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Gastrointestinal function in diabetes is affected regardless of asymptomatic appearance

Running title: The asymptomatic diabetic gut

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Abstract

Background: Gastrointestinal dysmotility may exist without concomitant symptoms. We hypothesise that asymptomatic individuals with diabetes have altered gastrointestinal function associated with age, cardiac vagal tone, and glycaemic control.

Methods: One-hundred and fifty-four asymptomatic participants (61 with type 1 diabetes (T1D), 70

type 2 diabetes (T2D), 23 healthy volunteers (HV)) underwent wireless motility capsule investigation. Transit times, motility indices, and pH were retrieved. Age, cardiac vagal tone, glucose, and haemoglobin A1c levels were collected.

Results: In T1D prolongation of colonic (p=0.03) and whole gut transit times (p=0.04) were shown. Transpyloric pH-rise was decreased in T1D (p=0.001) and T2D (p=0.007) and asso-

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ciated with cardiac vagal tone (p=0.03) or glucose (p=0.04) and haemoglobin A1c (p=0.005). Ileocecal pH-fall was decreased in T2D (p<0.001).

Discussion: Gastrointestinal function was altered in asymptomatic individuals with diabetes. These findings call for further investigations of gastrointestinal function in order to identify risk factors or even predictors for diabetic enteropathy, particularly when glycaemic control is impaired.

Key Words

Gastrointestinal Tract; Wireless Motility Capsule; Diabetes Mellitus; Signs and Symptoms, Digestive

Introduction

Gastrointestinal disorders are common and a cause of considerable morbidity in diabetes [1]. Clinical presentations span from asymptomatic appearance to severely debilitating symptoms [2], and investigations have primarily focused on patients with gastroparesis, diarrhoea, or constipation indicative of gut dysfunction [3,4]. However, associations between symptoms and gastrointestinal dysfunction are known to be poor [5,6], suggesting that symptoms are inadequate indicators of gastrointestinal function.

Gastrointestinal dysfunction is understood as a detrimental sequela to elevated glycaemic levels, which leads to glucose neurotoxicity due to an inability to regulate glucose uptake [7]. Consequently, local enteric neurons and inter-communication with the autonomic nervous system are injured. On top, pan-enteric hyposensitivity, presenting as increased tolerance of thermal, electrical, and mechanical pain [8], could diminish the symptoms reported by pa-

tients. As gastrointestinal deficiencies may arise in parallel or independently, it is plausible that gastrointestinal dysfunction may arise before symptom presentation or persist after sensory deprivation.

Gastrointestinal studies in asymptomatic patients are sparse due to the lack of clinical indication, high cost, potential harm, and the cumbersome procedures of current testing methods. The wireless motility capsule has provided a simple and minimally invasive investigation of gastrointestinal function as the ingestible capsule simultaneously evaluates transit time, motility, and pH [9].

We hypothesise that asymptomatic individuals with diabetes would have altered gastrointestinal function. The aim was to compare transit times, motility indices, and pH from the wireless motility capsule in asymptomatic individuals with type 1 (T1D) and type 2 diabetes (T2D) with healthy volunteers (HV) and analyse the associations to age, parasympathetic tone, and glycaemic control.

Methods

Study population

Data from 164 wireless motility capsule examinations in 61 participants with T1D, 70 with T2D, and 33 HVs were collected. All participants were recruited at Mech-Sense, Aalborg University Hospital, Denmark (The North Denmark Region Committee on Health Research Ethics, Denmark: N-20130077, N-20170045, N-20190020). Primary inclusion and exclusion criteria for diabetes participants have previously been described [5]. In addition, participants were excluded if they had a weighted gastrointestinal symptom score above 2.3, according to Okdahl et al.[10] (1.33x gastroparesis cardinals symptom index combined score + 0.89x gas-

trointestinal symptoms rating scale combined score times). HVs were recruited through advertisements and included based on normal bowel movements, lack of gastrointestinal symptoms, and no history of cardiovascular-, endocrine-, renal-, or chronic gastrointestinal disease or surgery hereof. None were taking laxatives or medications that influence motility or pH, such as proton pump inhibitors or H2 receptor antagonists.

Assessment of gastrointestinal function

The gastrointestinal function was investigated using a standardised wireless motility capsule (SmartPill, Given Imaging, Mansfield, MA, USA)) test to evaluate temperature, pH, and pressure simultaneously [9]. Data were analysed according to proposed standards with MotiliGI (version 3.0.20; Given Imaging). Transit times, motility indices, and median pH levels from the gastric, small bowel, and colonic regions were obtained along with whole gut transit time, the transpyloric pH-rise, and the ileocecal pH-fall. Data above the 95 percentile of published normative data [11,12] was considered abnormal.

Assessment of clinical factors

Demographic information, including age, gender, disease duration, smoking habits, and medication use, was obtained. Height and weight were measured to calculate body mass index. Blood pressure and heart rate were measured at rest. Blood samples for clinical biochemistry were drawn from patients before ingesting the capsule, including measures of glycaemic control as fasting blood glucose and haemoglobin A1c levels. Parasympathetic tone was measured as cardiac vagal tone, based on 5-minute electrocardiography using a validated algorithm.

Statistics

The transit times, motility indices, and pH measures are summarised on a group level using the number of observations, mean and standard deviation, median and 5^{th}, 25^{th}, 75^{th}, and 95^{th} percentiles. One-way ANOVA or Kruskal–Wallis test with Bonferroni correction or Dunn's test as post hoc analysis was used to compare the groups. Regression analysis between wireless motility capsule measures and clinical factors in each of the diabetes groups were performed, and coefficients plots were computed. All statistical analysis was performed in Stata (version 15.1, StataCorp, College Station, TX, USA), with a p-value of <0.05 considered significant.

Results

Participant characteristics

Participant characteristics can be found in Table S1. In short, participants with T2D were older, had higher body mass index, shorter disease duration, lower cholesterol levels, used statins more often, had lower haemoglobin A1c levels, and predominantly used other antihyperglycemic medications than insulin compared to T1D. 84% of T1D and 67% of T2D had hyperglycaemic glucose levels at the time of investigation (>7.8 mmol/L).

Gastrointestinal transit times

In diabetes participants, prolongation of transit time was shown in 14% (7 T1D and 11 T2D) for gastric emptying, 19% (11 T1D and 13 T2D) for small bowel and colonic transit, and 11% (3 T1D and 11 T2D) for whole gut transit. Participants with T1D had a 35% prolonged

colonic transit (p=0.03) and a 29% prolonged whole gut transit (p=0.04) in comparison to HV. Transit times are presented in Table 1 (elaborations in Tables S2 and S3).

Gastrointestinal pH

The transpyloric pH-rise was decreased in both T1D and T2D compared to HV (p=0.003), while the ileocecal pH-fall was decreased in T2D compared to both T1D and HV (p<0.001) as outlined in Figure 1. pH levels and pH changes transpyloric and ileocecal are presented in Table 1. No difference was found in segmental pH between diabetes and HV.

Gastrointestinal motility indices

No difference was found in segmental motility indices between diabetes and HV. Motility indices are presented in Table 1.

Clinical associations

The transpyloric pH-rise was positively associated with cardiac vagal tone (p = 0.03) in participants with T1D while negatively associated with HbA1c levels (p = 0.005) and glucose levels (p = 0.04) in T2D. No association were found between colonic or whole gut transit times, the ileocecal pH-fall and

age, cardiac vagal tone, HbA1c levels or glucose levels. Associations are outlined in Figure 2. Differences in transit times and pH rise or fall between participants with high or low haemoglobin A1c and glucose levels can be found in Table S5.

Discussion

Our data show that gastrointestinal function is affected in individuals with diabetes regardless of asymptomatic appearance. This was evident in T1D as prolonged colonic and whole gut

transit times. Furthermore, the transpyloric pH-rise was decreased in both T1D and T2D, while the ileocecal pH-fall was decreased in T2D. The transpyloric pH-rise was positively associated with parasympathetic tone in T1D, while negatively associated with glycaemic control in T2D.

Investigating gastrointestinal function in asymptomatic individuals with diabetes may seem contradictory, as extensive clinical investigations should arguably not be initiated without bothersome self-reported symptoms or complications. However, due to the progressive nature of the underlying pathophysiology, asymptomatic patients likely suffer from concealed gastrointestinal dysfunction [5,6]. Hence, investigating diabetic gastro-enteropathy is essential to unmask dysfunction that could alter nutrient absorption, microbial composition, and complicate glycaemic regulation due to an inability to coordinate meals to the administration of antihyperglycemic medications [13], creating a vicious circle of glycaemic dysregulation.

Increased focus on pan-enteric changes in diabetes has arisen in later years, albeit gastroparesis is still the best-known and most investigated entity due to characteristic symptoms [3,14]. However, these cardinal symptoms are poorly associated with gastric emptying [5,14], suspectedly due to an alteration of gastric emptying in both symptomatic and asymptomatic individuals. We confirmed this clinical suspicion as delayed gastric emptying (>5 hours) was found in 1 in 7 diabetes participants, despite their lack of symptoms. Hyperglycaemia is known to prolong gastric emptying, and in the current study, 3 out of 4 participants were hyperglycaemic at study initiation, which could be a possible explanation for the altered gastrointestinal function [15]. However, gastric emptying time for participants with type 1 and type 2 diabetes was comparable with healthy, despite this dysregulation. We have previously reported pan-enteric prolongation of transit times in T1D with polyneuropathy and autonomic neuropathy [14]. Interestingly, these findings were supported by the current dataset, where

constipation was evident as prolonged transit times in the colon and whole gut in a population with various degrees of neuropathy. This may indicate that enteric neurons and their intraneuronal synapses are more vulnerable to dysregulation, causing dysmotility and altered secretion prior to symptom development [7].

One study showed that cardiac vagal tone, a measure of parasympathetic vagal function, was diminished with prolonged colonic transit time [5]. However, no such association was apparent in the current study, supporting a more profound decrease in cardiac vagal tone before the onset of symptoms. Nor did we find an association between colonic or whole gut transit times and glycaemic control. Increased awareness focuses on the glucose fluctuations (hypo- and hyperglycaemia) and their neurotoxic effect on the nerves, and therefore HbA1C is a poor measure of glycaemic control compared to, e.g., continuous glucose monitoring. Nevertheless, our dataset reveals long-term dysregulation in most participants, and the lack of association to transit times calls for better glycaemic measures in the future. In addition to the influence of glucose, prolonged colonic transit time may be caused by hyposensitivity or diminished contractile activity within this segment [16].

A balanced gastrointestinal environment is crucial for food decomposition, absorption of nutrients, orally administered medicine, and thus general health. Increased transpyloric pH-rise was previously found in individuals with T1D and severe polyneuropathy [17], directed by decreased median gastric pH. Despite unaltered gastric and small bowel pH, the current findings showed a decreased transpyloric pH-rise in T1D and T2D. This could be attributed to diminished H^+ production, as gastric pH was increased in 10% of participants independent of proton pump inhibitor use. Another explanation is that the pH change could not be encompassed within the measured timeframe (30 minutes before and after sphincter passage) due to a prolonged transpyloric transition time [18]. In T2D, the diminished transpyloric pH-rise

was associated with fasting glucose levels, indicating that 67% of T2D participants with hyperglycaemia had either diminished H^+-production or prolonged pyloric transition time. Whether acute glycaemia or long-term heightened glycaemic levels causes altered pH intestinal environment directly or is a product of gastroenteropathic changed secretion is unknown. Nevertheless, the intraluminal micromilieu influences the absorption and bioavaibility of nutrients and human faecal transplant studies have shown that insulin sensitivity increases in response to shifts in the microbiome composition [19]. Hence, microbial changes caused by diabetes may alter the intestinal environment and influence blood glucose levels.

The decreased ileocecal pH-fall in T2D was not driven by altered small bowel or colonic pH. Consequently, it indicates an altered environment in the caecum, which hosts a flora of bacteria, including short-chain fatty acids-producing bacteria that lowers pH. Such bacteria have previously shown to be diminished in T2D due to, e.g., an altered, low fibre diet [20], however only mealtimes were monitored during the current study, not meal content.

This study is not without limitations. Firstly, we used a previously defined symptom score cut-off value based on data from healthy participants [10], which allowed participants with few and less severe problems to be included as asymptomatic. Hence, a more conservative cut-off value could alter the reported outcomes. Secondly, we used the wireless motility capsule with well-described limitations, including a test meal high on carbohydrates inconvenient in a diabetes population [9]. However, the drawbacks are outweighed by the simultaneous collection of pH, pressure, temperature, the ambulatory nature of the device, and the easily applicable and understandable testing protocol and analysis [9]. Thirdly, 3 out of 4 participants were hyperglycaemic (glucose levels >7.8 mol/L) at the time of investigation, possibly due to an individual correction in food intake and administration of antihyperglycemic medication. Moreover 80% were dysregulated (HbA1C >48 mmol/mol or 6.5%), calling for opti-

mized glucose regulation. In this dataset, neither glucose nor haemoglobin A1c level appeared to influence transit times overall, however, it may have had undetected influences on gastrointestinal function and sensation and should be kept in mind when interpreting the results. Lastly, besides the testing meal, we did not monitor the meal content during the study, though differences in subsequent meals or everyday dietary habits could influence the results.

Conclusion

We confirmed that gastrointestinal function is affected in dysregulated individuals with T1D and T2D regardless of asymptomatic appearance. These results suggest that gastrointestinal function in asymptomatic individuals with diabetes may hide functional impairment, especially when glycaemic dysregulation is inadequately explained. Thus, individual with dysregulated diabetes could be encouraged to initiate lifestyle changes including enhanced fluid intake and fibre content, together with physical exercise in order to minimize constipation.

Funding and Disclosures

The authors declare that there is no conflict of interest associated with this manuscript.

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Figures and Tables

Figure 1

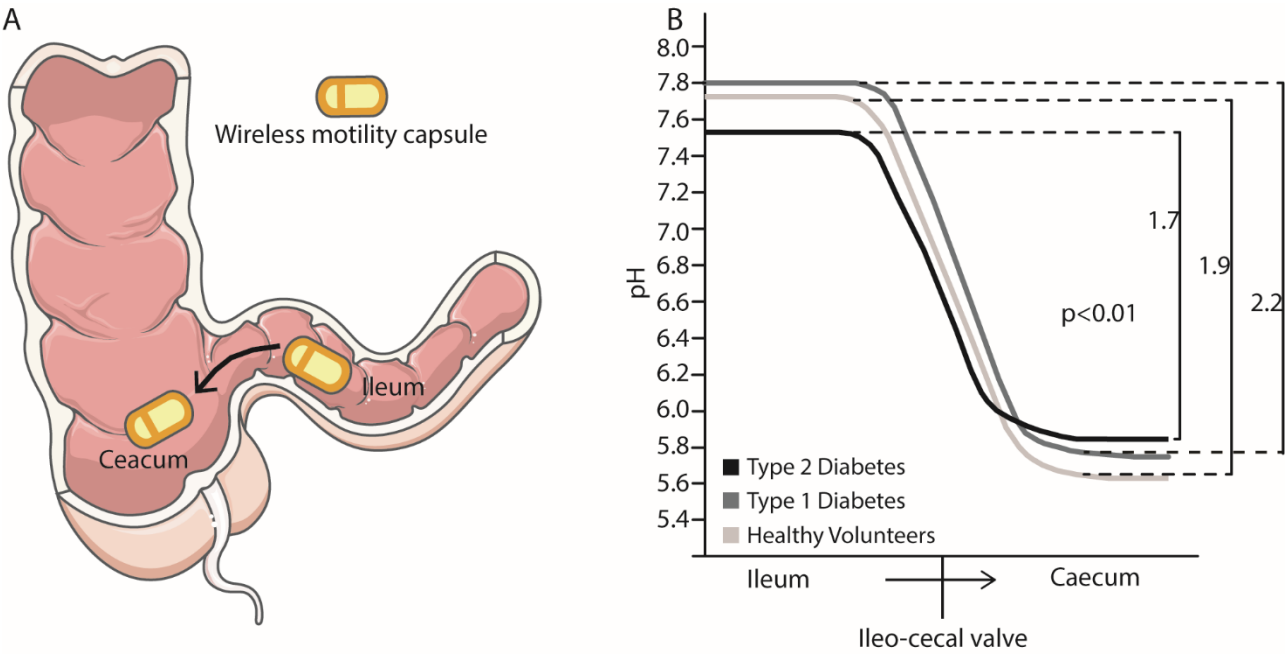

Figure 1: Outline of the ileocecal pH-fall. A) a sketch of the ileocecal area showing the passage of the wireless motility capsule. B) outline of the ileocecal pH-fall in the three patient groups.

Figure 2

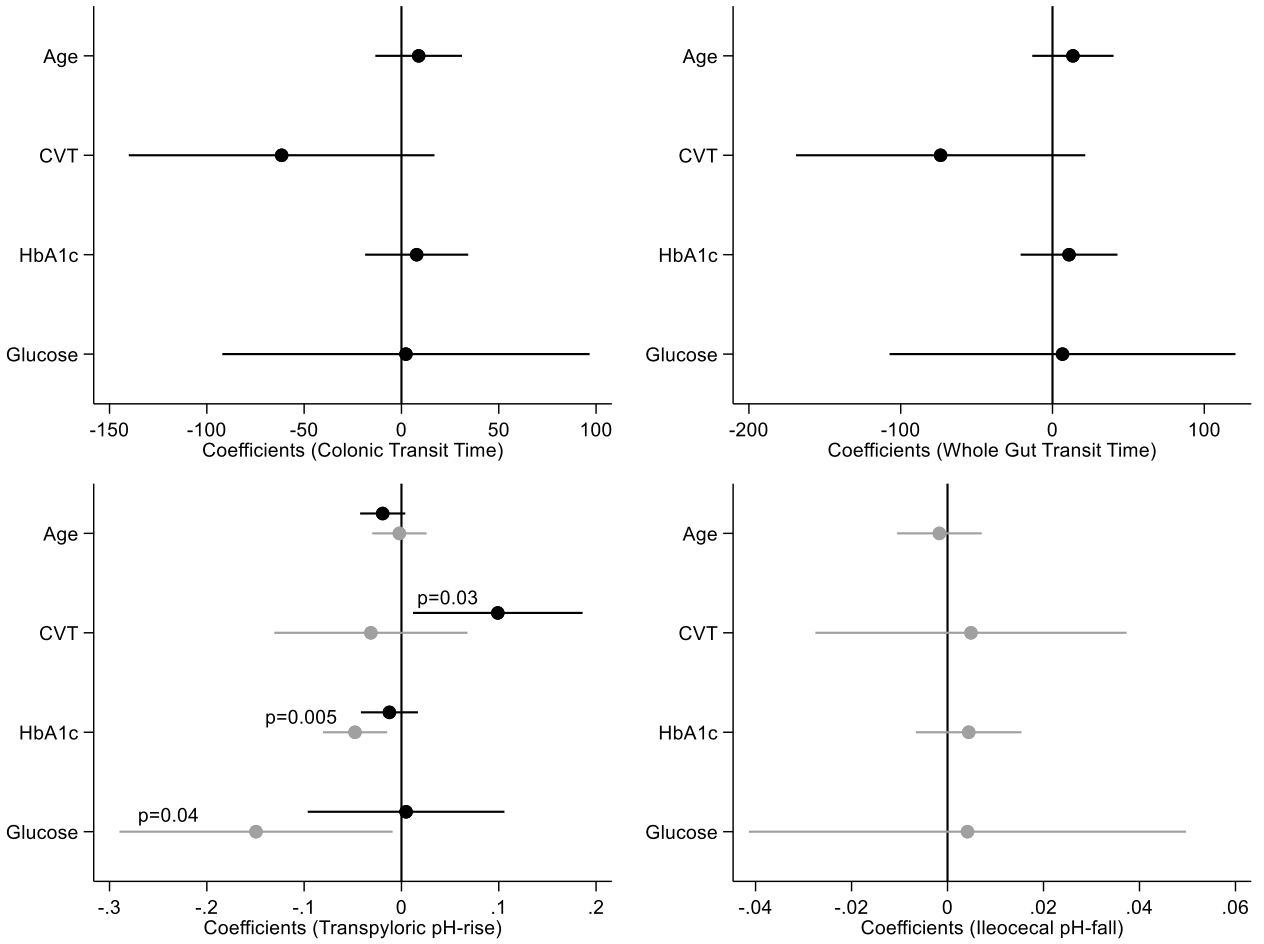

Figure 2: Coefficients plot of associations with clinical factors of age, cardiac vagal tone (CVT), haemoglobin (Hb) A1c, and glucose levels. The graphs show the regression coefficients (and confidence intervals) for each significant regression. Type 1 diabetes (T1D) is indicated as black, and type 2 diabetes (T2D) as grey.

Table 1: Gastrointestinal transit, pH and motility indices in healthy, type 1, type 2, and combined diabetes participants

Variable	Type	N	Mean	SD	Median	5th	25th	75th	95th	*p*
Gastric	HV	31	3:07	0:59	3:16	1:26	2:19	3:47	4:45	
Emptying	T1	51	2:25	0:59	3:02	1:40	2:20	3:47	4:41	
Time	T2	65	3:05	1:09	3:09	1:09	2:26	3:45	5:06	
	DM	120	3:05	1:04	3:08	1:20	2:22	3:47	5:02	
Small	HV	33	4:58	1:16	5:00	3:06	4:08	5:48	8:35	
Bowel	T1	57	5:17	2:03	5:02	2:54	3:39	6:07	7:52	
Transit	T2	68	4:54	2:00	4:53	2:11	3:24	6:28	8:11	
Time	DM	129	5:06	2:01	4:57	2:24	3:35	6:22	8:11	
Colonic	HV	33	23:07	19:57	18:54	4:12	13:25	25:49	59:56	†
Transit	T1	56	31:18	18:27	25:50	11:56	17:50	40:16	66:17	
Time	T2	65	29:26	22:03	22:10	2:23	16:05	38:51	69:30	
	DM	125	30:05	20:12	23:11	7:17	16:27	39:57	67:42	
Whole	HV	33	31:57	20:22	25:37	12:42	22:23	33:51	70:09	†
Gut	T1	56	41:10	22:17	33:44	22:02	24:07	48:48	79:04	
Transit	T2	66	39:18	23:59	30:22	14:30	23:38	47:53	98:01	
Time	DM	126	39:55	22:53	32:17	20:33	24:03	48:33	80:22	
Variable	Type	N	Mean	SD	Median	5th	25th	75th	95th	*p*
Gastric	HV	31	1.8	1.1	1.4	0.7	0.9	2.6	4.4	
pH	T1	53	1.9	1.5	1.4	0.5	1.0	2.3	5.9	
	T2	68	2.0	1.6	1.3	0.6	0.9	2.8	5.7	
	DM	125	2.0	1.6	1.4	0.6	0.9	2.7	5.9	
Trans	HV	31	6.4	0.5	6.4	5.5	6.0	6.7	7.2	†‡

pyloric	T1	55	5.7	1.2	6.0	2.3	5.4	6.4	6.8	
pH-rise	T2	70	5.7	1.2	6.1	2.4	5.6	6.5	6.9	
	DM	129	5.7	1.2	6.0	2.3	5.5	6.4	6.8	
Small	HV	33	7.0	0.4	7.1	6.3	6.8	7.4	7.6	
Bowel	T1	56	7.1	0.4	7.2	6.4	6.8	7.5	7.7	
pH	T2	68	7.0	0.4	7.0	6.3	6.8	7.3	7.5	
	DM	128	7.1	0.4	7.1	6.4	6.8	7.3	7.6	
Ileocecal	HV	33	2.1	0.4	2.2	1.4	1.8	2.4	2.7	‡‖
pH-fall	T1	56	1.9	0.4	1.9	1.2	1.6	2.2	2.7	
	T2	68	1.7	0.4	1.7	1.1	1.5	2.0	2.3	
	DM	128	1.8	0.4	1.8	1.2	1.5	2.1	2.5	
Colonic	HV	32	6.5	0.6	6.6	5.5	6.0	7.0	7.4	
pH	T1	53	6.6	0.6	6.7	5.5	6.1	7.1	7.6	
	T2	62	6.6	0.5	6.6	5.7	6.2	6.9	7.3	
	DM	118	6.6	0.6	6.6	5.7	6.1	7.0	7.4	
Variable	Type	N	Mean	SD	Median	5^{th}	25^{th}	75^{th}	95^{th}	*p*
Gastric	HV	32	59	31	53	21	35	84	111	
Motility	T1	54	72	38	71	25	39	93	138	
Index	T2	69	70	30	66	25	49	89	124	
	DM	127	72	33	67	25	48	90	127	
Small	HV	33	148	73	150	44	104	169	288	
Bowel	T1	57	177	90	167	54	98	234	351	
Motility	T2	68	152	84	129	56	92	189	333	
Index	DM	129	163	87	145	56	94	208	333	
Colonic	HV	32	178	80	174	50	116	248	315	

Motility	T1	54	201	154	162	55	122	230	406
Index	T2	64	208	126	174	62	117	276	467
	DM	122	203	137	166	59	122	240	407

HV: healthy participants, T1D: type 1 diabetes, T2D: type 2 diabetes, DM: diabetes mellitus (T1D + T2D). † HV vs. T1D, ‡ HV vs. T2D, ‖ T1D vs. T2D