Impaired β-cell Function is Associated with Evidence of Dysfunctional Gut Barrier

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INTRODUCTION

- Intestinal mucosal barrier function, or intestinal permeability (IP), is mediated by tight-junction proteins which prevent uncontrolled transport through the epithelium.[1]
- Disruption of IP has been linked to the development of several diseases including obesity, diabetes, and hepatosteatosis.[2]
- Gut barrier function can be assessed by determining the urinary excretion of large molecule sugars (e.g. cellobiose, raffinose), which are not absorbed under normal conditions, following oral administration.[3]
- The presence of certain sugars in the urine can be used to make region specific permeability determinations. Sucrose, for example, is hydrolyzed once it leaves the stomach, so permeability reflects gastroduodenal disease. Similarly, the presence of cellobiose in the urine suggests small intestine inflammation and increased intestinal permeability.[4]

OBJECTIVE

The objective of this analysis is to investigate if increased IP is more common in patients with prediabetes and whether it is associated with β-cell function.

METHODS

- A total of 29 subjects were studied of whom 19 had prediabetes (PD) and 10 had normoglycemia (Non-PD). Prediabetes was defined as a fasting plasma glucose (FPG) ≥100mg/dL and <126mg/dL and HbA1c ≤6.4% at screening.
- IP was assessed by a saccharide absorption test that measured urine concentrations of cellobiose, sucrose, mannitol, raffinose, and lactose (Nordic Laboratories, Copenhagen). The saccharide absorption test is non-invasive, well-tolerated, and highly reproducible.
- Prior to measurement, subjects were instructed to drink a test solution containing the aforementioned sugars in the evening and urine was collected during the subsequent 8 hour overnight fast.
- A subset of subjects from both cohorts (n=15) with a median HOMA-IR of 5.0 also underwent a mixed meal tolerance test (MMTT) to assess β-cell function.
- MMTT meals consisted of 80% carbohydrate (CHO), 15% protein, and 5% fat for breakfast, and 40% CHO, 15% protein, and 45% fat for lunch.
- Blood samples were collected for the measurement of FPG and serum insulin. Blood draws were performed in 15-30-minute intervals until 120 and 240 minutes relative to the start of the meal for breakfast and lunch, respectively.
- Serum zonulin, a modulator of intercellular tight junctions, was also measured.
- Spearman correlations were used to assess relation between saccharide levels and other continuous variables.
- Wilcoxon Rank Sum was used to assess the relation between categorical variables.
- Data are presented as median (Q1, Q3) or n (%).

RESULTS

- Subjects were adults aged 52 (45, 56), with excess weight (BMI: 34 [32.2, 36.9] kg/m^2), and a FPG of 99.6 (95.5, 102.7) and 108.1 (102.0, 112.0) mg/dL in the Non-PD and PD groups respectively **(Table 1).**

Table 1. Subject demographic information.

Parameter	Normoglycemic (n=10)	Pre-diabetes (n=19)	MMTT subset (n=15)
Female	6 (60%)	9 (47%)	8 (53%)
Weight, kg	100.3 (90.8, 111.6)	116.0 (92.2, 122.5)	102.8 (90.8, 122.5)
BMI, kg/m^2	33.3 (29.7, 36.7)	34.6 (33.0, 38.0)	34.0 (33.0, 36.8)
Pre-obesity	3 (30%)	0 (0%)	1 (7%)
Obesity class I	3 (30%)	10 (53%)	8 (53%)
Obesity class II	4 (40%)	9 (47%)	6 (40%)

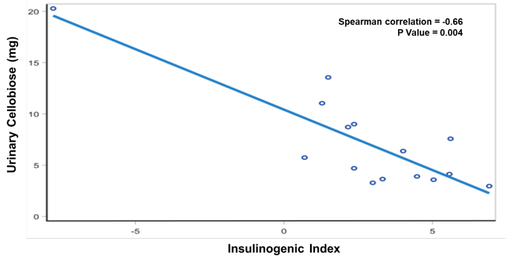
- Patients with PD had higher urine cellobiose levels than the Non-PD group (3.7 vs. 1.3, P=0.065). Urinary levels for other sugars were similar **(Table 2)**.

Table 2. Median urine sugar concentration for Non-PD and PD groups.

Sugar	Normal Range	Non-PD	PD	P Value
Mannitol (mg)	>90	305.1	335.6	0.325
Sucrose (mg)	0.00-2.50	5.6	8.3	0.303
Cellobiose (mg)	**0.00-3.00**	**1.3**	**3.7**	**0.065**
Raffinose/mannitol	**0.00-0.01**	**0.0**	0.0	0.092

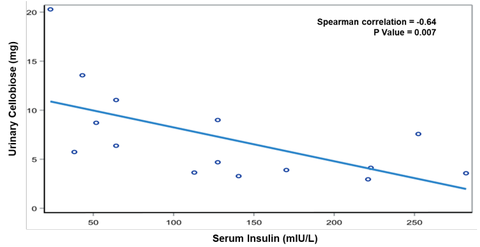
- Insulinogenic index following breakfast [$\Delta ins_{0\text{-}30min}/\Delta glu_{0\text{-}30min}$] and lunch [$\Delta ins_{0\text{-}15min}/\Delta glu_{0\text{-}15min}$] correlated inversely with cellobiose levels (r=-0.66, P=0.004, r=-0.59, P=0.015, respectively) **(Figure 1)**.

Figure 1. Inverse relationship between post-breakfast insulinogenic index and urinary cellobiose level.



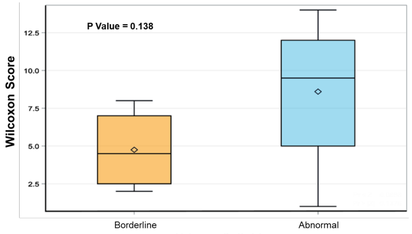
- Post-breakfast serum insulin$_{30min}$ also correlated inversely with cellobiose levels (r=-0.64,P=0.007) **(Figure 2).**

Figure 2. Inverse relationship between post-breakfast serum insulin and urinary cellobiose level.



- A trend for positive association between FPG and urinary cellobiose levels was observed (r=0.36, P=0.055)**.**
- Fasting zonulin levels trended higher in subjects with abnormal levels (i.e., >4.0mg) of urinary cellobiose (54.5 vs 35.4 ng/ml, P=0.1).

Figure 3. Distribution of Wilcoxon Scores for zonulin for subjects with abnormal vs. borderline abnormal urinary cellobiose levels.



- No significant correlations were observed between cellobiose levels and age, BMI, gender or HOMA-IR.

CONCLUSIONS

- This is the first analysis to describe an association between increased small intestine permeability and early loss of insulin response to a glucose stimulus.
- Interventions focused on intestinal barrier integrity should be further explored in the treatment of metabolic disorders.

REFERENCES

1. Arrieta M-C, Bistritz L, Meddings J. Gut 2006;55:1512-20. 2. Camilleri M, Nadeau A, Lamsam J, et al. J Neurogastroenterol Motil 2010;22:e15-e26. 3. Damms-Machado A, Louis S, Schnitzer A, et al. Am J Clin Nutr 2017;105:127-35. 4. Fasano A. J Gastroenterol Hepatoly 2012;10:1096-100.

DISCLOSURES

LEU and EC are employees of Gelesis, Inc.

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