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Inuit population have shorter gastric emptying, higher duodenal motility and altered pan-enteric micromilieu: a comparative study between Greenlandic and Danish populations with and without type 2 diabetes

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ABSTRACT

Gastrointestinal function plays a pivotal role in nutrient absorption and overall digestive health. Abnormal gastric emptying is closely linked to type 2 diabetes, impacting blood glucose regulation and causing gastrointestinal symptoms. This study aims to investigate and compare segmental transit times, motility indices, and micromilieu between Greenlandic Inuit and Danish individuals with and without type 2 diabetes. We included forty-four Greenlandic Inuit, twenty-three of whom had type 2 diabetes, and age and gender-matched Danish individuals. Segmental transit time, motility, and luminal environment were measured using the SmartPill®. Greenlandic controls displayed shorter gastric emptying time (GET) (163 min), higher gastric median pH (2.0 pH) and duodenal median contractions (18.2 mm Hg) compared to Greenlanders with type 2 diabetes (GET: 235 min, pH:1.9, median duodenal contraction 18.4 mm Hg) and Danish controls (GET: 190, pH:1.2 median duodenal contraction 17.5 mmHg). Despite similar anti-diabetic management efforts, variations in gastrointestinal physiology were evident, highlighting the complexity of diabetes and its interaction with ethnicity, suggesting potential dietary or even genetic influences, emphasising the necessity for personalised diabetes management approaches. Finally, the study opens possibilities for future research, encouraging investigations into the underlying mechanisms linking genetics, diet, and gastric physiology, as an understanding of factors can lead to more effective, tailored strategies for diabetes care and improved digestive health in diverse populations.

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Introduction

Gastrointestinal function plays a crucial role in the regulation of nutrient absorption, energy balance, and overall digestive health [1]. Delayed transit in one or more of the gastrointestinal segments, leading to gastroparesis, constipation, or other dysfunctions, can be accompanied by severe symptoms, and have serious consequences. Furthermore, disturbances in gastric emptying time can affect uptake, and thereby the effect, of orally prescribed medicine [2]. Type 2 diabetes is associated with abnormal pan-enteric dysmotility evident as altered gastric emptying, e.g. rapid gastric emptying in early type 2 diabetes, and gastroparesis found in long-standing type 2 diabetes. Both scenarios can cause gastrointestinal symptoms and contribute to difficulties in regulating blood glucose levels tightly [3,4]. Some antidiabetic drugs, and especially GLP-1 receptor agonists, are known to reduce gastric emptying [3] and shorten colonic transit [5], and thus, the increasing use of GLP-1 receptor agonist in diabetes care is likely to affect gastrointestinal function in individuals with type 2 diabetes.

Variability in gastrointestinal transit times among different populations has been attributed to genetic, dietary, and environmental factors [6,7]. For example, Han Chinese with type 2 diabetes have more rapid gastric emptying time in comparison to Caucasians with type 2 diabetes [7].

In Greenland, the ethnic majority are Inuit, and the current Inuit population are descendants of the Thule population, which settled in Greenland around the 12th century and were almost completely isolated until the colonisation from Denmark in 1721, resulting in a unique genetic homogeneity [8]. Historically, the Inuit diet is

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distinguished as ketogenic, being high in animal protein and fat, while low in carbohydrates. After the industrialisation, the Greenlandic diet has shifted more towards a classical European diet, especially in the larger towns where the genetic admixture is also larger compared to settlements [9]. While there is evidence to show that a high-fat diet will decrease gastric transit time [10,11], there is limited knowledge regarding genetic adaptation to specific diets. To our knowledge, there has been no previous examination of gastrointestinal transit times, motility, and intraluminal micromilieu among the Inuit population.

There are several methods for examining gastrointestinal transit, including scintigraphy (gold standard), breath tests, paracetamol tests, and ingestible electronic devices. The SmartPill is a wireless motility capsule (SmartPill®, Medtronic, Minneapolis, USA) that measures luminal pH, pressure, and temperature, and data are transmitted to an externally worn receiver. The examination provides detailed information regarding segmental transit times, motility, pH levels, etc., and offers a safe examination modality when compared to alternative testing methods [12].

We hypothesised that long-term genetic adaptation to a ketogenic diet could result in shorter gastric transit time amongst Inuit. Thus, this study aims to investigate and compare gastrointestinal transit time in people with type 2 Diabetes and healthy controls among Greenlandic Inuit and Danish individuals.

Methods

The study was conducted in Nuuk (total population 19,783), Greenland (total population 56,865), between April 2022 and January 2023.

Recruitment

Greenlandic participants: Greenlandic participants were recruited from a study focusing on cardiac arrhythmias in Greenland (The Committee of Research Ethics in Greenland: 2020–18/ClinicTrials.gov ID: NCT05200676). Inclusion criteria were 50 years or older, and Inuit ancestry was defined as at least one parent born in Greenland. MMJ and NA recruited participants, and oral and written information was given in Danish or Greenlandic per the participant's preference. Participants answered a questionnaire regarding ancestry, medical history, current medication, tobacco use, etc. Biochemical information, including HbA1c, creatine, total cholesterol, HDL and LDL, was available through the electronic biochemical records, but only for participants who had given separate consent for this. All participants signed an informed consent form.

Danish participants: Danish participants were recruited from three separate studies, one focusing on autonomic function in diabetes (The North Denmark Region Committee on Health Research Ethics, Denmark: N-20170045) and two with healthy controls to intervention studies (N-20130077 and N-20190020). All participants signed an informed consent form.

Contraindications for the SmartPill served as exclusion criteria: dysphasia, gastric bezoars, strictures, fistulas, bowel obstructions, diverticulitis, recent gastrointestinal surgery, implanted electromechanical medical devices and medications known to influence gastrointestinal transit time (except GLP-1 agonist).

Testing procedure: The participant arrived fasting (at least eight hours) and after a short recap of the procedure and contraindications, the SmartPill capsule was activated and calibrated using the MotiliGI™ Software (Medtronic). The participants then ingested a standardised meal bar consisting of 17% protein, 66% carbohydrate, 2% fat, and 3% fibre, followed immediately by the ingestion of the SmartPill. A SmartPill Motility Receiver (Medtronics) was strapped around the waist of the participants using an elastic belt or put around the neck with a neck strap, ensuring proximity between the recorder and the SmartPill. The participants were strongly encouraged to only remove the recorder during showers or baths. Finally, the participants were asked to refrain from food for at least six hours after swallowing the SmartPill to ensure that the pill had left the ventricle by the time of the subsequent meal and to note all meals, bowel movements, wake-up time and bedtime during the five-day testing period.

The Motility Receiver was removed after five days, and the results were uploaded to the MotiliGI™ Software for analysis. Preliminary analyses were done by MMJ and NA and checked by AMW and CB.

Regional transit times were identified by recognising the clear stereotypical landmarks:

1): Time for capsule ingestion: An abrupt rise in temperature and drop in pH reflect the gastric acidic environment; 2): Gastro-pyloric passage: An abrupt rise in pH of typically more than 3 pH units reflecting the duodenal alkaline environment; 3): Ilio-caecal passage: A more than 10 minute sustained drop in pH usually of more than 1 pH-unit reflecting the transition to the more acidic environment, 4): Time of capsule expulsion: An abrupt drop in temperature followed by loss in recorded signal combined with bowel movement. From these landmarks, gastric emptying time, small bowel transit time, colonic transit time, and whole gut transit times can be derived [13].

Statistical analyses

Continuous data were tested for normality using histograms and QQ Plots. Normally distributed data were described using means with Inter Quartile Range (IQR) while non normal distributed data was described with median and IQR. For, normally distributed data, differences between the means of the two groups were tested with the t-test and for more than two groups with the one-way ANOVA. For non-normally distributed data, differences between the median was tested with the Wilcoxon rank-sum (2 groups) and Kruskal-Wallis (>2 groups) Categorical data were compared using the Chi-squared test. P-values <0.05 were considered significant.

Results

In total, 44 Greenlandic Inuit were included and age- and gender-matched with Danish individuals. Twenty-one Greenlandic and 22 Danish participants had type 2 diabetes and 23 served as controls. The four groups were comparable in age and sex. Antidiabetic medication and HbA1c levels were similar between Greenlandic Inuit and Danish patients with type 2 diabetes. Among Greenlandic participants, 12 in each group identified both their parents as Inuit, while 10 healthy controls and 5 with type 2 diabetes identified only one parent as Inuit. Detailed participant characteristics can be seen in Table 1.

Gastric emptying time for Greenlandic controls (163 (113–209) min) was significantly decreased compared to Greenlanders with type 2 diabetes (235 (172–349) min). Greenlandic Controls showed shorter gastric emptying time and higher median gastric pH compared to Danish controls. No difference in transit time was found for the other segments. Detailed SmartPill information can be seen in Table 2.

Discussion

The findings of this study provide valuable insights into the complex interplay between gastric emptying time, segmental motility intestinal micromilieu, genetic backgrounds, and dietary habits in two populations: Greenlandic Inuit and Danish individuals, both with and without type 2 diabetes. We confirmed our hypothesis, that long-term genetic adaptation to a ketogenic diet could result in shorter gastric transit time amongst Inuit, as healthy Inuit controls exhibited notably shorter gastric emptying time in comparison to Inuit with type 2 diabetes, and Danish individuals regardless of diabetes. In addition, the pH change across the ileocaecal junction was higher compared to Inuit with type 2 diabetes. Furthermore, Inuit participants regardless of diabetes had increased small bowel amplitudes in comparison to Danish controls, supporting the shown faster gastric emptying time. Finally, Inuit controls had higher gastric pH and thus, lower antroduodenal pH rise than Danish controls.

Inuit controls displayed decreased gastric emptying time and increased small bowel motility in comparison to Danish controls, which may underscore the impact of diet and ethnicity on gastric physiology, further highlighting the need for a nuanced understanding of these factors. The study's focus on the Greenlandic Inuit population is particularly noteworthy due to their unique genetic homogeneity and historically distinct dietary habits, which may influence the intestinal micromilieu. Through thousands of years, the Inuit diet consisted mainly of a diet high in marine animal protein and fat, while low in carbohydrates. Furthermore, the population lived in extreme weather conditions where periods of food deprivation could have been frequent. In such inter-digestive periods, the gastrointestinal hormones ghrelin and motilin accelerate gastric emptying,

Table 1. Patient characteristics divided by country and diabetes status.

Characteristic	Greenland – Controls	Greenland – Type 2 Diabetes	Denmark – Controls	Denmark – Type 2 Diabetes	Total P-value	Greenland P-value	Denmark P-value	Controls P-value	DMT2 P-value
Number	23	21	23	22					
Mean age (IQR)	58 (53–63)	61 (56–63)	57 (53–63)	61 (56–63)	0.2*	0.2‣	0.12‣	0.7‣	>0.9‣
Female sex (%)	14 (61%)	10 (48%)	13 (57%)	10 (45%)	0.7•	0.6•	0.7•	>0.9•	>0.9•
Mean BMI (kg/m^2) (IQR)	30 (25–32)	31 (28–34)	25 (23–27)	33 (30–35)	0.004*	0.5‣	<0.001‣	0.01‣	0.4‣
Tobacco use					<0.001•	0.037•	0.14•	0.001•	<0.001•
Yes	3 (14%)	8 (42%)	7 (32%)	1 (8.3%)					
Previous	10 (45%)	9 (47%)	0 (0%)	1 (8.3%)					
HbA1c (mmol/mol) (IQR)	40 (36–44)	54 (47–61)	34 (33–36)	55 (47–64)	<0.001*	0.003‣	<0.001‣	0.004‣	>0.9‣
Creatine (µmol/L) (IQR)	93 (69–91)	81 (67–85)	77 (66–86)	72 (61–81)	0.070*	0.4‣	0.2‣	0.2‣	0.12‣
Metformin (yes)	0 (0%)	12 (67%)	0 (0%)	18 (82%)	<0.001•	<0.001•	<0.001•	-	0.5•
Antihypertensive (yes)	6 (29%)	13 (72%)	0 (0%)	18 (82%)	<0.001•	0.017•	<0.001•	0.02•	0.7•
Statins (yes)	0 (0%)	12 (67%)	0 (0%)	14 (64%)	<0.001•	<0.001•	<0.001•	-	>0.9•
Insulin (yes)	0 (0%)	3 (17%)	0 (0%)	6 (27%)	0.007•	0.2•	0.024•	-	0.7•
GLP-1 (yes)	0 (0%)	5 (28%)	0 (0%)	6 (27%)	0.004•	0.035•	0.024•	-	>0.9•

Data is shown as mean (IQR) or number (%). Significance tested with one-way ANOVA (*), chi-squared (•), and T-test (‣) values > 0.05 were considered significant. P-values < 0.05 were considered significant.

Table 2. Median (IQR) SmartPill results.

	Greenland – Controls	Greenland – Type 2 diabetes	Denmark – Controls	Denmark – Type 2 Diabetes	Total p-value	Greenland p-value	Denmark p-value	Controls p-value	DMT2 p-value
	N = 23	*N* = 21	*N* = 23	*N* = 22					
Median Gastric emptying time (min)) (IQR)	163 (113–209)	235 (172–349)	190 (128–227)	200 (163–239)	0.053	**0.013**	0.41	0.48	0.19
Median small bowel transit time (min) (IQR)	267 (210–352)	251 (186–330)	320 (255–334)	236 (214–341)	0.28	0.35	0.16	0.25	0.66
Median colonic transit time (min) (IQR)	1280 (833–2638)	2088 (1182–3514)	1549 (919–2379)	1127 (1000–2289)	0.28	0.14	0.86	0.97	0.072
Median whole gut transit time (min) (IQR)	1757 (1305–3077)	2847 (1593–3982)	1970 (1375–2953)	1598 (1420–2974)	0.30	0.12	0.86	0.85	0.096
Median gastric median pH (IQR)	2.0 (1.3–5.5)	1.9 (1.0–5.0)	1.2 (0.9–1.7)	1.6 (1.0–3.4)	**0.036**	0.41	0.21	**0.005**	0.38
Median antro-duodenal pH rise (IQR)	6.0 (4.5–6.4)	5.7 (3.4–6.1)	6.5 (6.0–6.9)	6.0 (4.9–6.5)	**0.011**	0.43	**0.025**	**0.018**	0.22
Median small bowel median pH (IQR)	7.0 (6.7–7.2)	7.0 (6.6–7.2)	7.0 (6.6–7.3)	7.0 (6.7–7.2)	0.91	0.74	0.61	0.91	0.9
Median ileo-ceacal pH drop (IQR)	2.1 (1.8–2.4)	1.8 (1.4–2.1)	2.2 (1.5–2.4)	1.7 (1.6–2.0)	**0.044**	**0.015**	0.17	0.61	0.71
Median colonic median pH (IQR)	6.7 (6.4–7.0)	6.7 (6.3–6.8)	6.8 (6.0–7.1)	6.6 (6.0–6.9)	0.83	0.37	0.60	0.87	0.98
Median gastric peak amplitude (mm Hg) (IQR)	17.8 (17.1–20.7)	19.1 (16.6–20.2)	18.3 (16.6–20.4)	18.9 (18.0–21.6)	0.66	0.78	0.26	0.87	0.53
Median small bowel peak amplitude (mm Hg) (IQR)	18.2 (16.9–19.8)	18.4 (17.1–20.17)	17.5 (15.7–18.2)	19.5 (18.0–24.0)	**0.007**	0.50	**< 0.001**	0.097	0.31
Median colonic peak amplitude (mm Hg) (IQR)	22.3 (18.7–25.4)	24.8 (17.1–21.7)	21.0 (18.3–24.4)	22.2 (19.5–24.6)	0.23	0.46	0.47	0.24	0.17
Median gastric contraction frequency (contraction/min) (IQR)	2.2 (1.6–3.4)	2.0 (1.6–3.2)	2.0 (1.4–2.8)	1.8 (1.4–2.1)	0.36	0.60	0.39	0.42	0.21
Median small bowel contraction frequency (contraction/min) (IQR)	4.3 (2.7–5.5)	5.0 (3.9–6.6)	3.7 (3.0–4.8)	3.5 (2.1–4.6)	0.069	0.14	0.49	0.48	**0.021**
Median colonic contraction frequency (contraction/min) (IQR)	2.0 (1.5–2.3)	1.8 (1.4–2.1)	2.0 (1.4–2.2)	1.6 (1.3–2.0)	0.28	0.19	0.13	0.65	0.77
Median gastric motility index (IQR)	68 (52–105)	68.6 (38.5–77.6)	62 (39–87)	65 (52–84)	0.74	0.39	0.60	0.31	0.73
Median small bowel motility index (IQR)	137 (83–228)	182.4 (133.6–271.9)	127 (106–157)	133 (82–186)	0.18	0.21	0.55	0.45	0.087
Median colonic motility index (IQR)	218 (148–281)	249.4 (113.4–302.8)	216 (102–255)	170 (112–237)	0.66	0.81	0.70	0.56	0.37

Significance calculated with Wilcoxon rank sum (2 groups) or Kruskal Wallis (> 2 groups) where a p-value > 0.05 was considered significant.

partly by stimulating the gastric excitatory vagal motor circuitry [14]. Consequently, the recent transition from a restricted traditional Inuit diet to a more Western diet without food deprivation, may not yet be reflected in the gastrointestinal physiology and thus has potential physiological implications that are not fully understood. The findings here, specifically the lower gastric emptying time in Greenlandic controls, might consequently be indicative of dietary, environmental, and genetic influences. Likewise, genetics are also thought to change the disease expression of type 2 diabetes among Inuit, which could explain why the difference in median gastric emptying time in controls and type 2 diabetics is larger among Inuit than among Danes. In the capital Nuuk, the genetic admixture is relatively high due to a historically high presence of people born outside of Greenland, which accounted for almost 50% of the population in 1977 [15]. In this study, 12 in both groups of Greenlandic participants identified their parents as Inuit, while 5 participants with type 2 diabetes and 9 Greenlandic controls identified only one parent as Inuit. Four participants with type 2 diabetics and two without did not answer the questionnaire regarding ancestry but had before inclusion verbally confirmed that at least one of their parents was of Inuit descent, as this was part of the inclusion criteria. As our findings suggest an ethnic difference in gastric emptying, this could be more profound in the populations living in the smaller settlements in Greenland where there is less genetic admixture and the lifestyle is closer to the traditional Inuit way of life. However, further research is warranted to explore these connections in depth. The rate of gastric emptying and motility affects oral drug absorption, which poses a challenge for drug suppliers in providing an accurate half-life. Changes in gastric emptying lead to unpredictable delivery of nutrition (and thus glucose) and oral pharmacotherapeutic agents into the small bowel, thereby challenging normal drug half-lives [16]. However, it is not known whether chronic poor glycaemic control is the cause or the consequence of gastroparesis, but in reality, it is likely that these factors inter-act with one another. Notwithstanding the significant symptom burden, gastroparesis is also associated with significant healthcare expenditure. Notably, clinical examinations and hospitalisations due to gastroparesis are increasing as well as the length of stay This is of special interest since, Factors such as gastrointestinal transit time and pH are known to alter the uptake of food and, more importantly, medicine is absorbed. This means that the variations we observed in this study could lead to changes in how orally administered medicine is absorbed in the Inuit population.

Healthcare is generally transitioning from a "one-size -fits-all" model to a more personalised approach. However, in smaller ethnic groups such as the Inuit, there is often a lack of knowledge about specific factors that could affect treatment outcomes. Therefore, our findings could provide valuable insights for healthcare professionals working in all Arctic regions. However, more research is needed to validate our findings before any changes can be made to clinical practice.

In our study population, around a quarter of all participants with type 2 diabetes were treated with a GLP-1 analog, which is known to prolong gastric emptying time. Therefore, the numerical transit time difference between controled participants and participants with type 2 diabetes would most likely be influenced, but our population is too small to make meaningful statistics between subgroups.

Additionally, the comparable antidiabetic medication usage and HbA1c levels between Greenlandic and Danish patients with type 2 diabetes highlight the consistent glycaemic control efforts across these populations. Despite this, the disparities in gastric emptying time emphasise the multifaceted nature of diabetes and the need for personalised approaches to its management.

We did not find any differences in small bowel transit times, despite higher motility index in the Inuit population. In fact, the opposite situation where enteric hypomotility is present is often more frequent than gastroparesis itself. Thus, the rapid gastric emptying and the duodenal hypermotility are physiologically linked [14,17]. Furthermore, these findings also contrast a previous study investigating patients of comparable ages, who have had type 1 diabetes for 30 years and had confirmed distal symmetrical polyneuropathy, where panenteric prolongation of gastrointestinal transit times was shown with Smartpill [18]. However, since we do not have the status of diabetic peripheral neuropathy in these cohorts, the studies cannot be directly compared.

In conclusion, this study significantly contributes to our understanding of gastric emptying dynamics in diverse populations. By focusing on both genetic, and dietary factors, this research highlights the intricate relationship between ethnicity, diabetes, and gastro-intestinal physiology. The findings emphasise the importance of tailored interventions, considering individual differences in gastric emptying time, to enhance diabetes management strategies and improve overall digestive health.

Furthermore, this study opens avenues for future research, encouraging investigations into the underlying mechanisms linking genetics, diet, and gastric physiology, thereby paving the way for more effective, personalised diabetes care strategies.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

As Denmark and Greenland are under strict data protection laws, data cannot be made publically available, even in anonymised form. However, data can be provided by contacting the corresponding author, and will be made available to researcher who hold the required authorisations from the Danish and Greenlandic authorities.

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