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A longitudinal study on patients with diabetes and symptoms of gastroparesis – associations with impaired quality of life and increased depressive and anxiety symptoms

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ABSTRACT

Aims: To examine patient reported outcomes (PRO) in patients previously assessed for diabetic gastroparesis, and to investigate how symptoms of gastroparesis evolve over time. In addition, to further evaluate outcomes in those with versus without diabetic gastroparesis at baseline.
Methods: Thirty-four patients with diabetes and gastrointestinal (GI) symptoms, diagnosed with or without diabetic gastroparesis in 2011–2013, were included in this follow-up study. PRO were measured with the Patient assessment of upper gastrointestinal symptom severity index (PAGI-SYM), 36-Item Short Form Survey (SF-36), Patient assessment of upper gastrointestinal disorders-quality of life (PAGI-QOL) and Hospital Anxiety and Depression Scale (HADS). Demographic factors and clinical variables were also recorded.
Results: Participants diagnosed with gastroparesis had improved glycemic control ($p = 0.04$) and less GI symptoms ($p = 0.001$), after a follow-up time of 3.2 years (mean). Both groups reported severely impaired quality of life (QoL). In total 47% reported symptoms of anxiety, 38% symptoms of depression (scores ≥ 8). GI symptom severity or other PRO could not differentiate between the two groups.
Conclusions: Patients diagnosed with diabetic gastroparesis, as well as those with gastroparesis symptoms - but normal gastric emptying, suffer from severely impaired QoL and a high burden of anxiety and depressive symptoms.

1. Introduction

Gastrointestinal (GI) symptoms occur more frequently in patients with diabetes mellitus (DM) than in the general population, and are associated with impaired quality of life.[1,2] Complaints typically include nausea, vomiting, early satiety, bloating, and/or pain in the upper abdomen, often resulting in an evaluation for gastroparesis (GP).[3] This condition is defined as delayed gastric emptying without any mechanical obstruction. Autonomic neuropathy is believed to be a major pathomechanistic player, however a host of other causes have been implicated, including loss of interstitial cells of Cajal, autoantibodies, and direct effects of hyperglycemia.[4] On the other hand, clinical experience as well as numerous trials, have demonstrated poor – if any – correlation between gastric emptying and GI symptom severity in diabetes.[5–7] Consequently, a substantial proportion of such patients have normal gastric emptying. Existing treatment guidelines offer little advice for this patient group, and available research evidence is scant. In particular, the natural history of GI symptoms in DM, and their impact on quality of life and mental health is not well known.

Previous research suggests that patients with diabetic gastroparesis have reduced quality of life.[8,9] However, these data were not systematically or prospectively collected. Looking at depression and anxiety in these patients, Hasler et al. found higher prevalences, although these correlated only with patient and physician reported severity of gastroparesis, not with gastric emptying rate.[10] Between 2011 and 2013, a survey investigating autonomic and somatic neuropathy among people with DM and GI symptoms was conducted at Haukeland University Hospital, Bergen, Norway (the "DINGO trial"). In the study, gastric emptying rate and other autonomic functions such as heart rate variability and orthostatism were examined. Some participants were diagnosed with diabetic gastroparesis (GP group), some received other explanations to their symptoms, and others did not get any organic (somatic) diagnosis (non-GP group). The aim of the present follow-up study was to re-evaluate this patient cohort in order to investigate how symptoms of gastroparesis evolve over time, and to examine patient

Conflict of interest: The authors declare that there are no conflicts of interest.

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reported outcomes such as quality of life and symptoms of anxiety and depression. In addition, we also aimed to further characterize those diagnosed with vs. without diabetic gastroparesis at baseline.

2. Subjects, material and methods

We invited all patients who were previously (2011–2013) referred to Haukeland University Hospital with a clinical suspicion of diabetic gastroparesis to participate. Inclusion criteria at baseline (2011–2013) were age between 18 and 80 years, DM and symptoms suggestive of gastroparesis. Exclusion criteria were pregnancy or lactation, hypersensitivity to food items used in the tests, severe renal failure, heart failure or unstable cardiovascular or cerebrovascular disease, mental or other physical disease that by investigator assessment could impede participation. All patients underwent gastroscopy prior to referral to exclude obstructive processes or other pathology that could explain the symptoms (i.e. peptic ulcers, gastritis). Those who used drugs that were known to affect gastrointestinal motility (in total six patients) were advised to put these on hold at least 24 h prior to – as well as during – testing. Medical treatment at baseline, as well as at follow-up is listed in Supplementary Table A. All gastric emptying tests were performed on an intravenous glucose-insulin infusion, aiming at avoiding excessive glucose levels that might impact the results. The gastroparesis diagnosis was based on a clinical evaluation on the basis of three tests of gastric emptying (^{13}C-octanoic acid breath tests of liquid and solid meals, as well as radiopaque marker examinations). Two or more pathological tests were defined as gastroparesis.[11,12] Finally, two groups could be defined: those with delayed gastric emptying (GP group, n = 19) and those with normal emptying (non-GP group, n = 15).

The GP group received advice on blood glucose handling and medical treatment, as well as dietary counseling (one session upon diagnosis, near baseline). However, the escalation of GP treatment was primarily at the discretion of the referring physician. The suggested medications were metoclopramide, erythromycin and prucalopride. Furthermore, eight patients also had surgical implantation of gastric electric stimulator. The patients in the non-GP group received no specific intervention in the study. They were followed by their primary diabetologist, and were only provided with general advice on the importance of good glucose control.

As part of the present follow-up study, GI symptoms were re-evaluated after a mean period of 3.2 years. Those who were diagnosed with other organic diseases explaining the GI symptoms at baseline, and pregnant or lactating women were excluded from the follow-up (n = 6). In total, 40 eligible participants were invited. Thirty-four of these patients were included in this prospective cohort study, the rest are non-responders or did not wish to participate (n = 6) (Fig. 1).

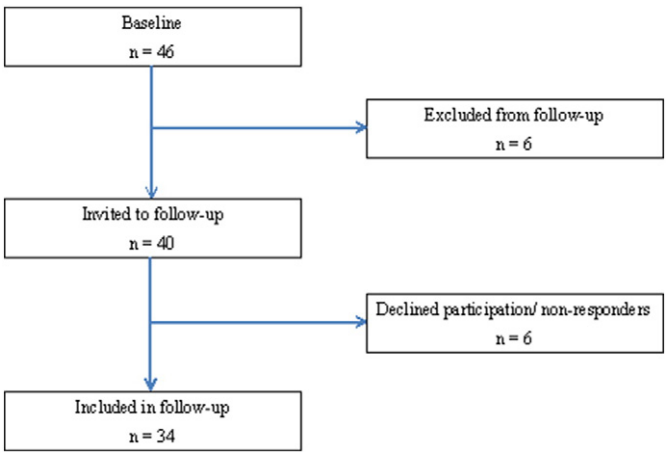

Fig. 1. Study participants.

2.1. Demographics and clinical variables

At the follow-up visit demographics, assessment of treatment regime since baseline, dietary changes and development of diabetes complications were registered. Also, glycated hemoglobin (HbA1c) levels, as well as other relevant urine and blood biochemistry, were assessed. Microalbuminuria was defined as urine albumin/creatinine ratio > 3.0 mg/mmol and nephropathy as serum creatinine > reference area (gender/age specific) or GFR < 60 ml/min/1.73 m^2. Other complications were based on patient-reported medical history.

2.2. Questionnaires

To assess symptoms of gastroparesis, quality of life and symptoms of anxiety and depression, patients were asked to complete the following questionnaires:

2.2.1. Severity of GI symptoms

To assess the severity of symptoms of gastroparesis, "Patient assessment of upper gastrointestinal symptom severity index" (PAGI-SYM) was used.[13] This validated questionnaire is designed to assess the severity of gastrointestinal symptoms in people with gastroesophageal reflux disease, dyspepsia and gastroparesis. The questionnaire contains 20 symptom descriptions within six categories. Each symptom should be marked on a scale of 0–5 depending on how serious symptoms have been in the past two weeks; with zero being no symptoms and five very serious symptoms. Sub-scale scores are calculated by taking the mean of non-missing items in each subscale, total score is calculated by taking the mean of the subscales. If >50% of items in a sub-scale are missing, the sub-scale score and total score are defined as missing.[13] The questionnaire has previously been translated, validated and used in Norwegian.[9,14] The instrument has shown satisfactory sensitivity and specificity.[13,15]

2.2.2. Health-related quality of life

General health-related quality of life (HRQoL) was measured with the 36-Item Short Form Survey (SF-36).[16,17] The instrument assesses and measures eight dimensions of quality of life, as well as one question for identifying health development over the past year. For each question the answers are transcoded into a 0–100 scale for each dimension, and higher scores indicate better HRQoL. The questionnaire has shown good psychometric properties in patients with gastroparesis, and is significantly correlated with worsening of the total PAGI-SYM scores and measures.[18,19] The instrument is translated and validated into a Norwegian version, and the scales and items have been shown to have a satisfactory reliability and validity.[20,21] This generic and global QoL tool may capture more commonly experienced health domains, but may not accurately reflect the experience of gastroparesis symptoms.[22]

2.2.3. Disease-specific quality of life

The Patient Assessment of Upper GastroIntestinal Disorders-Quality of Life (PAGI-QOL) questionnaire assesses symptom-specific quality of life in patients with upper gastrointestinal diseases, has been validated for use in patients with dyspepsia, gastroesophageal reflux and gastroparesis, and has shown good psychometric properties.[18] This instrument consists of 30 questions each having a 6-point scale within five categories. A sub-scale score is calculated as the mean of the items in the sub-scales after reversing item scores. Sub-scale scores range from zero (lowest QoL) to five (highest QoL). A total score is defined as the mean of all sub-scale scores. In case of missing data, the half-scale rule was applied (as for the PAGI-SYM questionnaire).[18]

2.2.4. Symptoms of anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) questionnaire consists of seven questions relating to anxiety and seven questions

relating to depression. Each item consists of a scale from zero to three. For both subscales (anxiety and depression) a score of 8–10 is considered a possible case, and a score of 11 or more is considered to be a probable case of anxiety or depression.[23,24] Missing substitution was performed for individuals who responded to five or six of the seven HADS-subscale questions. This was done by multiplying the score obtained by 7/5 if five of the seven questions were answered and by 7/6 if six questions were answered.[24] The questionnaire is validated, has been used in Norway and has shown good psychometric properties, including sensitivity and specificity.[25,26]

2.3. Data analysis

Continuous data are presented as mean and standard deviation (SD) unless otherwise stated, while nominal values are presented as number of cases with percentages. Throughout, the statistical significance level was defined as $p < 0.05$. To compare the two groups, *t*-test was used for continuous data and chi-square test was used for nominal/categorical values. Fisher's exact test was used instead of chi-square when assumptions for expected counts were not met. Paired t-test was used to examine differences between baseline and follow-up in the two groups. Scores from questionnaires were treated as continuous variables. Additional non-parametric tests have been performed and no differences in significance levels were detected (not reported). For patient reported outcomes, Cohens's d was reported as measurement of effect size, where effect sizes were classified as small (d = 0.2), medium (d = 0.5), and large (d ≥ 0.8).[27] SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

2.4. Ethics

The study was approved by The Western Norway Regional Medical Ethics Committee (REK 2014/2169). Oral and written informed consent was obtained from all participants, prior to study participation and any study-related procedures.

3. Results

3.1. Clinical characteristics

Participants' clinical characteristics at baseline and follow-up are presented in Table 1. There were no differences between the two groups (i.e. GP vs. non-GP at baseline) in terms of age, DM duration, demographic characteristics or life style variables such as alcohol consumption and smoking status. The two groups had similar distribution of gender and diabetes type, although overall there were more women (68%) than men, and a higher proportion of participants with type 1 (85%) vs. type 2 DM. HbA1c at baseline was significantly higher in the GP group (10.4% (SD 2.5)) than in the non-GP group (8.0% (SD 1.2)), $p = 0.001$. At follow-up this difference was no longer present ($p = 0.11$). Hence, glycemic control improved from baseline to follow-up in the GP group (mean HbA1c changed by 1.1%, $p = 0.04$), whereas in the non-GP group there was no significant change ($p = 0.33$). Between-group comparisons showed that BMI (Body Mass Index) was higher in non-GP patients at follow-up ($p = 0.02$), whereas the GP group was more likely to be diagnosed with retinopathy, both at baseline ($p = 0.02$) and at follow-up ($p = 0.01$). Finally, at follow-up a history of diabetic foot ulcer was seen more frequently in the GP group ($p = 0.01$).

3.2. Patient reported outcomes

3.2.1. Severity of GI symptoms

Baseline and follow-up data showed no significant differences between groups in terms of severity of gastroparesis symptoms, measured by the PAGI-SYM sub-scales or total score (Table 2). However, there was a significantly improved (lower) PAGI-SYM total score within the GP group from baseline to follow up (2.9 (SD 0.6) vs. 2.1 (SD 0.8), $p = 0.001$, Cohen's d = 1.19). This improvement was not seen in the non-GP group (2.7 (SD 1.1) versus 2.4 (SD 1.1), $p = 0.11$, Cohens's d = 0.29) (Table 3).

3.2.2. Health–related quality of life

There were no significant differences between the groups with and without diabetic gastroparesis in terms of HRQoL, as measured by the

Table 1
Clinical characteristics.[a]

Variables	Baseline					Follow-up				
	Total	Missing n (%)	GP group	Non-GP group	*p*-Value	Total	Missing n (%)	GP group	Non-GP group	*p*-Value
Age, years (SD)	45.7 (10.1)	0	43.0 (7.3)	49.1 (12.2)	0.10	48.9 (9.9)	0	46.2 (7.3)	52.3 (11.9)	0.10
Gender		0			1.00					
Male, n (%)	11 (32)		6 (32)	5 (33)						
Female, n (%)	23 (68)		13 (68)	10 (67)						
Diabetes type 1, n (%)	29 (85)		17 (89)	12 (80)						
Diabetes type 2, n (%)	5 (15)	0	2 (11)	3 (20)	0.63					
Diabetes duration, years (SD)	24.2 (9.6)	0	26.1 (7.9)	21.9 (11.2)	0.23	27.0 (9.7)	1 (3)	28.4 (8.1)	25.3 (11.3)	0.37
BMI (kg/m^2) (SD)	24.3 (4.5)	25 (77)	23.2 (4.7)	26.6 (3.9)	0.30	26.2 (4.9)	2 (6)	24.5 (4.7)	28.5 (4.4)	**0.018**
HbA1c (%) (SD)	9.5 (2.3)	2 (6)	10.4 (2.5)	8.0 (1.2)	**0.001**	8.4 (1.7)	3 (9)	8.8 (1.9)	7.9 (1.2)	0.11
$HbA1_c$ (mmol/mol)	80 (25.1)		90 (26.9)	64 (12.6)		68 (18.6)		73 (20.8)	63 (13.1)	
Smoking, n (%)	11 (34)	2 (6)	8 (42)	3 (23)	0.45	8 (26.7)	4 (12)	7 (41)	1 (8)	0.09
Alcohol units/week, median (range)	1.25 (0–8)	12 (35)	0.25 (0–4)	2.00 (0–8)	0.20	0.50 (0–11)	5 (15)	0.13 (0–11)	1.00 (0–8)	0.07
Retinopathy, n (%)	21 (68)	3 (9)	14 (88)	7 (47)	**0.02**	22 (69)	2 (6)	16 (89)	6 (43)	**0.008**
Nephropathy, n (%)	9 (33)	7 (21)	7 (54)	2 (14)	0.05	8 (27)	4 (12)	7 (41)	1 (8)	0.09
Microalbuminuria[b], n (%)	13 (50)	8 (24)	8 (57)	5 (42)	0.43	12 (39)	3 (9)	7 (41)	5 (36)	0.76
Neuropathy, n (%)	16 (53)	4 (12)	11 (69)	5 (36)	0.07	18 (64)	6 (18)	11 (69)	7 (58)	0.70
History of foot ulcer, n (%)	8 (31)	8 (24)	7 (44)	1 (10)	0.10	13 (45)	5 (15)	11 (65)	2 (17)	**0.01**
CVD[c], n (%)	3 (12)	9 (27)	2 (15)	1 (8)	1.00	6 (22)	7 (21)	4 (24)	2 (20)	1.00

Data are means (±SD) unless otherwise indicated. Significant *p*-values in bold.

[a] Total population n varies somewhat for each characteristic depending on the actual completion of the questionnaires or tests (missing range 0–25).

[b] Microalbuminuria is defined as u-albumin/creatinine ratio > 3.0 mg/mmol and nephropathy is defined as s-creatinine > reference area (gender/age specific) or GFR <60 ml/min/1,73 m^2. Other complications, including cardiovascular.

[c] Are reported based on patient-reported medical history.

Table 2
PAGI-SYM scores.

Sum score (0–5)	Baseline			Follow-up		
	Total n = 30[a]	GP group n = 17	Non-GP group n = 13	Total n = 33[a]	GP group n = 18	Non-GP group n = 15
Nausea/vomiting (SD)	2.3 (1.3)	2.6 (1.2)	2.0 (1.4)	1.2 (1.0)	1.3 (0.9)	1.1 (1.2)
Post-prandial fullness/early satiety (SD)	3.1 (1.1)	2.8 (1.0)	3.4 (1.1)	2.6 (1.2)	2.3 (1.1)	2.9 (1.3)
Bloating (SD)	3.4 (1.6)	3.6 (1.5)	3.0 (1.7)	3.0 (1.3)	3.0 (1.3)	3.1 (1.4)
Upper abdominal pain (SD)	3.0 (1.7)	3.4 (1.3)	2.4 (2.0)	2.5 (1.3)	2.8 (1.2)	2.1 (1.5)
Lower abdominal pain (SD)	2.9 (1.4)	2.7 (1.3)	3.1 (1.6)	2.3 (1.5)	2.2 (1.3)	2.4 (1.7)
Heartburn/regurgitation (SD)	2.1 (1.4)	2.1 (1.3)	2.1 (1.5)	1.2 (1.2)	1.0 (1.1)	1.5 (1.2)
Total score (SD)	2.8 (0.8)	2.9 (0.6)	2.7 (1.1)	2.1 (0.9)	2.1 (0.7)	2.2 (1.1)

Data are means (±SD).
[a] Four missing at baseline, one missing at follow-up. All *p*-values > 0.05.

SF-36 sub-scale scores and physical health and mental health summary scores. The GP group reported the lowest score (29 (SD 21)) in "General Health" whereas the non-GP group reported the lowest score in "Bodily Pain" (28 (SD 23)) and "Vitality" 28 (SD 27)) (Table 4).

3.2.3. Disease-specific quality of life

PAGI-QOL scores showed no significant differences in symptom specific quality of life between the two groups. The GP group reported a total score of 3.1 (SD 1.2), while the non-GP group reported a total score of 2.7 (SD 1.5) (NS), where a higher score indicate higher quality of life (Table 4).

3.2.4. Symptoms of anxiety and depression

In total, 47% (18 of 34) of the participants reported anxiety symptoms (score ≥ 8) and 38% (13 of 34) depressive symptoms (score ≥ 8). Mean anxiety symptom scores were 7.2 (SD 5.5) in the GP group and 8.9 (SD 5.8) in the non-GP group (NS), while depression scores were 5.4 (SD 5.0) in the GP group versus 7.4 (SD 5.1) in the non-GP group (NS). In the GP group 42% reported an elevated anxiety symptom level (score ≥ 8) and 32% an elevated depression symptom level (score ≥ 8), while in the non-GP group the corresponding rates were 53% and 47% (NS) (Table 4).

4. Discussion

In DM patients with gastroparesis, GI symptoms and glycemic control improved from baseline to follow-up. However, the same improvements in GI symptoms were not seen in those not diagnosed with gastroparesis. Moreover, there were no differences in patient reported outcomes (symptoms of gastroparesis, quality of life and symptoms of anxiety and depression) between the two groups at follow-up.

4.1. Clinical characteristics

Improved HbA1c levels in the GP group at follow-up may reflect successful treatment of delayed gastric emptying, thus improving the glucose control. Another possibility is a reverse relationship between these variables, i.e. that poor glycemic control at baseline induced slowing of the gastric emptying. It is, at present, not completely clear how much long-term glucose control affects the gastric emptying.[3,8] Due to the cross-sectional nature of the baseline data, this cannot be conclusively decided.

At baseline, the GP group had higher HbA1c and more frequently retinopathy, while at follow-up this group also had more often a history of foot ulcers. These findings harmonize with the theory that autonomic neuropathy often develops in patients with poor glycemic control, and in tandem with other diabetic complications.[28]

4.2. Patient reported outcomes

Interestingly, in terms of GI symptoms severity, no differences were found between those with and without gastroparesis. Hence, from a clinical perspective, GI symptom questionnaires are not useful biomarkers when it comes to distinguishing these two groups. In concordance with our finding, a number of previous studies have shown that there is only a weak – if any – correlation between symptom severity and degree of delayed gastric emptying.[5–7,29] Measuring and comparing the gastric emptying rate is challenging, due to several tests available, large inter- and intraindividual variability, as well as the influence of acute hyperglycemia. In this study, the groups were defined based on the results of three different tests measuring gastric emptying, thus increasing the robustness of the results. Also, all patients were on glucose-insulin infusion, limiting the effects of acute glycemia. Therefore, our outcomes add further support to the notion that delayed gastric emptying is not necessarily associated with the GI symptom burden. At follow-up, on average 3.2 years later, there were still no differences in symptom severities. Both groups tended to have less symptoms at follow-up, however this was clearly more pronounced in the GP group. This improvement from baseline to follow-up may reflect treatment effects or it might reflect the positive gain of getting a diagnosis and receiving an explanation for burdensome symptoms.

Patients in both groups reported very low HRQoL scores at follow-up. This result indicates that both groups have a heavy disease burden. We did not detect a difference between the groups. If any, the non-GP patients tended to have the worst results. Both groups reported SF-36 scores that were 30–60% lower than the Norwegian population in

Table 3
Repeated measures of PAGI-SYM scores.

Sum score (0–5)	GP group n = 16[a]				Non-GP group n = 13[a]			
	Baseline	Follow up	Cohen's d	*p*-Value	Baseline	Follow up	Cohen's d	*p*-Value
Nausea/vomiting (SD)	2.5 (1.2)	1.3 (1.0)	1.10	**0.005**	2.0 (1.4)	1.3 (1.2)	0.55	**0.02**
Post-prandial fullness/early satiety (SD)	2.8 (1.1)	2.2 (1.2)	0.49	0.07	3.4 (1.1)	3.2 (1.3)	0.24	0.27
Bloating (SD)	3.8 (1.4)	3.1 (1.3)	0.54	0.10	3.0 (1.7)	3.3 (1.5)	−0.15	0.52
Upper abdominal pain (SD)	3.5 (1.1)	2.8 (1.2)	0.64	**0.04**	2.4 (2.0)	2.3 (1.4)	0.02	0.92
Lower abdominal pain (SD)	2.8 (1.3)	2.2 (1.3)	0.49	0.07	3.1 (1.6)	2.5 (1.8)	0.36	0.06
Heartburn/regurgitation (SD)	2.1 (1.3)	1.1 (1.2)	0.78	**0.03**	2.1 (1.5)	1.6 (1.2)	0.35	0.22
Total score (SD)	2.9 (0.6)	2.1 (0.8)	1.19	**0.001**	2.7 (1.1)	2.4 (1.1)	0.29	0.11

Data are means (±SD).
[a] Three missing in GP group, two missing in non-GP group. Significant *p*-values in bold.

Table 4
SF 36, PAGI-QOL and HADS score.

Score	Total n = 34[a]	GP group n = 19[a]	Non-GP group n = 15[a]
SF 36 score (0–100)			
Physical function sum score (SD)	66 (27)	69 (25)	61 (29)
Role physical sum score (SD)	39 (42)	42 (43)	35 (41)
Bodily pain sum score (SD)	36 (27)	43 (28)	28 (23)
General health sum score (SD)	33 (23)	29 (21)	39 (25)
Vitality sum score (SD)	34 (29)	39 (31)	28 (27)
Social function sum score (SD)	56 (34)	61 (29)	48 (39)
Role emotional sum score (SD)	54 (45)	67 (46)	38 (40)
Mental health sum score (SD)	63 (25)	64 (27)	61 (23)
Physical health summary score (SD)	37 (10)	37 (9)	37 (11)
Mental health summary score (SD)	41 (15)	43 (16)	38 (14)
PAGI-QOL score (0–5)			
Daily activities (SD)	2.8 (1.4)	3.0 (1.3)	2.5 (1.6)
Clothing (SD)	2.8 (1.7)	3.0 (1.6)	2.7 (1.9)
Diet (SD)	2.8 (1.5)	3.0 (1.4)	2.5 (1.6)
Relationship (SD)	3.3 (1.7)	3.3 (1.5)	3.2 (1.9)
Psychological (SD)	2.9 (1.3)	3.1 (1.3)	2.7 (1.4)
Total score (SD)	2.9 (1.3)	3.1 (1.2)	2.7 (1.5)
HADS			
Anxiety score (SD) (0–21)	8.0 (5.6)	7.2 (5.5)	8.9 (5.8)
Depression score (SD) (0–21)	6.3 (5.1)	5.4 (5.0)	7.4 (5.1)
Anxiety score ≥ 8	47%	42%	53%
Anxiety score ≥ 11	35%	32%	40%
Depression score ≥ 8	38%	32%	47%
Depression score ≥ 11	21%	16%	27%

Data are means (±SD) except for HADS score presented in percentage. All p-values > 0.05.
[a] Total population (n) varies some for each characteristic depending on the actual completion of the questionnaires (missing range 0–1).

general.[20] This is in line with reports from studies including patients with gastroparesis, diabetic gastroparesis and patients with DM and GI symptoms.[2,8,9,30]

Our results emphasize that the non-GP patients have at least as much symptoms of anxiety and depression as those with diabetic GP. Previous research has reported an association between gastroparesis, the reporting of GI symptoms and a high level of anxiety and/or depressive symptoms in people with DM[30,31,42]. In spite of being a burdensome diabetes complication, merely 19% of persons with DM and a history of foot ulcer reported anxiety symptoms (score ≥ 8) in a large Norwegian population-based survey (the HUNT2 study), whereas the corresponding rates in our study were 42% and 53% (with and without GP).[32] Furthermore, in the HUNT2 study, 19% of persons with DM and foot ulcer reported depressive symptoms (score ≥ 8), while the corresponding findings in our study were 32% and 47% (with and without GP). Although direct comparison is inappropriate due to differences in terms of population and study context, the results still indicate a high rate of such symptoms in our patient cohorts.

Based on the above, it seems fair to conclude that patients with DM and symptoms of gastroparesis, struggle with a heavy burden of anxiety and depressive symptoms, and severely impaired quality of life. While those diagnosed with gastroparesis are offered ample medical attention such as dietary counselling, drug treatment etc., those with symptoms but no gastroparesis diagnosis may be lacking a structured health care follow-up. As GI and anxiety/depression symptoms may negatively affect one another, we postulate that this group might need more medical attention in order to break this vicious circle. Future prospective intervention studies should investigate this issue further.

4.3. Patients with symptoms of gastroparesis but normal gastric emptying (the non-GP group)

Our study describes the symptoms and quality of life of a poorly understood subgroup with DM and symptoms compatible with gastroparesis, but with normal gastric emptying. A number of possible explanations of their complaints could be postulated. Based on established diagnostic criteria (the Rome IV), the patients could be classified as suffering from various functional gastroduodenal disorders, such as functional dyspepsia, belching, and/or nausea and vomiting disorder.[33] Indeed, diabetes – being a challenging chronic condition, is associated with a near doubled lifetime prevalence of anxiety and two to three times elevated risk of depression.[34,35] Other studies have shown that psychological distress – as well as anxiety and depression – are associated with GI symptoms in DM.[31,36] On the other hand, a common finding in functional GI conditions is visceral hypersensitivity, whereas we have previously found hyposensitivity in a mixed cohort of diabetes patients with GI symptoms and both delayed and normal gastric emptying.[9,37] Our results indicate that other mechanisms may be involved. These could include enteric and/or visceral neuropathies that do not affect gastric emptying, other gastrointestinal (i.e. intestinal) dysmotilities, altered central processing of gut signals etc. Recently, new technologies such as wireless motility capsules, have enabled a more thorough investigation of total GI motility.[38,39] Such techniques are likely to further characterize and possibly sub-classify this patient group.

4.4. Study strength and limitations

The main strength of this study is that we systematically and prospectively collected data in patients with clinical suspicion of diabetic gastroparesis, regardless of gastric empting rates. Few – if any – studies have prospectively followed and characterized patients with symptoms but normal gastric emptying (non-GP group), thus our results could have impact on the understanding of this condition. Another major strength of the study is that we relied on a wide array of validated patient reported outcome instruments to measure health-related quality of life, disease specific quality of life, anxiety- and depressive symptoms and GI symptoms. However, this study has several limitations. First of all, the small number of participants clearly limits the statistical power, in particular when reporting on PROs. Nevertheless, these results may still give implications for further research by highlighting a group of patients that has not previously been well described. Sampling bias is always of concern. Being recruited from a tertiary university hospital, the original "DINGO" study probably included the most severe cases, not necessarily representative of all DM patients with GI complaints. In our follow-up study a total of 85% of the potential participants

were included. We believe this response-rate should limit the possibility for responder bias.[40] Non-responders tend to report more advanced disease than responders, hence the burden of this patient group might even be underestimated.[41] Further, several of the patient-reported outcomes are only available at follow-up, hence these data are therefore cross-sectional. Causal directions cannot be inferred from these cross-sectional data for which predictor and outcome variables were reported simultaneously. Finally, a number of medications may affect both gastric emptying results, as well as GI symptoms. Although attempts were made to limit such confounders, we cannot rule out an impact on our findings. In spite of these limitations, this study should provide a reasonable representation of patients with symptoms of diabetic gastroparesis.

5. Conclusion

We conclude that the symptom burden – as well as quality of life – was not different in diabetes patients with GI symptoms with versus without gastroparesis. Hence, commonly used symptom scores could be unable to differentiate between these conditions. We postulate that the group with GI symptoms but normal gastric emptying is particularly poorly understood and in need of increased clinical attention. In line with this, glycemic control, as well as symptom severity improved from baseline to follow-up in the gastroparesis group only. In both groups, with and without gastroparesis, a higher proportion of the patients reported symptoms of anxiety and depression and impaired quality of life, compared to normal population or patients with other chronic conditions, indicating the strong influence of GI symptoms on general health as perceived by the patient.

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