.5%): 45 subjects (20 F - 25 M) - mean age 14.6 years (SD 3.5)

*Controls:* 182 subjects (102 F - 79 M) - mean age 12.5 years (SD 3.5)

## Phase 1 – Differences in food preferences/habits

### Methods

For both cases and controls, perception of salty taste (NaCl), bitter (PROP and quinine), sour (citric acid) and sweet (sucrose) was evaluated using impregnated paper strips with different compounds. The perceived taste evaluation was conducted using the **GLMS scale** (General Labeled Magnitude Scale), ranging from 0 ("barely detectable") to 100 ("strongest imaginable").

Liking of each taste will also be established using a **7-point scale**. Between a strip and the subsequent, there will be a pause of 120 seconds, during which they must rinse their mouth with water.

Through a questionnaire of food preferences for each participant will be asked to indicate his/her approval for different foods with a rating from 1 (= I do not like at all) to 7 (= I love it). Questionnaire will also include some questions needed to assess the neofobia, namely the rejection of new foods. It will also be given a questionnaire on familiar eating habits.

### Results

We found a significant difference in parental practices associated to metabolic control:

	Good control	Poor control	p value
<b>Restricting access to food</b> mean (SD)	2.8 (0.8)	3.4 (0.8)	0.006
<b>Pressure to eat</b> mean (SD)	2.6 (1.0)	3.2 (1.1)	0.02

We also found differences in errors in identification of tastes

	T1DM	Controls	p value, OR (CI)
<b>Errors in identification of PROP (bitter)</b>			
YES	<b>24%</b>	<b>10%</b>	0.003 2.9 (1.4-6.0)
NO	76%	90%	
<b>Errors in identification of CITRIC ACID (sour)</b>			
YES	<b>34%</b>	<b>19%</b>	0.001 2.6 (1.5-4.8)
NO	66%	81%	

No differences were found in food preferences (i.e., sweets; pasta-pizza-bread; orange juice, strawberry, pear; cauliflower, broccoli, radicchio; etc.) between T1D patients and controls and between patients with good or poor metabolic control.

### Interpretation

While hypogeusia (reduced ability to taste things) has already been reported in T1D patients (73% vs 16% controls), dysgeusia (distortion of the sense of taste) has never been reported before in T1D. With regard to hypogeusia, there are 2 main hypothesis:

- it could be the first marker of neuropathy, as it is linked with age, diabetes duration and peripheral neuropathy and it is more common in uncontrolled diabetic patients
- it is hyperglycemia that induces a concentration-dependent impairment of sweet taste perception, because hypogeusia is also present in newly-diagnosed patients (without complications) and it is partially reversible

## Future plan

To better understand whether dysgeusia is linked to a neuropathic mechanism and it is a precocious marker of complications, or it is related to glycemic levels, we are planning to further study taste perception in correlation with glucose levels and to perform electrogustometry/gustatory evoked potentials

## References

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Bustos-Saldaña R, Rev Med Inst Mex Seguro Soc. 2009  
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## Phase 2 – Role of genes involved in taste perception and food preferences

### Methods

For each patient and control, a saliva sample has been collected from which DNA has been extracted using the DNA kit Saliva Collection and Preservation of the device Norgen (Biotek corporation, Canada), as per protocol. All samples have been genotyped using Illumina arrays MEGAEX chip. A candidate gene association study has been conducted to identify the contribution of related-taste perception genes on T1D, on its metabolic control and on parameters related to the disease. All analyses have been performed using specific packages as GenABEL and ProbABEL. The SKAT package will be used instead for the study of rare variants.

### Results

No differences have been found between T1DM and controls and between good and poor metabolic control in the following genes:

- TAS1R3 (sweet taste receptor)
- TAS1R2 (sweet taste receptor)
- PKD1L3 (sour taste receptor)
- PKD2L1 (sour taste receptor)
- TAS2R38 (bitter taste receptor)
- CA6 (bitter taste receptor)
- GLUT2 (glucose transporter)
- PDE1A (transduction signal)
- PLCB3 (transduction signal)
- GNAT3 (transduction signal)
- TRPM5 (transduction signal)

We did find an association with polymorphism at DRD2 (dopamine receptor D2) gene:

	Good metabolic control	Poor metabolic control	p-value
<b>DRD2 GENE</b>			
rs2734833			0.0005
A/A	27%	60%	
A/G	52%	36%	
G/G	21%	4%	

### **Interpretation**

DRD2 (dopamine receptor D2) is implicated in modulating the rewarding effects of foods high in sugar. Genetic variations in DRD2 might explain some of the interindividual differences in sugar consumption and food selection. Moreover DRD2 is expressed in pancreatic beta cells, and in DRD2 knock out mice there is an impaired glucose metabolism (blunted insulin response), a diminished beta-cell mass and a decreased beta-cell replication. It is also known that bromocriptine (a DRD2 agonist) is used in T2D and can lower HbA1c by 0.4-0.8% (as monotherapy or in combination). A trial on the adjunctive use of bromocriptine in T1D patients is now run in USA.

### **Future plan**

We are planning to perform DRD2 gene sequencing and possibly to perform functional studies in order to establish the role of this gene in the metabolic control of T1D patients.

### **References**

Eny KM, J Nutrigenet Nutrigenomics. 2009  
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**Publication plan:** the preliminary results of this trial will be presented at ISPAD annual meeting in Hyderabad, India and considered for publication in a scientific journal. ISPAD-JDRF support will be acknowledged.