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Wireless motility capsule compared with scintigraphy in the assessment of diabetic gastroparesis

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Abstract

Background: Gastroparesis is a potentially severe late complication of diabetes mellitus. Today, delayed gastric emptying (GE) is mandatory for establishing the diagnosis. In this study, we compared wireless motility capsule (WMC) with gastric emptying scintigraphy (GES).

Methods: Seventy-two patients (49 women) with diabetes mellitus (59 type 1) and symptoms compatible with gastroparesis were prospectively included between 2014 and 2018. Patients were simultaneously examined with GES and WMC. Symptoms were assessed with the Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM) questionnaire. All patients were on intravenous glucose-insulin infusion during testing.

Key Results: WMC and GES correlated $r = .74$, $P < .001$. Compared to GES, WMC at ordinary cutoff for delayed GE (300 minutes) had a sensitivity of 0.92, specificity 0.73, accuracy 0.80, and Cohen's kappa $\kappa = 0.61$ ($P < .001$). By receiver operating characteristics (ROC), the area under the curve was 0.95 ($P < .001$). A cutoff value for delayed GE of 385 minutes produced sensitivity 0.92, specificity 0.83, accuracy 0.86, and Cohen's kappa $\kappa = 0.72$ ($P < .001$). Inter-rater reliability for GE time with WMC was $r = .996$, $\kappa = 0.97$, both $P < .001$. There was no difference in symptom severity between patients with normal and delayed GE.

Conclusions & Inferences: Our findings demonstrate the applicability of WMC as a reliable test to assess gastric emptying in diabetic gastroparesis showing very high inter-observer correlation. By elevating the cutoff value for delayed emptying from 300 to 385 minutes, we found higher specificity without reducing sensitivity.

KEYWORDS
diabetes mellitus, gastric emptying, gastric emptying scintigraphy, gastroparesis, wireless motility capsule

1 | INTRODUCTION

Diabetic gastroparesis is a condition characterized by upper gastrointestinal (GI) symptoms and delayed gastric emptying (GE) without gastric outlet obstruction.[1] In addition to potentially debilitating symptoms of nausea, vomiting and upper abdominal pain, the condition may have profound implications for the patients' ability to regulate their blood glucose levels.[2,3] Delayed GE is associated with both short- and long-term hyperglycemia.[4] Gastroparesis may also influence the absorption of oral medications, emphasizing the need for reliable, inexpensive, and accessible tests for measuring GE.[5]

Gastric emptying scintigraphy (GES) has long been considered gold standard for evaluating GE in both research and clinical practice.[6] By radiolabeling a liquid or solid meal and tracking it by a gamma camera, the method gives a physiological, quantitative measurement of GE.[7] Unfortunately, a number of local variants of the test exist, both in terms of meal composition, and duration and frequency of imaging.[6,8] The radiation dosage also limits its applicability in certain patient groups.[9] Moreover, the availability of gamma cameras is reduced, in part due to high acquisition costs.

The wireless motility capsule (WMC; SmartPill, Medtronic) measures pH, pressure, and temperature throughout the GI tract, thereby providing the means for calculating GE.[10] WMC has since 2009 been approved by The United States Food and Drug Administration for the investigation of suspected gastroparesis and has in previous studies shown good agreement with scintigraphy.[8,11] However, there are few studies validating WMC against GES, highlighting the need for further research. To our knowledge, this is the first European study comparing the two methods in a cohort of diabetes patients with suspected gastroparesis.

The primary aim of this study was to assess the diagnostic reliability of WMC compared to GES for the measurement of GE. We also wanted to determine the WMC test's inter-rater reliability and identify the optimal cutoff value for delayed GE by WMC. A secondary aim was to identify proportions with rapid, normal, and delayed gastric emptying by the two methods. We also aimed to illuminate why some patients presented inconsistent test results (one positive/ one negative), by comparing with those showing delayed emptying on both tests. Finally, we wanted to compare symptom severity between patients with rapid, normal, and delayed gastric emptying.

2 | MATERIALS AND METHODS

2.1 | Study population

Seventy-two patients (49 women) with diabetes mellitus (DM) and symptoms consistent with gastroparesis were prospectively included between 2014 and 2018 (Table 1). Patients were recruited from all over Norway after being referred to Haukeland University Hospital for diagnostic evaluation. They were previously examined with upper endoscopy to rule out obstructing lesions or other pathology explaining their symptoms. Patients under 18 years of

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Key Points

- Gastroparesis is an important complication of diabetes mellitus, and detecting delayed gastric emptying is currently mandatory for establishing the diagnosis.
- Examining gastric emptying in a cohort of symptomatic diabetes patients, wireless motility capsule showed substantial agreement with scintigraphy.
- We found no differences in symptom severity between patients with normal and delayed gastric emptying by any of the tests.

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age and pregnant or breastfeeding women were not included in the study. During examinations, all patients were admitted to the hospital where they, in addition to tests and questionnaires, gave blood samples and were interviewed and examined by a physician. Medications potentially altering GI motility were paused in advance and during the study: proton pump inhibitors (seven days in advance), histamine H_2-receptor antagonists, opioid analgesics, nonsteroidal anti-inflammatory drugs, antidiarrheal drugs, prokinetic agents, and antiemetic drugs (3 days), laxatives (2 days), and other antireflux medications (24 hours).

2.2 | Gastric emptying tests

After an overnight fast of minimum 8 hours, GES and WMC testing were initiated simultaneously at 09:00 AM. Patients first consumed a standardized 260 kilocalorie (kcal; 66% carbohydrate, 17% protein, 2% fat, 3% fiber) nutrient bar (SmartBar, Medtronic), and a boiled egg (90 kcal; 1.1% carbohydrate, 13% protein, 11% fat, 0% fiber) radiolabeled with Tc-99m-nanocolloid.[12] Then, the WMC was swallowed, and scintigraphic imaging commenced immediately afterward. During the meal, patients could drink 120 mL of water. After swallowing the WMC, they fasted for another six hours, but were allowed to drink an additional 100 mL of water. During the fasting and examination period, all patients were on intravenous glucose-insulin infusion with frequent blood glucose measurements by finger-prick. Target levels were 4-10 mmol/L, and patients received intravenous glucose if they fell below 4 mmol/L.

2.2.1 | Gastric emptying scintigraphy

Simultaneous anterior and posterior planar scintigraphy of the upper abdomen (1 minute per view) were performed on a double-headed camera system (Siemens e.cam; Siemens Healthineers). Pictures were taken at 0, 30 minutes, 1, 2, 3, and 4 hours in accordance with current guidelines.[13] Images were quantified using Segami Oasis 1.9.4.9 (Segami Corp., Inc) by drawing a region of interest around the outline of the stomach at 0 minutes, which was

then copied onto images taken at other time-points (Figure 1). Gastric retention was quantified as the root mean square of the counts in the anterior and posterior regions of interest relative to the acquisition at 0 minutes.[13]

Normal retention value for GES at 4 hours is <10%.[6] Retention at 4-hour GES can be graded into mild (10%-15%), moderate (15%-35%), and severe (>35%).[14] Normative retention values for other time-points are given in Table 2.

2.2.2 | Wireless motility capsule

WMC is a 26.8 × 11.7 mm, non-digestible, single-use capsule, containing sensors for pH, temperature and pressure, a battery and a transmitter.[10,15] After activation, it transmits data to a portable receiver, which the patient carries close to the body during the entire examination.[15] Our patients were instructed to return the receiver after 5 days, whereupon data were downloaded to a personal computer using a USB docking device.

WMC transit times were calculated using MotiliGI software (Medtronic). WMC gastric emptying time (WMC GET) was defined as the time between capsule ingestion and passage through the pylorus, as marked by a rapid rise of >3 pH units (Figure 1). Delayed WMC GET is defined as >300 minutes (5 hours), severely delayed WMC GET >720 minutes (12 hours).[10,16,17] In cases of uncertainty, results were based on a consensus of two or more examiners. To calculate inter-rater reliability, all tests were re-analyzed by a different examiner, blinded for previous results. We also compared with automatically generated results by the MotiliGI software.

2.3 | Autonomic function tests

Cardiac autonomic function was assessed by a simple five-minute supine heart rate variability (HRV) recording, using the Heart Rhythm Scanner PE (Biocom Technologies). The system investigates both time and frequency domain parameters, and has been described and validated in detail elsewhere.[18] All recordings were performed in a fasting state by the same trained technician. The HRV recordings were reviewed offline by the second author, and minor editing (missing or misplaced beats) was performed. Recordings with persistent ectopic activities or frank arrhythmias were excluded from subsequent analyses.

2.4 | Questionnaires

Patients' symptoms were evaluated by the validated questionnaire Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM).[19] PAGI-SYM can be grouped into six subsets (Table 4), where the average of subset 1-3 make up the Gastroparesis Cardinal Symptom Index (GCSI).[20]

TABLE 1 Clinical characteristics

Variables	Results
All patients, n	72
Gender (♀/♂), n	49/23
Diabetes type (1/2), n	59/13
Employment status (on disability benefits/employed/student/retired), n	47/14/3/7
Marital status (single/married or cohabitant), n	23/48
Age, y	50 (19)
Diabetes duration, y	27 (22)
Symptom duration, y	4 (8)
BMI, kg/m^2	25.9 (7.5)
Smoking (never/current/previous), n	22/23/27
Alcohol (0/<1/1-7/>7 units/wk), n	26/24/17/4
Comorbid conditions (per patient), number	7 (6)
All medications (per patient), number	8 (7)
Opioid users, n (%)	19 (26%)
Diabetes treatment	
Insulin, n (%)	64 (89%)
Insulin pump, n (%)	27 (38%)
CGM, n (%)	7 (10%)
Metformin, n (%)	10 (14%)
GLP-1 agonists, n (%)	3 (4%)
SGLT-2 inhibitors, n (%)	3 (4%)
DPP-4 inhibitors, n (%)	2 (3%)
Other antidiabetic medication, n (%)	2 (3%)
Late complications	
All complications (0/1/≥2), n	20/18/34
Retinopathy, n (%)	40 (56%)
Nephropathy, n (%)	20 (28%)
Polyneuropathy, n (%)	34 (47%)
Diabetic wounds, n (%)	8 (11%)
Cardiovascular disease, n (%)	7 (10%)
Any other complication, n (%)	11 (15%)
Blood glucose values	
P-Glucose at test start, mmol/L	9.2 (4.3)
HbA1c, mmol/mol	65 (21)
Heart rate variability	
Mean HR at rest, BPM	74.1 (21.1)
SDNN, ms	21.5 (18.6)
RMSSD, ms	12.2 (16.1)

Note: Data are given as median and interquartile range unless otherwise indicated. Frequencies are given as n and valid percent.

Abbreviations: BMI, body mass index; CGM, continuous glucose monitor; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose co-transporter-2; DPP-4, dipeptidyl peptidase-4; HbA1c, glycated hemoglobin; HR, heart rate; BPM, beats per minute; SDNN, standard deviation of NN intervals (inter-beat intervals where artifacts are removed); RMSSD, root mean square of successive RR interval differences.
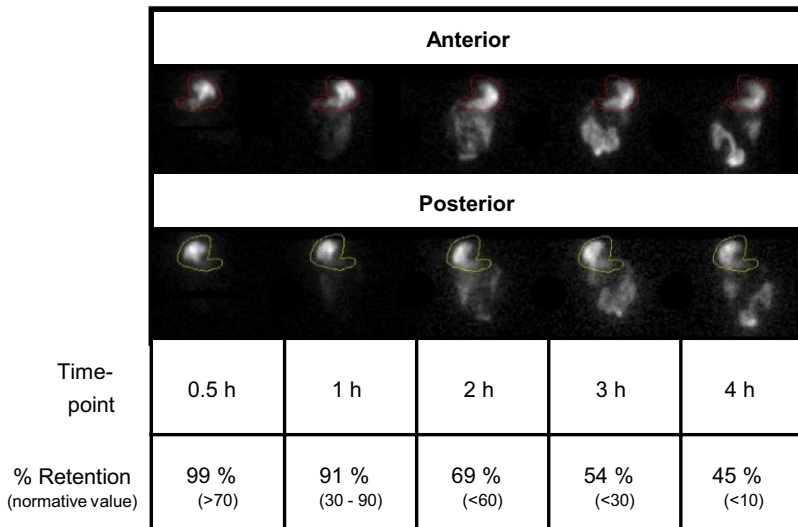
FIGURE 1 GES (top) and WMC results from a patient with diabetic gastroparesis. Both tests showed severe delay in gastric emptying, with 45% retention on 4-hour GES and a GET of 22 h 30 min. Abbreviations: GES, gastric emptying scintigraphy. WMC, wireless motility capsule. GET, gastric emptying time. IN, capsule ingestion. PY, pylorus. ICJ, ileocecal junction. EX, capsule expulsion

TABLE 2 Gastric emptying by GES and WMC
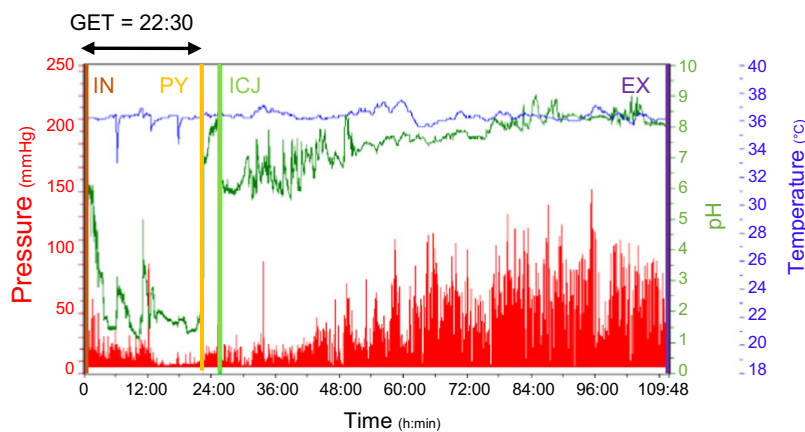
Variables (normative values)	Median (IQR)	Rapid	Normal	Delayed
GES (% retention)				
GES 30 min (>70)	91 (13)	7 (10.0%)	63 (90.0%)	–
GES 1 hour (30 - 90)	75 (28)	3 (4.2%)	53 (74.6%)	15 (21.1%)
GES 2 hours (<60)	35 (41)	–	51 (71.8%)	20 (28.2%)
GES 3 hours (<30)	15 (34)	–	47 (66.2%)	24 (33.8%)
GES 4 hours (<10)	5 (19)	–	43 (60.6%)	28 (39.4%)
WMC (min)				
GET (105-300)	350 (1397)	0	32 (47.8%)	35 (52.2%)

Note: Data are given as n (%) unless otherwise indicated. Normative values for GES from Abell et al (2008); for WMC from Wang et al (2015).[6,10]

Abbreviations: GES, gastric emptying scintigraphy; GET, gastric emptying time; IQR, interquartile range; WMC, wireless motility capsule.

2.5 | Statistical analysis

Results are stated as median (interquartile range, IQR). We treated sum scores from questionnaires as continuous variables. Spearman's rank-order correlation test was used for estimation of associations between continuous variables. Differences between groups were evaluated by Mann-Whitney *U* test for continuous variables and Pearson's chi-square test with Yates' continuity correction for categorical variables. For assessing the diagnostic performance of WMC compared to GES, we calculated correlation, sensitivity, specificity, positive and negative predictive values, accuracy, positive and negative likelihood ratios, Cohen's kappa measure of agreement, and a receiver operating characteristics (ROC) curve. To find the optimal cutoff value for GE by WMC, we calculated the maximum Youden's

index. $P \leq .05$ was defined as the level of statistical significance. Analyses were performed using IBM SPSS Statistics (Ver. 25, IBM Corporation).

2.6 | Ethical considerations

The study was approved by The Western Norway Regional Medical Ethics Committee (2015/58) and was conducted in accordance with the Declaration of Helsinki. Participants received oral and written information, and signed an informed consent prior to any study-related procedures.

3 | RESULTS

The study flowchart is shown in Figure 2. Detailed clinical characteristics are given in Table 1. Due to suspected capsule retention during test analysis, one patient was examined with an abdominal radiograph at her local hospital upon our request. No capsule was identified. Except for worsening of symptoms in some patients due to pause of medication, no other test related adverse events were reported during the study.

3.1 | Diagnostic test comparison

WMC and 4-hour GES correlated $r = .74$ ($P < .001$). Calculating the ROC curve, we found an area under the curve (AUC) of 0.95 ($P < .001$, 95% CI 0.89-1.00). The ROC curve is depicted in Figure 3. We identified 385 minutes as the optimal cutoff value for delayed WMC GET (Youden's $J = .75$). Detailed measures of accuracy for both WMC GET cutoff values are presented in Table 3.

Inter-rater correlation for identifying WMC GET between the two examiners was $r = .996$, while agreement was Cohen's kappa $\kappa = .97$ (95% CI 0.90-1.00), both $P < .001$. MotiliGI calculated WMC GET in 51 patients (75.0%). Correlation between examiner 1 and MotiliGI was $r = .967$, Cohen's kappa $\kappa = .96$ (95% CI 0.88-1.00), both $P < .001$. Correlation between examiner 2 and MotiliGI was $r = .965$ and agreement $\kappa = .92$ (95% CI 0.81-1.00), both $P < .001$.

3.2 | Gastric emptying test results

Median GE values and proportions with rapid, normal, and delayed GE are presented in Table 2. Using the 300 minutes cutoff, WMC identified 35 patients (52.2%) with delayed GE, compared to 28 patients (39.4%) with 4-hour GES, χ^2 (1) = 23.86, $P < .001$. With the 385 minutes cutoff value, 31 patients (46.3%) had delayed WMC GET, compared to 4-hour GES, χ^2 (1) = 32.21, $P < .001$. Twenty-seven (40.3%) had severely delayed WMC GET, compared to 10 (14.1%) with GES, χ^2 (1) = 9.48, $P < .01$. Severe retention by WMC and 4-hour
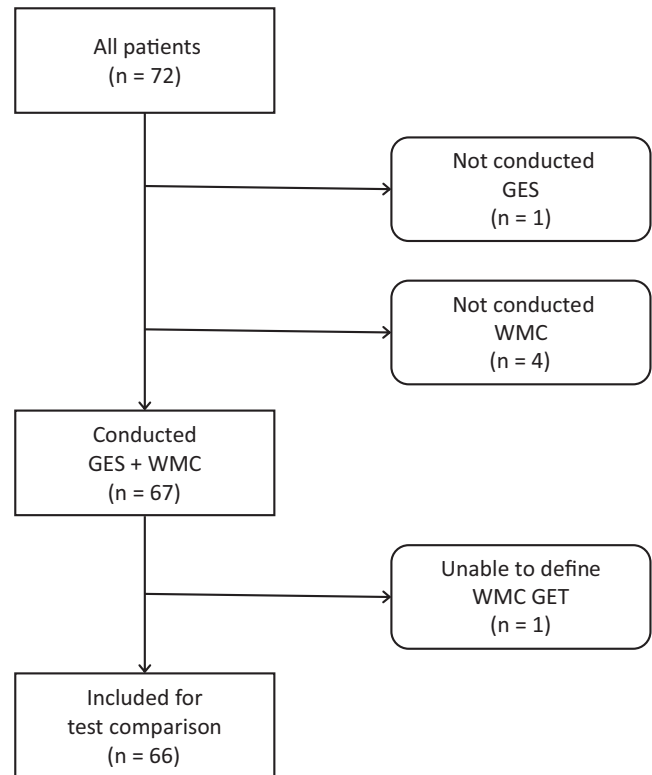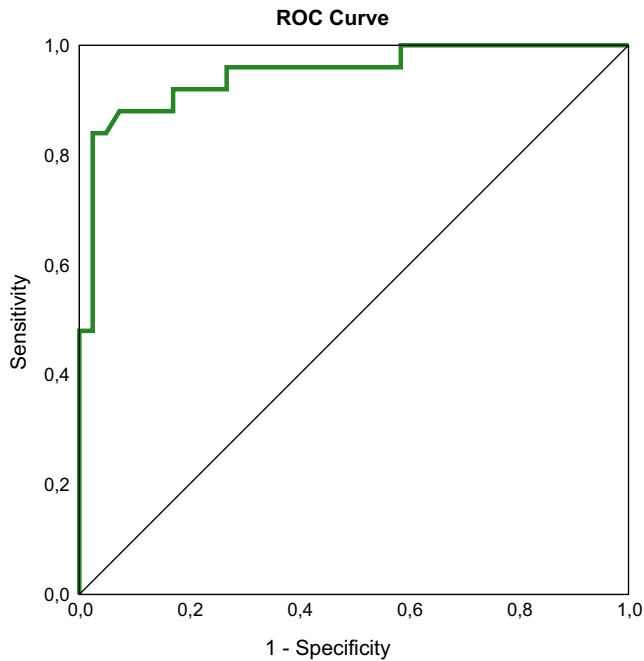

FIGURE 2 Study flowchart. Abbreviations: GES, gastric emptying scintigraphy. WMC, wireless motility capsule. GET, gastric emptying time

GES had an agreement of $\kappa = .34$ ($P < .001$, 95% CI 0.14-0.54). Five patients had mild (7.0%) and 13 (18.3%) moderate retention by GES.

In patients with Type 1 diabetes mellitus (T1DM), median WMC GET was 611 minutes (2372 minutes); in Type 2 diabetes mellitus (T2DM), it was 229 minutes (155 minutes), $P = .01$. Using the ordinary 300 minutes cutoff value, 32 out of 55 (58%) T1DM patients had delayed WMC GET; the same proportion in T2DM was 3 out of 12 (25%), χ^2 (1) = 3.12, $P = .08$. With the 385 minutes cutoff value, 31 (56%) with T1DM and 0 with T2DM had delayed GE, χ^2 (1) = 10.42, $P < .01$. Median retention at 4-hour GES was 8% (22%) in patients with T1DM; in T2DM, it was 2% (4%), $P = .02$. Using GES, 27 out of 59 (47%) with T1DM and only 1 out of 13 (8%) with T2DM had delayed GE, χ^2 (1) = 5.19, $P = .02$.

Making a cross-tabulation of test results, we found that 23 patients (35%) had delayed emptying in both 4-hour GES and WMC GET, while 11 (17%) had normal GES and delayed WMC GET. Only two patients (3%) had delayed GES and normal WMC GET, this group being too small for further statistical comparisons. In Table 4, we have compared selected clinical characteristics, symptom scores, gastric emptying test results, blood glucose values, and heart rate variability parameters (HRV) between those with consistent GE test results (both tests delayed; true positives) and those with inconsistent results (normal GES and delayed WMC GET; false positives).

ROC Curve

FIGURE 3 ROC curve for WMC GET compared to 4-hour GES showing an AUC of 0.95 (P < .001, 95% CI 0.89-1.00). Abbreviations: ROC, receiver operating characteristics. WMC, wireless motility capsule. GET, gastric emptying time. GES, gastric emptying scintigraphy. AUC, area under the curve. CI, confidence interval

3.3 | Symptom scores

Table 5 contains results for GCSI, PAGI-SYM, and all subsets, including a comparison between patients with normal and delayed GE by WMC (300 minutes cutoff) and GES at 4 hours. We found no difference between patients with normal and delayed emptying at any WMC GET cutoff values or GES time-points, both looking at each diabetes type separately and all patients combined. There was no difference in symptom severity between patients with normal and severe gastric retention at any of the tests. Neither WMC GET nor GES at any time point correlated with PAGI-SYM, GCSI or any of its subsets. Furthermore, we found no difference in symptoms between patients with normal and rapid GE. Finally, there was no difference in symptom severity between patients with T1DM and T2DM.

4 | DISCUSSION

In this prospective study, we aimed to validate WMC against GES in a patient cohort with DM and symptoms compatible with gastroparesis. We found a strong correlation between WMC and 4-hour GES, $r = .74$ ($P < .001$). With the standard cutoff value of 300 minutes, both sensitivity (0.92) and specificity (0.73) for identifying delayed GE were high, and the two methods showed substantial agreement demonstrated by Cohen's kappa $\kappa = .61$ ($P < .001$). These results are similar to previous studies comparing WMC and GES, where Kuo et

TABLE 3 Measures of diagnostic accuracy

Parameters	WMC GET (cutoff 300 min)	WMC GET (cutoff 385 min)
Sensitivity	0.92 (0.74-0.99)	0.92 (0.74-0.99)
Specificity	0.73 (0.57-0.86)	0.83 (0.68-0.93)
Positive predictive value	0.69 (0.57-0.79)	0.78 (0.64-0.87)
Negative predictive value	0.93 (0.79-0.98)	0.94 (0.81-0.98)
Accuracy	0.80 (0.69-0.89)	0.86 (0.76-0.94)
Positive likelihood ratio	3.43 (2.04-5.76)	5.39 (2.72-10.68)
Negative likelihood ratio	0.11 (0.03-0.42)	0.10 (0.03-0.37)
Cohen's kappa (κ)	0.61 (0.43-0.79, $P < .001$)	0.72 (0.55-0.89, $P < .001$)

Note: Data are given as number (95% confidence interval) unless otherwise indicated.

Abbreviations: GET, gastric emptying time; WMC, wireless motility capsule.

al found a correlation between WMC GET and 4-hour GES of $r = .73$ and Lee et al found a device agreement of $\kappa = .61$ in the diabetes subgroup.[8,11] However, in the latter study overall agreement was only moderate when also including patients without DM. In comparison with other methods for determining gastric emptying, WMC has a similar diagnostic accuracy to [13]carbon-labeled gastric emptying breath tests for solids (GEBT) and is far superior to gastric emptying of radiopaque markers (ROMs).[21,22] Other methods have not gained widespread usage outside research settings.[16]

We also found a near perfect inter-rater correlation ($r = .996$, $P < .001$) and Cohen's kappa ($\kappa = .97$, $P < .001$) for identifying WMC GET. For the evaluation of delayed GE, our findings indicate a high diagnostic accuracy of WMC, with interpretation of results being examiner independent. Interestingly, the correlations between each examiner and the MotiliGI software for estimating GET were also very strong. However, in as many as 25% of tests the software did not manage to calculate GET, compared to the one patient where manual analysis failed to make an estimation. Until further refinement of the software, manual test analysis is therefore essential.

Current normative transit time values for WMC are based on a study by Wang et al, examining 215 healthy, asymptomatic volunteers.[10] To identify the optimal cutoff value for delayed GE in our symptomatic DM cohort, we used ROC curve coordinates to find the maximum Youden's index. A value of 385 minutes increased the specificity to 0.83 without reducing sensitivity. Cohen's kappa was also increased to $\kappa = .72$ ($P < .001$). Consequently, by elevating the cutoff value, the risk of identifying false positives is reduced. One might therefore argue for the establishment of separate cutoff values for symptomatic diabetes patients, although we recommend further follow-up studies to confirm our findings.

At both cutoff values, a larger proportion of patients had delayed GE by WMC than GES. Lee et al propose a reasonable explanation for this discrepancy in the different physiological mechanisms used by the two tests: While GES examines the emptying of a gradually dissolving solid meal, the indigestible WMC is expelled from the

TABLE 4 Comparison of groups with false and true positive WMC GET results

Variables	GES normal/ WMC delayed	Both delayed	P-value
Clinical characteristics			
Age, y	55 (16)	38 (18)	<.01
Diabetes duration, y	31 (21)	24 (18)	.08
Symptom duration, y	12 (16)	6 (8)	.21
BMI, kg/m^2	25.1 (7.9)	23.1 (6.1)	.27
Symptom scores			
1) Nausea/vomiting	1.7 (2.7)	2.0 (2.0)	.33
2) Fullness/early satiety	2.3 (2.3)	3.3 (1.8)	.56
3) Bloating	3.0 (2.0)	3.3 (2.9)	.89
4) Upper abdominal pain	3.0 (2.5)	2.3 (2.4)	.76
5) Lower abdominal pain	4.0 (2.0)	2.3 (1.8)	.06
6) Heartburn/ regurgitation	1.6 (3.4)	1.5 (1.7)	.56
GCSI	2.2 (2.1)	2.9 (1.6)	.74
PAGI-SYM (total)	2.9 (2.2)	2.6 (1.3)	.64
Gastric emptying tests			
GES 4 hours, %	5 (4)	26 (36)	<.001
WMC GET, min	611 (811)	2737 (2155)	<.001
Blood glucose values			
P-Glucose at test start, mmol/L	7.8 (3.3)	9.5 (4.9)	.44
HbA1c, mmol/mol	62 (11)	72 (37)	.09
Heart rate variability			
Mean HR at rest, BPM	79.8 (19.1)	79.3 (23.1)	.98
SDNN, ms	23.8 (20.7)	17.6 (12.6)	.92
RMSSD, ms	10.6 (15.0)	10.9 (8.3)	.90

Note: In the table, we have compared patients with normal 4-hour GES and delayed WMC GET (false positives, left column) with patients with delayed emptying on both tests (true positives). Data are given as median and interquartile range unless otherwise indicated.

Abbreviations: BMI, body mass index; BPM, beats per minute; GCSI, Gastroparesis Cardinal Symptom Index; GES, gastric emptying scintigraphy; GET, gastric emptying time; HbA1c, glycated hemoglobin; HR, heart rate; PAGI-SYM, Patient Assessment of Upper Gastrointestinal Symptom Severity Index; P-Glucose, plasma glucose; RMSSD, root mean square of successive RR interval differences; SDNN, standard deviation of NN intervals (inter-beat intervals where artifacts are removed); WMC, wireless motility capsule.

stomach by the returning phase III of the migrating motor complex (MMC). In addition to measuring GE, the WMC may therefore also measure impairment of the MMC and dyscoordination of gastric and small bowel motility, leading the authors to argue that the WMC in fact has higher sensitivity for detecting gastroparesis than GES.[11]

Indeed, passage of the WMC does not occur before >90% of the meal has emptied.[8] As underlined by Kloetzer et al, WMC is therefore able to provide information about both gastric fasting and fed-state.[17] Interestingly, doing subgroup analyses, Lee et al found the same proportions with delayed emptying by both tests in diabetes patients.[11] The overall difference in their study was thus driven by the higher proportion with delayed emptying by WMC in the non-diabetic group.[11] To better understand the discrepancies in test results between the two methods, we compared patients with false-positive (normal GES and delayed WMC GET) and true-positive (both delayed) test results (Table 4). While glucose levels, HRV parameters, symptom scores, and clinical characteristics except for age were similar in both groups, the median WMC GET was more than 35 hours longer in the true positive group. This finding further bolsters the argument for increasing the cutoff value for delayed emptying in diabetes patients.

Wireless motility capsule also identified a higher proportion of patients with severe retention than GES. In this respect, we only found a fair agreement between the two methods ($\kappa = .34$, $P < .001$), similar to previous studies.[11] The most likely explanation is that definite cutoff values for severely delayed GET are not clearly established. WMC failed to identify any patients with rapid gastric emptying, while GES found three (4.2%) and seven (10.0%) at the 60 and 30 minutes time-points, respectively. Previous studies also found a higher share with rapid GE using GES.[11] Still, given that 20% of symptomatic diabetes patients may have rapid GE, it was surprising that we did not identify any cases using WMC.[23] Interestingly, the prevalence with delayed GE increased at each GES time point. This underlines the importance of following the recommended protocol of taking pictures until four hours to avoid false-negative tests.[6,14]

Previous studies comparing the symptom severity between patients with normal and delayed GE have shown inconsistent results.[24-26] In this study, we found no difference in PAGI-SYM, GCSI or any of their subsets between patients with normal and delayed GE. Neither did we find any differences comparing patients with normal and rapid emptying. This lack of association between GE and patient-reported symptoms is one of the main challenges in the field of gastroparesis research. The explanation is likely multifactorial. Firstly, patients with suspected diabetic gastroparesis often present a diversity of unspecific symptoms, not only limited to cardinal symptoms of nausea, vomiting, early satiety, fullness, and bloating, but often also abdominal pain, reflux, diarrhea, constipation, and fecal incontinence.[27-30] Adding to the confusion, delayed GE is present in 30%-50% with longstanding diabetes regardless of symptoms, probably as a consequence of autonomic neuropathy.[5,31-33] Secondly, there are multiple pathophysiological alterations associated with diabetic gastroparesis, both locally in the gut and in the autonomic and central nervous system.[28] Some of these, like the loss of interstitial Cells of Cajal, can be directly linked to the development of delayed GE.[34] Others may explain the genesis of gastrointestinal symptoms through different mechanisms, like abnormal central neuronal activity.[35,36] Although mostly

TABLE 5 Symptom scores and gastric emptying by GES and WMC

Variables	All patients	GES 4 hours			WMC GET 300 min		
		Normal	Delayed	P-value	Normal	Delayed	P-value
PAGI-SYM							
1) Nausea/vomiting	1.7 (2.3)	1.7 (2.1)	2.0 (2.0)	.37	1.3 (2.1)	2.0 (2.0)	.49
2) Fullness/early satiety	3.3 (1.8)	3.0 (1.75)	3.25 (1.5)	.39	3.3 (1.5)	3.3 (2.0)	.72
3) Bloating	3.4 (2.4)	3.5 (2.5)	3.0 (2.5)	.73	3.8 (2.4)	3.0 (2.5)	.95
4) Upper abdominal pain	3.0 (2.5)	3.5 (2.5)	3.0 (2.0)	.39	3.5 (2.0)	3.0 (2.5)	.32
5) Lower abdominal pain	2.5 (2.5)	3.0 (3.5)	2.0 (2.0)	.65	2.0 (3.3)	3.0 (2.0)	.26
6) Heartburn/regurgitation	1.6 (2.3)	2.3 (2.6)	1.4 (1.7)	.18	2.5 (2.6)	1.6 (1.7)	.30
GCSI	2.8 (1.5)	2.8 (1.6)	2.7 (1.3)	.72	2.9 (1.7)	2.8 (1.9)	.69
PAGI-SYM (total)	2.5 (1.4)	2.4 (2.1)	2.6 (1.3)	.75	2.5 (2.1)	2.6 (1.4)	.94

Note: Data are given as median and interquartile range unless otherwise indicated.

Abbreviations: GCSI, Gastroparesis Cardinal Symptom Index; GES, gastric emptying scintigraphy; GET, gastric emptying time; PAGI-SYM, Patient Assessment of Upper Gastrointestinal Symptom Severity Index; WMC, wireless motility capsule.

controlled for in studies, the influence of medication side-effects and other comorbidities on gastrointestinal symptoms, can also be a confounder. Finally, more than a quarter of patients with functional dyspepsia, a highly prevalent condition with symptoms mimicking gastroparesis also present with delayed GE.[24] An important goal for future gastroparesis studies must therefore be to identify other biomarkers better correlated to patient-reported symptoms. By expanding focus beyond the pylorus, recent studies have indeed uncovered a possible link between small bowel dysmotility and symptoms suggestive of gastroparesis.[37-39] Here, the WMC may play an important role in further research, providing pH and pressure profiles from gut segments otherwise largely unavailable for examination.[5,40,41]

Nevertheless, as the rate of GE is pivotal in determining postprandial glycaemia, its measurement will still be of great importance in diabetes patients, especially those presenting with unexplained fluctuations in blood glucose levels.[3] Consequently, the latest consensus statement on investigation of gastric motility recommends GE studies to be performed in patients with poorly controlled diabetes.[42] Furthermore, as clinical presentation alone can rarely differentiate between rapid and delayed emptying, it is recommended to determine GE in patients with symptoms compatible with gastroparesis, where upper GI endoscopy has not provided an explanatory diagnosis.[42] This is important, as the two entities of rapid or delayed GE may respond to entirely different therapeutic approaches.[26,43]

Compared to GES and other methods for evaluating gastric emptying, WMC has the great advantage of examining several GI regions during the same test. This is especially relevant in diabetes patients, often presenting multiregional dysmotility.[5,44] In contrast to GES, it does not involve radiation and has a universally standardized meal.[45] Furthermore, conduction of the test requires little training, transit time results are mostly easy to interpret, and the test equipment is not space consuming. It may therefore be suitable for regular

out-patient clinics, although its availability is so far mostly limited to tertiary centers.[46] Costs are comparable to GES, both tests being more expensive than GEBT and ROMs.[16,22] However, unlike other GE tests, where patients need to stay in the clinic for at least half a workday, commencing WMC testing rarely takes more than 30 minutes. During the rest of the examination, patients are ambulant. Consequently, the associated loss of productivity is less for both patients and clinicians.

There are some limitations to our study. To make the WMC protocol most similar to clinical practice, we used the standardized cereal bar supplied by the producer. To be able to perform the two GE tests simultaneously, we had to serve a radiolabeled egg as an addendum. This increased the total energy content of the meal by approximately 90 kcal. Higher calorie meals are expected to empty more slowly from the stomach, potentially increasing the proportion of patients with delayed GE. Furthermore, our cohort had a predominance of women and patients with Type 1 DM (Table 2). The gender distribution of gastroparesis between women and men is 4:1, while the cumulative incidence of gastroparesis is higher in Type 1 DM.[47] Still, the higher prevalence of Type 2 DM in the society makes this group underrepresented in the study population. While evaluating the WMC test's inter-rater reliability, we unfortunately did not perform an inter-observer agreement evaluation of GES. Finally, the study was conducted at a tertiary center receiving referrals from secondary healthcare institutions. Accordingly, our patient cohort may be more severely affected by their disease than diabetes patients treated in primary care.

A strength of the study was its prospective design and the simultaneous assessments with WMC and GES, thereby avoiding intra-individual variations in GE. During the study, all patients were admitted to the hospital, where they were on intravenous glucose-insulin infusion during both fasting and testing. Consequently, we were able to avoid major fluctuations in blood sugar levels potentially affecting GE, as well as preventing

iatrogenic hypoglycemia. Finally, our study is the largest prospective study validating the WMC in DM patients, increasing the robustness of our results.

In conclusion, our findings confirm the applicability of WMC as a highly reliable test for determining GE in diabetic gastroparesis diagnostics. By elevating the cutoff value for delayed GE from 300 to 385 minutes, we managed to improve the method's diagnostic accuracy further, possibly implying the need for separate cutoff values in symptomatic diabetes patients.

CONFLICT OF INTEREST
The authors have no competing interests.

AUTHOR CONTRIBUTIONS
Georg Dimcevski (GD) is guarantor of the article. Dag A. Sangnes (DS), Eirik Søfteland (ES), Martin Biermann (MBI), Odd Helge Gilja (OHG), and GD contributed to the design of the study. Mattis Bekkelund (MBE), MBI, and DS analyzed the tests. OHG and GD assisted for consensus evaluations. Jakub Frey (JF), MBE, and DS contributed to data entry. DS performed the statistical analysis. DS drafted the manuscript with contributions from MBI, ES, and GD. All authors were involved in critical revisions and approved the final version of the manuscript.

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DATA AVAILABILITY STATEMENT
Preliminary data from the study was presented at the NeuroGASTRO congress in Istanbul, Turkey, June 4-6, 2015.[40] An abstract from the study was presented at the NeuroGASTRO congress in Lisbon, Portugal, September 5-7, 2019.[48] Full study protocol can be accessed upon request.

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APPENDIX A

STARD 2015

Section & Topic	No	Item	Reported on page #
Title or Abstract			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
Abstract			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	1

Section & Topic	No	Item	Reported on page #
Introduction			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	2
	4	Study objectives and hypotheses	2
Methods			
Study design	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	2
Participants	6	Eligibility criteria	2
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	2
	8	Where and when potentially eligible participants were identified (setting, location and dates)	2
	9	Whether participants formed a consecutive, random or convenience series	2
Test methods	10a	Index test, in sufficient detail to allow replication	3
	10b	Reference standard, in sufficient detail to allow replication	2-3
	11	Rationale for choosing the reference standard (if alternatives exist)	2
	12a	Definition of and rationale for test positivity cutoffs or result categories of the index test, distinguishing prespecified from exploratory	3
	12b	Definition of and rationale for test positivity cutoffs or result categories of the reference standard, distinguishing prespecified from exploratory	2
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	3
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	2
Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy	4
	15	How indeterminate index test or reference standard results were handled	3
	16	How missing data on the index test and reference standard were handled	5 and Figure 2
	17	Any analyses of variability in diagnostic accuracy, distinguishing prespecified from exploratory	-
	18	Intended sample size and how it was determined	2, 5 and Figure 2
Results			
Participants	19	Flow of participants, using a diagram	Figure 2
	20	Baseline demographic and clinical characteristics of participants	Table 1
	21a	Distribution of severity of disease in those with the target condition	-
	21b	Distribution of alternative diagnoses in those without the target condition	-
	22	Time interval and any clinical interventions between index test and reference standard	2
Test results	23	Cross-tabulation of the index test results (or their distribution) by the results of the reference standard	5
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	5, Table 3 and Figure 3
	25	Any adverse events from performing the index test or the reference standard	5
Discussion			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalizability	8
	27	Implications for practice, including the intended use and clinical role of the index test	6-8
Other information			
	28	Registration number and name of registry	4
	29	Where the full study protocol can be accessed	9
	30	Sources of funding and other support; role of funders	1