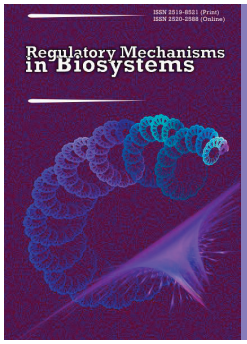

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Risk factors and early detection of gastroparesis in patients with type 2 diabetes mellitus

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Nowadays, diabetes mellitus is considered as one of the greatest global problems in internal medicine as it results in multiple organ damage and irreversible changes in the vital functional systems of the body. Unfortunately, there are no statistical data on the prevalence of gastrointestinal autonomic neuropathy in patients with type 2 diabetes mellitus in the Ukrainian population; making an early accurate diagnosis can be a clinical challenge since its manifestations are often considered as the manifestations of other diseases. Multifaceted clinical manifestations of gastroparesis cause difficulties in making a timely diagnosis, which can lead to an unfavourable prognosis. Diabetic gastroparesis symptoms were found in 45.5% of patients with type 2 diabetes mellitus: mild gastroparesis was observed in 29 (18.6%) patients; moderate gastroparesis was seen in 32 (20.5%) subjects; the signs of severe diabetic gastroparesis were present in 10 (6.4%) patients only. According to the assessment of the Neuropathy Disability Score, in patients with type 2 diabetes mellitus (disease duration of more than 10 years) and severe manifestations of polyneuropathy, the presence of risk factors for hypoglycemia as well as cigarette smoking are predictors of the development and progression of diabetic gastroparesis symptoms. They include a positive family history of diabetes mellitus, chronic microvascular complications of diabetes mellitus, concomitant cardiovascular diseases. Diabetes mellitus duration of more than 10 years, severe manifestations of polyneuropathy, increase in the incidence of hypoglycemic episodes as well as cigarette smoking should be considered as risk factors for gastroparesis in type 2 diabetes mellitus. We developed a mathematical model to assess the risk of developing gastroparesis in patients with type 2 diabetes mellitus using the results of a questionnaire (the Gastroparesis Cardinal Symptom Index, the Hypoglycemia Fear Survey-Total), and the Neuropathy Disability Score. For future research into diabetic gastroparesis, we recommend that a multicenter study is performed with an increased sample size because the early detection of delayed gastric emptying in this study was as high as we expected. Importantly, a case study of the complete disease history and questionnaires for the early diagnosis of delayed gastric emptying are required for studying the exact risk factors of autonomic neuropathy of the stomach in patients with type 2 diabetes mellitus.

Keywords: predictors; questionnaires; delayed gastric emptying; ^{13}C-octanoic acid breath test.

Introduction

Diabetes mellitus (DM) is known to be a disease which may be controlled and only its microvascular and macrovascular complications worsen quality of life as well as lead to disability and high mortality rates among patients. According to the data of the All-Ukrainian Register of Endocrinology Service Indicators, approximately 13.0% of diabetic patients reach the state of carbohydrate metabolism compensation, while 87.0% of diabetic patients progress to a decompensated state which increases the risk of severe long-term DM complication progression among such patients (Fadieienko & Cherneshov, 2011; Tkach, 2017; Lacy et al., 2018).

In patients with type 2 DM, the development and progression of gastrointestinal complications should be considered as one of the leading factors affecting the clinical course of the disease. Therefore, early diagnosis of gastroparesis is a relevant problem which needs to be scientifically studied. The correction of the initial impairment of gastric motor-evacuation function contributes to the preservation of ability to work as well as the improvement of quality of life in patients, reducing the risk of the progression of microvascular and macrovascular complications associated with DM (Friedenberg et al., 2013; Krishnan et al., 2013; Krishnasamy & Abell, 2018).

One of the most important and underdiagnosed complications of diabetes is gastroparesis. Patients admitted with diabetic gastroparesis (DG) require more procedures, have a longer hospital stay and incur higher charges than the mean. Thus, there are currently insufficient data regarding the predictors of gastroparesis in patients with type 2 DM and the relationship between them. The slowing down of gastric motor-evacuation function in patients with type 2 DM is attracting increasing scientific and clinical interest as one of the key mechanisms of gastroparesis development (Babak & Kolesnikova, 2012; Dickman et al., 2014; Kumar et al., 2018). The absence of carbohydrate metabolism compensation as well as a labile course of DM usually accompanies a number of chronic complications of the disease. Asymptomatic DG may manifest solely as a disturbance of glucose control, because slow gastric emptying reduces the postprandial glucose peak and the need for insulin (Rod-

rigues & Motta, 2012; Avalos et al., 2018). According to the results of a clinical trial aimed at determining the risk of mortality among patients with DM considering all the complications, gastroparesis is not associated with the increase in the number of fatal cases. Several studies aimed at determining the prevalence of gastroparesis and the gender differences among patients with DM (Syed et al., 2015; Parkman et al, 2015; Koch et al., 2016) have proven that the presence of comorbid factors (age, cigarette smoking, alcohol consumption) significantly reduce quality of life in patients. Jung et al. (2009) have found that DG is associated with the increase in incidence and hospitalization rates as well as the volume and costs of medical care and mortality rates among the working-age population (Jung et al., 2009; Zhao et al., 2015). While gastroparesis has multiple etiologies, in a large single-center study of 146 gastroparesis patients, 29% were found to have diabetes, 13% developed symptoms after gastric surgery and 36% were idiopathic (Darwiche et al., 2014; Almogbel et al., 2016; ADA, 2018). It has been estimated that approximately 4% of the adult population suffer from this disease and the results of epidemiological study have indicated that the prevalence of gastroparesis in the USA is 24.2 cases per 100,000 of the population: 37.8 cases per 100,000 inhabitants for women and 9.6 cases per 100,000 inhabitants for men (Intagliata & Koch, 2007; Elson, 2010). Indeed, up to 40% of patients with DG can be asymptomatic. The prevalence of gastroparesis in type 2 DM varies widely. The analysis of a population-based study in Olmsted County (Minnesota, USA) has demonstrated that gastroparesis is diagnosed only in 0.1% of individuals without DM, 4.8% of patients with type 1 DM and 1.0% of patients with type 2 DM (Edula et al., 2014; Kempler, 2016). According to the results of scintigraphy, the slowing down of gastric motor-evacuation function is typical for 25–55% of patients with type 1 DM and 18–30% of patients with type 2 DM (Halland & Bharucha, 2016; Huang et al., 2017). The prevalence of delayed gastric emptying in patients with diabetes has been reported to be between 28% and 65%. Gastroparesis affects 20–50% of the diabetic population, especially those with type 1 DM or those with long-standing (> 10 years) type 2 DM. It is usually associated with retinopathy, neuropathy and nephropathy as well as poor early glycemic control, as noted in the DCCT-EDIC study (Reddy et al., 2009; Lee & Hasler, 2017).

Unfortunately, in our country, the actual prevalence as well as social and economic significance of gastroparesis among patients with DM is currently not determined as late diagnosis of severe clinical course is made by scientists but not physicians at the stage of primary care (Tronko et al., 2015; Pop-Busui et al., 2017).

Most clinicians still believe that early manifestations of gastroparesis in patients with DM are the symptoms of various gastrointestinal diseases and gastroenterologists often do not detect any organic changes in the stomach, diagnosing the given complication too late. Severe DG has unfavourable prognostic value while medication – assisted correction of gastric motor-evacuation function in patients with moderate bradygastria contributes to the normalization of carbohydrate metabolism and prevents a labile course of the underlying medical condition.

The predictors of DG remain insufficiently studied. Therefore, the objective of our research was to study the most probable factors contributing to the development and progression of delayed gastric emptying in patients with type 2 DM.

Materials and methods

A total of 156 patients with type 2 DM who had presented to the endocrinology dispensary and the endocrinology department of the Ivano-Frankivsk Regional Clinical Hospital were included in the study. After signing the informed consent form to participate in a clinical trial, all the patients received printed materials with information on the examination methods – a step-by-step diagnostic algorithm with the use of two questionnaires, clinical as well as laboratory and instrumental examinations. All patients received of insulin therapy and/or in combination with different classes of oral antidiabetic drugs according to individually adjusted schemes.

The degree of gastrointestinal DG manifestation severity was determined applying the disease-specific questionnaires (the Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) and the Gastroparesis Cardinal Symptom Index (GCSI)) (Revicki et al., 2012, 2018). The questionnaire results were interpreted as follows: all the symptoms were rated on a 5-point scale (0 – absent, 1 – very mild, 2 – mild, 3 – moderate, 4 – severe, 5 – extremely severe). The interpretation of the PAGI-SYM results: the total score ranging from 1 to 20 indicates a very mild degree of gastroparesis; the total score ranging from 21 to 40 indicates a mild degree of severity; the total score ranging from 41 to 60 indicates a moderate degree of severity; the total score ranging from 61 to 80 indicates severe gastroparesis; the total score ranging from 81 to 100 indicates an extremely severe degree of gastroparesis. The GCSI consists of three subscales of the PAGI-SYM, selected to measure important symptoms related to gastroparesis, that is nausea/vomiting, postprandial symptoms/early satiety, and bloating. The nausea/vomiting subscale includes the following three items: nausea, retching, and vomiting. The postprandial fullness/early satiety subscale examine stomach fullness, inability to finish a normal-sized meal, feeling excessively full after meals, and loss of appetite. The bloating subscale is comprised of the following two items: bloating, and visibly larger stomach or belly after meals. The interpretation of the GCSI results: the total score ranging from 1 to 11 indicates a mild degree of severity, while the total score ranging from 12 to 22 indicates a moderate degree of severity; the total score ranging from 23 to 33 indicates a severe degree, while the total score of more than 34 indicates an extremely severe degree of the disease (Intagliata & Koch, 2007; Edula et al., 2014).

The incidence and severity of low blood sugar were assessed using the Hypoglycemia Fear Scale (HFS) – a questionnaire developed to measure the fear of hypoglycemia. The Behaviour subscale (HFS-B) measures behaviours used to avoid hypoglycemia and its negative consequences (the HFS-B score ranges from 0 to 60) (Lam et al., 2017). The Worry subscale (HSF-W) measures different emotional aspects of hypoglycemia (the HFS-W score ranges from 0 to 72). The total assessment of hypoglycemic episode severity was made considering the total score of both scales (HFS-T); in the presence of positive symptoms, the minimum score – 33 points and the maximum one – 132 points (Polonsky et al., 2017; Yu et al., 2017; Yun et al., 2017).

Body mass index was calculated according to the formula: body mass index (kg/m^2) = weight (kg) / height $(m)^2$. Waist circumference was measured at the umbilical level in the late exhalation phase while the patient was standing. The state of autonomic tone was assessed using the Kerdo autonomic index: the Kerdo autonomic index = the state of eutonia; the Kerdo autonomic index < 0 is typical for hyperparasympathicotonia; the Kerdo autonomic index > 0 is typical for hypersympathicotonia.

To assess the severity of diabetic polyneuropathy symptoms, a generally accepted scale measuring neurological symptoms and objective signs included into the Neuropathy Disability Score – the Neurological Symptoms Score was used. Mild diabetic polyneuropathy or its subclinical form were observed in patients with the Neurological Symptoms Score score of 5 points; moderate manifestations of diabetic polyneuropathy were found in patients with Neurological Symptoms Score of 5–13 points; severe diabetic polyneuropathy was seen in patients with the Neurological Symptoms Score of more than 14 points (Choung et al., 2011; Chuenyong et al., 2018).

Blood glucose levels were measured by glucose oxidase method using an automatic glucose analyzer AGKM-01K (Kvertimed, Ukraine). The glycated hemoglobin (HbA1C) levels were measured using the ion exchange liquid chromatography method (Accent-200 HbA1C Direct, PZ S.A. Cormay).

To diagnose type 2 DM as well as to evaluate the degree of carbohydrate metabolism compensation, the Ukrainian national standards were used (the Order of the Ministry of Health of Ukraine of 05.08.2009 No 574; the Order of the Ministry of Health of Ukraine of 21.12.2012 No 1118; "Unified Clinical Protocols of Primary, Secondary (Specialized) and Tertiary (Highly Specialized) Medical Care in type 2 DM".

The motor-evacuation function of the stomach was determined using the ^{13}C-octanoate breath test (^{13}C-OBT). A non-radioactive ^{13}C-labeled substrate (octanoic acid) is added to a standardized solid. The analysis of breath samples was carried out using isotope-ratio infrared spectroscopy with the measurement of $^{13}CO_2$ concentration. The results were assessed

considering gastric emptying half time ($T_{½}$): normal reference range for $T_{½}$ is 40–75 min; $T_{½}$ < 40 min indicates gastric motility acceleration; $T_{½}$ of 75–95 min indicates mild gastric motility deceleration; $T_{½}$ of 96–155 min indicates moderate gastric motility deceleration; $T_{½}$ > 155 min indicates severe gastric motility deceleration (Parkman et al., 2015; Zviahintseva & Chernobai, 2015; Sayyar et al., 2016). This test is well validated, simple to administer outside the hospital setting and is relatively inexpensive.

Exclusion criteria for participation in the study included the presence of clinically significant concomitant pathology of other organs and systems, namely gastrointestinal diseases, renal diseases; chronic cardiovascular diseases with the development of New York Heart Association functional class III and IV circulatory failure; systemic connective tissue diseases; chronic allergic diseases (bronchial asthma); mental diseases; acute inflammatory disease and/or the exacerbation of acute inflammatory disease; cancer; other endocrine diseases; pregnancy, lactation; taking medications affecting gastric motility. No subject had a history of upper gastrointestinal surgery or peptic ulcer disease.

The distribution of quantitative indicators was tested against Gauss' law using the Fisher criterion. Quantitative variables were presented as the arithmetic mean ± the standard error of the arithmetic mean. The relationship between the indicators was determined using the linear regression analysis and B coefficient, the 95% CI for B for both genders, the duration of DM and the body mass index applying IBM SPSS 23.0 Statistics (IBM Corporation, USA, 2015) for Microsoft Windows. The difference was considered statistically significant at $P < 0.05$.

The study was carried out in compliance with human rights and medical ethics. The analysis of complaints of the upper and lower gastrointestinal tract in DM is very important as delayed diagnosis puts patients at risk. To make a correct diagnosis of DG is crucial; this includes the study of symptom characteristics, detection of abnormal patterns of gastrointestinal function (like gastric emptying, oro-cecal and colonic transit, ano-rectal function), potential involvement of the autonomic nervous system (sympathetic, parasympathetic), and the overall impact on the patient's quality of life (Lacy et al., 2019). The diagnosis of gastroparesis was made based on gastroparesis severity classification (Abell et al., 2006; Camilleri, 2016). Grade 1 – mild gastroparesis – is characterized by easily controlled symptoms of dyspepsia. The patients can maintain an adequate body weight and nutritional status following a regular diet or a diet with some minor modifications. If there is an optimal control of carbohydrate metabolism, hyperglycemia has no negative effect on the stomach function. Grade 2 – compensated gastroparesis – is characterized by moderately severe symptoms which may be partially controlled with pharmacological agents (the combination of prokinetic and antiemetic agents). The patients can maintain adequate nutrition after their diet and life style correction. Patients with grade 3 (gastric failure) gastroparesis are medication-unresponsive. They cannot maintain adequate nutrition or hydration. Intensive care is needed including hospitalization for intravenous hydration and insulin infusion, intravenous administration of prokinetic and antiemetic agents and/or surgery (Borges et al., 2013; Tayupova et al., 2015).

Results

The study included 156 patients with type 2 DM and disease duration of 9.7 ± 0.5 years; the patients' average age was 59.5 ± 0.7 years; there were 80 males and 76 females. The body mass index – 32.4 ± 0.3 kg/m^2; the waist circumference – 97.4 ± 1.2 cm; the Kerdo autonomic index – –1.1 ± 0.1; the Neuropathy Disability Score – 17.6 ± 0.4 points; HbA1C – 8.9 ± 0.1%, fasting glycaemia – 7.8 ± 0.1 mmol/L, postprandial glycaemia – 9.7 ± 0.1 mmol/L. The mean body mass index was 32.4 ± 0.3 kg/m^2, over 58.4 % were obese, while 32.8% were overweight and only 8.8% had normal body mass index. With regard to glycemic control status, this survey revealed that most type 2 DM in our diabetes clinics had poor glycemic control. Other comorbidities were also recorded as follows: diabetic nephropathy 32.6%, diabetic retinopathy 33.3%, macrovascular complications (central nervous system and cardiovascular system) 14.5%, autonomic neuropathy presumption by the presence of orthostatic hypotension 9.8%, hypertension 52%, and hypercholesterolemia 46%.

According to the questionnaire results, physical examination data as well as additional laboratory and instrumental investigations, mild DG was found in 29 (18.6%) patients with type 2 DM, moderate DG was observed in 32 (20.5%) patients and the signs of severe gastroparesis were present in 10 (6.4%) patients only. Thus, the proportion of patients with gastric dysfunction among patients with type 2 DM was 45.5% which slightly exceeded the results of epidemiological studies.

In order to search for the predictors/markers of the slowing down of gastric motor-evacuation function in patients with type 2 DM, the impact of age, gender, disease duration, a positive family history of DM, cigarette smoking, concomitant cardiovascular and gastrointestinal diseases, disorders of the nervous system, the severity of polyneuropathy, the state of carbohydrate and lipid metabolism compensation, the incidence and fear of future hypoglycemic episodes, the degree of obesity, and the association of other microvascular and macrovascular DM complications with DG were analyzed.

According to the linear regression analysis, in patients with type 2 DM, there was a positive correlation between the degree of gastric motor-evacuation function slowing down and the duration of the underlying medical condition, diabetic polyneuropathy manifestations, cigarette smoking and the severity of hypoglycemic episodes (Table 1).

Table 1

Adjusted Relative Risk (95% Confidence Intervals) of developing delayed gastric emptying for 156 patients with type 2 DM

Relative Risk (RR) Factors developing delayed gastric emptying (results of ^{13}C-OBT, $T_{½}$, min) for patients with type 2 DM (95% confidence intervals)	Age-adjusted		Sex-adjusted		Body mass index-adjusted	
	RR	95% CI	RR	95% CI	RR	95% CI
Type 2 DM duration, years	0.85	–0.06–1.75	0.99	0.11–1.86	1.01	0.11–1.92
Harmful habit (cigarette smoking), years	–15.72	–29.64––1.79	–15.30	–30.57–0.14	–17.59	–31.77–3.40
Neuropathy Disability Score (Neurological Symptoms Score), points	2.06	0.99–3.12	2.08	0.97–3.19	2.26	1.18–3.34
Risk of hypoglycemia, HFS-T, points	0.82	0.58–1.06	0.85	0.59–1.11	0.85	0.61–1.10

Notes: The data are presented as B (95% CI); relationship between gastric motor-evacuation function (according to the ^{13}C-OBT, $T_{½}$, min) and type 2 DM duration (according to anamnestic data), severity degree of functional changes in the Neuropathy Disability Score (Neurological Symptoms Score, points), risk of hypoglycemia (the HFS-T, points).

We conclude that the presence of abdominal bloating/fullness but not any other upper gastrointestinal symptom is associated with DG and that gastric emptying is slower in female than male.

Several studies have proven the pathogenic relationship between gender and gastric motor-evacuation function state in patients with DM: bradygastria is more often diagnosed in women, which may be associated with hormonal characteristics of both males and females as estradiol and oxytocin directly affect gastric motility. The results of our study have not confirmed a statistically significant dependence between gender and gastric motor-evacuation function when distributing all the patients according to gender only as well as considering the ^{13}C-OBT results.

It is worth noting that, according to the ^{13}C-OBT results, in patients with type 2 DM, there was no relationship between the patients' age, the degree of gastroparesis severity, the state of carbohydrate and lipid metabolism compensation, various chronic microvascular and macrovascular DM complications as well as concomitant cardiovascular diseases.

Since there was a strong correlation between the subjective evaluation of gastroparesis symptoms according to the questionnaire results (the PAGI-SYM, the GCSI) and instrumental confirmation (the ^{13}C-OBT) of the slowing down of gastric motor-evacuation function ($r = 0.91$, $r = 0.85$, respectively $P < 0.01$), the impact of various factors on the degree of gastroparesis severity according to the questionnaire results was assessed. The GCSI is a validated questionnaire which assists in assessing the presence of gastroparesis symptoms and its severity.

The results revealed that overall prevalence of symptoms compatible with DG as assessed by GCSI was 43%. The most common symptoms were bloating, stomach fullness and early satiety (38.5%, 44.2% and 44.9% respectively) (Table 2).

Table 2
Frequency of gastroparesis symptoms
among study participant with type 2 DM (n = 156)

Gastroparesis symptoms	n, %
Nausea	33.4
Retching	14.2
Vomiting	3.9
Stomach fullness	44.3
Not able to finish a meal	44.9
Excessive fullness after meals	37.9
Loss of appetite	21.8
Bloating	38.5
Belly visibly larger	34.7

Thus, bradygastria contributes to the development of symptoms of "gastric" postprandial hypoglycemia. The highest risk of developing hypoglycemic conditions was found in patients with DG who underwent insulin therapy for the correction of carbohydrate metabolism. The determination of the motor-evacuation function of the stomach is recommended for patients with type 2 DM for both the prevention of postprandial hypoglycemia and early diagnosis of gastroparesis. There was a positive correlation between the assessment of the disease-specific questionnaires and relative risk factors of gastroparesis in diabetics (Table 3).

Table 3
Relative Risk Factors of developing gastroparesis
in patients with type 2 DM for different clusters

Relative Risk (RR) Factors developing gastroparesis with disease-specific questionnaire results and different clusters	Disease-specific questionnaires			
	PAGI-SYM, points		GCSI, points	
	RR	95% CI	RR	95% CI
Anamnestic data – a positive family history of DM	7.82	0.25–15.38	3.28	0.04–6.52
Concomitant cardiovascular diseases	6.57	2.99–10.16	2.74	1.20–4.28
Chronic microvascular complications of type 2 DM	9.05	5.49–12.62	3.71	2.18–5.25
Hypercholesterolemia	5.75	2.43–9.07	2.51	1.09–3.93

Notes: the data are presented as B (95% CI); relationship between results of disease-specific questionnaires (PAGI-SYM, points and GCSI, points) and different diseases.

However, according to the ^{13}C-OBT results, there was no direct correlation between the given factors. Therefore, the obtained data confirmed, to a certain extent, the impact of additional factors on the development/deterioration of gastrointestinal complications associated with DM.

In the present study, we have confirmed that the combination of various factors, namely DM duration of more than 10 years, severe manifestations of polyneuropathy, frequent hypoglycemic episodes as well as cigarette smoking serves as the main factor for slowing down gastric motor-evacuation function in patients with type 2 DM. They should be considered when stratifying the risk of DG and selecting pathogenetically substantiated therapy. The disadvantages of our study were the lack of data in relation to the prevalence of gastroparesis in diabetics without peripheral neuropathy to enable comparison, and the interpretation method, which was different from that in the standard guidelines.

Early detection and treatment of gastroparesis in patients with type 2 DM is necessary to improve the quality of life and to avoid premature clinical deterioration due to intolerance to treatment.

Mathematical models to assess the risk of developing gastroparesis in patients with type 2 DM using the questionnaire results (the GCSI, the HFS-T), the levels of anthropometric parameters (the body mass index), the Neuropathy Disability Score have been developed. The most unfavourable prognostic criteria for the development of diabetic gastrointestinal autonomic neuropathy, which can be used in the development of prophylactic measures for preventing the development and progression of DG, have been identified. Using the pairwise correlation between the identified indicators and gastric motor-evacuation function velocity when not all indicators are known, the following calculation was made:

$$Y = 62.73 + 0.70 \cdot X_1 + 0.81 \cdot X_2 + 0.29 \cdot X_3,$$

where Y – gastric motor-evacuation function; X_1 – the Neuropathy Disability Score (Neurological Symptoms Score), points; X_2 – the total score of the GSCI, points; X_3 – the total score of the HFS-T, points.

The coefficient of multiple determination (R^2) was 0.51 for the Neuropathy Disability Score, 0.83 for the GCSI, 0.64 for the HFS-T. The calculated F-value was 12.73, while the critical F-value was 2.87; P = 0.000008. The calculated F-value was greater than the critical F-value, thereby indicating the model's reliability.

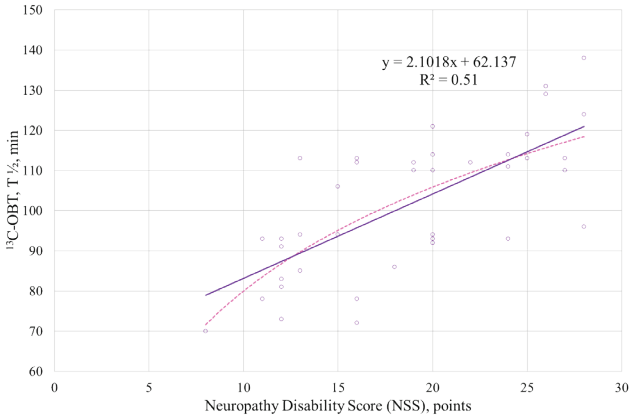

Fig. 1. Coefficient of multiple determination (R^2) between gastric motor-evacuation function velocity according to the ^{13}C-OBT ($T_{½}$, min) results and the total score of the Neuropathy Disability Score (Neurological Symptoms Score, points) (n = 46)

In patients with type 2 DM, who in most cases suffered from excess body weight or obesity, no correlation was revealed between body mass index and the ^{13}C-OBT results.

We calculated the diagnostic significance of the Neuropathy Disability Score results as the manifestation of diabetic polyneuropathy symptoms to the state of gastric motor-evacuation function according to the ^{13}C-OBT results in patients with type 2 DM. Figure 1 presents the coefficient of multiple determination between the indicators.

In patients with type 2 DM, subjective symptoms of gastroparesis were evaluated according to the results of the GCSI. The coefficient of multiple determination between gastric motor-evacuation function velocity according to the ^{13}C-OBT results and the total score of the GCSI questionnaire was calculated (Fig. 2).

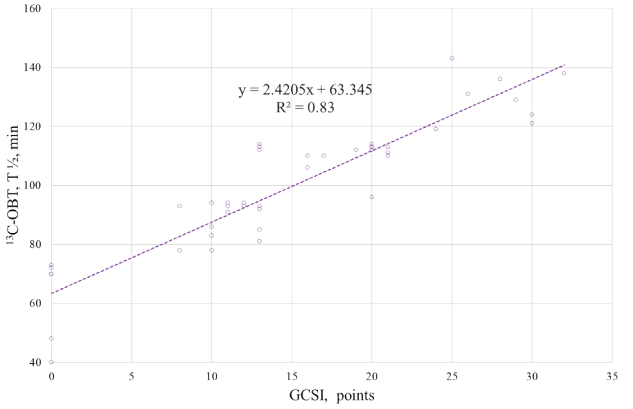

Fig. 2. Coefficient of multiple determination (R^2) between gastric motor-evacuation function velocity according to the ^{13}C-OBT ($T_{½}$, min) results and the total score of the GCSI (points) questionnaire (n = 46)

In patients with type 2 DM, the total assessment of hypoglycemic episode severity was made according to the results of the HFS-T questionnaire. Asymptomatic or timely undiagnosed glycemia alongside the labile course of the main disease and frequent episodes of hypoglycemia alternating with hyperglycemia episodes should be considered as clinically significant deterioration in the patient's general condition due to the lack of glycemic control compensation. The coefficient of multiple

determination between the total score of the HFS-T questionnaire and gastric motor-evacuation function velocity according to the ^{13}C-OBT results was calculated (Fig. 3).

Thus, as evidenced by the implications of using questionnaires, the calculations obtained should be widely implemented in daily practice of family physicians, general practitioners and single-discipline specialists. The evaluation of the questionnaire results allows one to identify the main complaints and choose the laboratory and instrumental methods of examination to confirm or exclude diagnosis without high financial burden.

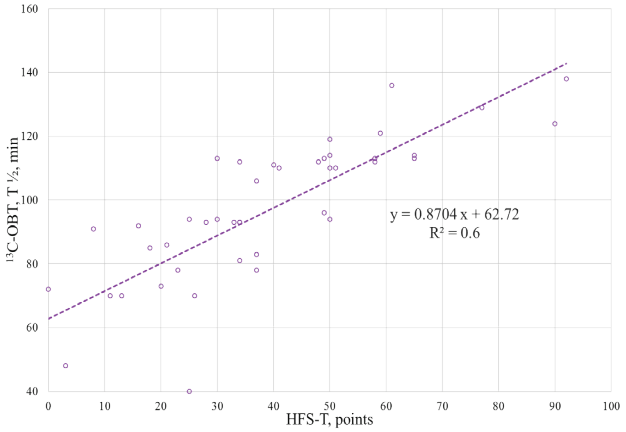

Fig. 3. Coefficient of multiple determination (R^2) between gastric motor-evacuation function velocity according to the ^{13}C-OBT ($T_{½}$, min) results and the total score of the HFS-T (points) questionnaire (n = 46)

Thus, in the examined patients with type 2 DM, the slowing down of gastric motor-evacuation function was caused by the variation in symptom severity according to the Neuropathy Disability Score – by 50.4%; the patients' subjective evaluation of gastroparesis symptoms according to the GCSI questionnaire results – by 82.8%; the risk of hypoglycemia according to the HFS-T questionnaire results – by 63.6%.

In a patient at high risk of developing DG, mathematical and instrumental determination of gastric motor-evacuation function was carried out. The results obtained can be summarized in a clinical case.

A 57-year-old patient K. presented with type 2 DM (disease duration of 10 years). To prevent the progression of chronic complications, planned hospitalization once or twice a year was indicated. According to the patient, during the previous month, she felt unwell, experienced a decrease in appetite, vomiturition, nausea, bloating and stomach heaviness after eating, as well as sharp and uncontrolled blood sugar level fluctuations throughout the day from 6.0 to 16.6 mmol/L. The patient was hospitalized at the endocrinological department of the Ivano-Frankivsk Regional Clinical Hospital due to the aforementioned complaints. In her past medical history, there were no comatose states or hypoglycemic episodes. Family history of DM and allergic events was negative. No cardiovascular, bronchopulmonary, urogenital and digestive disorders were detected. There were no traumas and skeletal fractures. The patient had never undergone surgery. She had never suffered from tuberculosis, sexually transmitted diseases, viral hepatitis. There were no bad habits to correct. The patient received antidiabetic agents: basal insulin (insulin glargine) at a dose of 32 IU/day subcutaneously in a combination with oral tablets (metformin) that belong to a group of medicines called biguanides lowering blood sugar level at a daily dose of 2,000 mg and derivatives of sulfonamides (gliclazide) at a daily dose of 90 mg.

Physical examination data: height – 160 cm, weight – 93 kg, body mass index – 36.33 kg/m^2, waist circumference – 121 cm, class II obesity. The patient's general condition was moderate. The skin and visible mucous membranes were clear and moist. Peripheral lymph nodes were not enlarged. The thyroid gland was not enlarged as well; there were no symptoms of thyrotoxicosis and hypothyroidism. The tongue was clean, dry, without acetone breath. The throat was clean as well. During auscultation, vesicular breaths were heard across the lung surface. Heart sounds were rhythmic, clear with heart rate of 70 beats per minute; the average blood pressure level was 120/80 mm Hg; the Kerdo autonomic index was –0.71. The abdomen was enlarged due to subcutaneous fat deposits and was involved in the act of breathing, painless on palpation; there were signs of flatulence. Percussion of the liver borders showed their enlargement by 1.0 cm; the spleen was normal. Kehr's signs and Ortner's symptom were negative. Bowel and bladder functions were impaired – frequent urination at night, up to two-three times. Peripheral swellings were seen. No varicose changes in the saphenous veins of the both lower extremities were observed. Arterial pulsation in the lower extremities weakened sharply. Trophic changes in the skin of the legs and feet were observed. The Neurological Symptoms Score was 28 points, which corresponds to pronounced diabetic polyneuropathy manifestations.

Questionnaire results: the PAGI-SYM – 49 points; the GCSI – 19 points; the SF-36: the physical health score – 36.61; the mental health score – 24.76; the HFS-T – 56 points. Laboratory and instrumental findings: blood and urine samples (complete blood count and urinalysis) were within the normal lab values. Ketone bodies were negative. Carbohydrate metabolism indicators: HbA1C – 11.3%; glycemic profile – 9.3–11.4–10.2–9.7 mmol/L (the signs of type 2 DM decompensation without ketosis). Biochemical and electrolyte panels within the normal range. The signs of dyslipoproteinemia were present in the lipid profile: total cholesterol – 6.1 mmol/L; triglyceride – 2.0 mmol/L; high-density lipoprotein cholesterol – 0.78 mmol/L; low-density lipoprotein cholesterol – 6.23 mmol/L; very low-density lipoprotein cholesterol – 0.4 mmol/L; atherogenic index – 6.82. The thyroid stimulating hormone was 2.11 μIU/mL (normal level – 0.23–3.40 μIU/mL). Microalbuminuria was 460 mg per day. A normal sinus rhythm with heart rate of 78 beats per minute; signs of diffuse changes in the myocardium were seen on the ECG: The signs of hepatosis were detected on the abdominal ultrasound. The result of thyroid's ultrasound was age normal. The lungs and heart were within the age norm on the X-Ray of chest. The result of esophagogastroduodenoscopy was gastroduodenopathy with preserved acidity. The result of ^{13}C-OBT was $T_{½}$ – 114 min (moderate gastric motility deceleration).

Diagnosis: Type 2 diabetes mellitus. Metabolic syndrome. Grade 2 diabetic gastroparesis. Stage 2 diabetic angiopathy of the lower extremities. Stage 1 chronic arterial insufficiency of both extremity vessels. Preproliferative diabetic retinopathy of both eyes. Diabetic distal symmetrical neuropathy of the lower extremities. CKD: diabetic nephropathy, microalbuminuria. Ischemic Heart Disease: diffuse cardiosclerosis. Functional class II, stage 0–1. Dyslipidemia. Class II obesity. Non-alcohalic fatty liver disease: diabetic hepatosis.

The predicted gastric motor-evacuation function velocity was calculated by the following formula: Y = 62.73 + (0.70 • 28) + (0.81 •19) + (0.29 • 56) = 113.96.

Thus, the result of the mathematical calculation of the predicted gastric motor-evacuation function velocity in the examined patient was 113.96 min, which corresponded to the results of the instrumental examination method – the ^{13}C-OBT: $T_{½}$ – 114 min.

Discussion

This is the first study that has assessed the prevalence of clinical symptoms of gastroparesis among the Ukrainian population with type 2 DM. In a review by Kenneth & Jorge (2015), it is estimated that up to 40% of type 1 DM patients have gastroparesis and 10–30% of type 2 DM patients have gastroparesis. Our result showed that 45.5% of Ukrainians with type 2 DM have clinical symptoms of gastroparesis, on screening subjects with disease-specific (PAGI-SYM and GCSI) questionnaires. It is comparable to the estimated prevalence reported by Almogbel & Algeffari (2016), 10.8% and also corresponding well to previous estimates. These variations in the prevalence may be related to difference in selection of study population, methods of diagnosis or differences in definition of grade DG.

Our results are opposite to those presented in the research of Chuenyong & Kuanrakcharoen (2018), who reported that diabetic peripheral neuropathy was not strong enough be used as a surrogate marker of DG. This implied that diabetic peripheral neuropathy was the chronic diabetic complication with the earliest onset; therefore, it may be the best risk factor for screening of autonomic neuropathy of the stomach. Prevalence and severity of symptoms suggestive of delayed gastric

emptying is particularly high among obese patients with long standing and poorly controlled type 2 DM.

The only indication of DG is erratic blood-glucose control and life-threatening hypoglycemic episodes. The chronic hyperglycemia and asymptomatic hypoglycemia are important risk factors for gastroparesis. For instance, early indicators of gastroparesis in patients with type 2 DM are the symptoms of poor glycemic control.

Several studies have been conducted to identify a non-invasive parameter for predicting a correlation with gastroparesis, and body mass index, fasting blood glucose, and HbA1C values didn't demonstrate a reliable correlation; however, investigations concerning cardiovascular autonomic regulation have shown striking correlations with DG (Valeriani et al., 2013; Woodhouse et al., 2017).

DG was found to affect individuals with DM duration of more than 10 years (Elson, 2010; Anudeep et al., 2016). Scientists argue that cigarette smoking dramatically increases the rate of lipid peroxidation; therefore, this harmful habit should be considered as one of the leading factors of diabetic polyneuropathy symptom progression as well (Rodrigues & Motta, 2012; Rakan et al., 2016). Hence, the patients' smoking status was thoroughly studied.

Obesity is one of the factors contributing to the development of DG symptoms and, in some cases, it may worsen the clinical course of DG (Li et al., 2014; AlOlaiwi et al., 2018). In total, 16 multicenter studies have been conducted to evaluate the role of obesity as a risk factor for DG: 7 studies have proven gastric motility acceleration in patients with excess body weight whereas 4 studies have found bradygastria, and 5 studies confirmed normal gastric motor-evacuation function in obese individuals. In the present study, we have revealed no relationship between excess body weight/obesity degree and gastric motor-evacuation function rate in the studied patients.

Several studies have demonstrated a dose dependent inverse relationship between the rate of gastric emptying and the blood glucose concentrations in both healthy subjects and patients with uncomplicated diabetes (Pasricha et al., 2017; Chuenyong et al., 2018). Our work has shown that upper gastrointestinal symptoms were more severe and more common among type 2 DM than non-diabetic control groups. Our results do not concur with the literature (Darwiche et al., 2014; Dickman et al., 2014; Almogbel et al., 2016), who indicate that female gender emerged as a significant risk factor of symptoms suggestive of DG. The underlying mechanism for this phenomenon isn`t fully understood. Other studies have also reported that female gender was associated with delayed gastric emptying in patients with DM. Despite a high prevalence of gastroparesis among patients with type 1 DM, the number of patients with type 2 DM and the signs of gastroparesis is significantly larger, which may be associated with a high prevalence of type 2 DM among the population (Lee & Hasler, 2017).

Most scientists assert that the incidence of DG increases with age and with inadequate glycemic control (Reddy et al., 2009; Polonsky et al., 2017), while we have not established such dependence; however, other scientists hold the same opinions, namely, that there is a dependence between DG incidence and both age and inadequate glycemic control (Kostitska & Mankovsky, 2017). Due to poor carbohydrate metabolism control, in patients with DG, various cardiovascular diseases, hypertension and retinopathy were detected more often (Yun et al., 2017; Chuenyong et al., 2018). In most cases, clinicians underestimate the role of the patient's subjective evaluation of gastroparesis symptom severity; however, when studying the long-term effects 5–10 years after the onset of the disease, this type of examination is considered as highly effective and reliable (Kempler et al., 2016; Kumar et al., 2018).

In patients with type 2 DM, DM duration of more than 10 years, severe manifestations of Neuropathy Disability Score, past hypoglycemic episodes, hypercholesterinemia, cigarette smoking and the presence of microvascular and macrovascular DM complications have been proven to be statistically significant predictors of developing DG (Kostitska, 2015). Based on the Expert Committee Recommendations and the results of epidemiologic studies, we can draw the conclusion that the GCSI questionnaire is an effective tool for early stratification of gastroparesis symptoms and the evaluation of treatment results (Pasricha et al., 2017). Furthermore, the results of the questionnaire GCSI are known to be a reliable, accurate and validated score by ^{13}C-OBT. The present research was the first Ukrainian's study of DG to include type 2 DM with diabetic polyneuropathy. Our results regarding diabetic complications showed that, among those with diabetic peripheral neuropathy, other complications were less commonly found, for example, diabetic macrovascular complications (central nervous system and CVS) were found in only 14.5% of cases.

Many scientists state a positive effect of early diagnostic for DG, represented by resolution of clinical symptoms and some laboratory test and results of stomach scintigraphy. We obtained interesting results of mathematical and instrumental determination of gastric motor-evacuation function carried out in a patient with high risk of DG using the ^{13}C-OBT.

Conclusion

DM duration of more than 10 years, severe manifestations of polyneuropathy, increase in the incidence of hypoglycemic episodes as well as cigarette smoking should be considered as major risk factors for gastroparesis in patients with type 2 DM. The additional risk factors for DG in patients with type 2 DM include a positive family history of DM, concomitant cardiovascular diseases, various chronic microvascular DM complications and increased level of total cholesterol.

There was no relationship between the degree of DG severity and the patients' age, gender, the state of carbohydrate and lipid metabolism compensation, the degree of obesity and other comorbidities, namely gastrointestinal diseases, diseases of the nervous system as well as the genitourinary system.

Routine use for patients with the disease – specific questionnaires by family physicians, general practitioners and single-discipline specialists helps prevent overdiagnosis, as well as allows them to determine the severity of gastroparesis and the effectiveness of therapy for patients with type 2 DM. Thus, for the formation of risk groups and early detection of DG, the prevention of labile clinical course of DM, high financial costs for treatment of the gastrointestinal tract, these formulae for calculating the predicted velocity value of gastric motor-evacuation function and the diagnostic algorithm should be implemented for widespread use by clinicians in daily medical practice.

As a conclusion, the detection of risk factors for early DG manifestations as well as the development of the recommendations for the prevention of gastrointestinal complications in patients with type 2 DM will allow us to improve the diagnostic algorithm.

References

Almogbel, R., Alhussan, F., Alnasser, S., & Algeffari, M. (2016). Prevalence and risk factors of gastroparesis-related symptoms among patients with type 2 diabetes. International Journal of Health Sciences, 10(3), 397–404.

AlOlaiwi, L., AlHarbi, T., & Tourkmani, A. (2018). Prevalence of cardiovascular autonomic neuropathy and gastroparesis symptoms among patients with type 2 diabetes who attend a primary health care center. PLoS One, 13(12), e0209500.

American Diabetes Association (2017). Comprehensive medical evaluation and assessment of comorbidities. Diabetes Care, 40(Suppl. 1), S25–S32.

Anudeep, V., Vinod, K. V., Pandit, N., Sharma, V., Dhanapathi, H., Dutta, T., & Sujiv, A. (2016). Prevalence and predictors of delayed gastric emptying among Indian patients with long-standing type 2 diabetes mellitus. Indian Journal of Gastroenterology, 35, 385–392.

Avalos, D., Sarosiek, I., Loganathan, P., & McCallum, R. (2018). Diabetic gastroparesis: Current challenges and future prospects. Clinical and Experimental Gastroenterology, 11, 347–363.

Babak, O., & Kolesnikova, E. (2012). Patologija verhnih otdelov zheludochno-kishechnogo trakta i saharnyj diabet: V chem skryvaetsja ugroza dlja pacienta? [Pathology of the upper gastrointestinal tract and diabetes mellitus: What is the threat to the patient?]. Ukrajins'kyj Terapevtychnyj Zhurnal, 2, 116–120 (in Russian).

Borges, C., Secaf, M., & Troncon, L. (2013). Clinical features and severity of gastric emptying delay in Brazilian patients with gastroparesis. Arquivos de Gastroenterologia, 50, 270–276.

Camilleri, M. (2016). Functional dyspepsia and gastroparesis. Digestive Diseases, 34, 491–499.

Choung, R., Locke, G., Schleck, C., Zinsmeister, A., Melton, L., & Talley, N. (2011). Risk of gastroparesis in subjects with type 1 and 2 diabetes in the general population. American Journal Gastroenterology, 107, 82–88.

Choung, R., Locke, G., Schleck, C., Zinsmeister, A., Talley, N., & Nicholas, M. (2008). Cumulative incidence of gastroparesis in people with type 1 and 2 diabetes in the general population. American Journal Gastroenterology, 103, S399.
Chuenyong, K., Pornananrat, A., Sarinnapakorn, V., & Kuanrakcharoen, P. (2018). Early detection of diabetic gastroparesis in type 2 diabetes using diabetic peripheral neuropathy as a surrogate marker: A pilot study in Rajavithi hospital. Asian Journal of Pharmaceutics, 12(2), S.538–S.544.
Darwiche, G., Mohammed, S., Aldawi, N., Skaria, S., & Tesfa, Y. (2014). Gastroparesis among type 1 and type 2 diabetic patients in the United Arab Emirates. Journal of Diabetes Mellitus, 4(2), 96–106.
Dickman, R., Wainstein, J., Glezerman, M., Niv, Y., & Boaz, M. (2014). Gender aspects suggestive of gastroparesis in patients with diabetes mellitus: A cross-sectional survey. BMC Gastroenterology, 19, 14–34.
Edula, R., Roque, M., & Bouras, E. (2014). How reliable is a diagnosis of gastroparesis? Gastroenterology, 146(5), 617–618.
Elson, C. (2011). Epidemiology, mechanisms, and management of diabetic gastroparesis. Clinical Gastroenterology Hepatology, 9, e6–e8.
Friedenberg, F., Kowalczyk, M., & Parkman, H. (2013). The influence of race on symptom severity and quality of life in gastroparesis. Journal of Clinical Gastroenterology, 47(9), 757–761.
Halland, M., & Bharucha, A. (2016). Relationship between control of glycemia and gastric emptying disturbances in diabetes mellitus. Clinical Gastroenterology and Hepatology, 14(7), 929–936.
Huang, Y., Zhang, H., Zhang, M., Li, W., Wang, J., & Hu, J. (2017). The Association between fasting C-peptide and gastrointestinal symptoms of gastroparesis in type 2 diabetic patients. Journal of Neurogastroenterology and Motility, 23(2), 254–261.
Intagliata, N., & Koch, K. (2007). Gastroparesis in type 2 diabetes mellitus: Prevalence, etiology, diagnosis, and treatment. Current Gastroenterology Reports, 9(4), 270–279.
Jung, H., Choung, R., Locke, G., Schleck, C., Zinsmeister, A., Szarka, L., Mullan, B., & Talley, N. (2009). The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. Gastroenterology, 136, 1225–1233.
Kempler, P., Várkonyi, T., Körei, A., & Horváth, V. (2016). Gastrointestinal autonomic neuropathy in diabetes: The unattended borderline between diabetology and gastroenterology. Diabetologia, 59, 401–403.
Koch, K., Hasler, W., Yates, K., Parkman, H., Pasricha, P., Calles-Escandon, J., Snape, W., Abell, T., McCallum, R., Nguyen, L., Sarosiek, I., Farrugia, G., Tonascia, J., Lee, L., Miriel, L., & Hamilton, F. (2016). Baseline features and differences in 48 week clinical outcomes in patients with gastroparesis and type 1 vs type 2 diabetes. Neurogastroenterology and Motility, 28, 1001–1015.
Kostitska, I. (2015). Vykorystannja opytuval'nykiv pacijentiv dlja rann'oji diagnostyky diabetychnogo gastroparezu [Patients using questionnaires for early diagnosis of diabetic gastroparesis]. Problemy Endokrynnoji Patologiji, 3, 32–37 (in Ukrainian).
Kostitska, I., & Mankovsky, B. (2017). Vzajemozv'jazok mizh diabetiyhnym gastroparezom i ryzykom rozvytku gipoglikemichnyh staniv [Relationships between diabetic gastroparesis and risk of developing hypoglycemic conditions]. Mezhdunarodnyi Endokrinologicheskii Zhurnal, 13, 41–47 (in Ukrainian).
Krishnan, B., Babu, S., Walker, J., Walker, A., & Pappachan, J. (2013). Gastrointestinal complications of diabetes mellitus. World Journal of Diabetes, 4(3), 51–63.
Krishnasamy, S., & Abell, T. (2018). Diabetic gastroparesis: Principles and current trends in management. Diabetes Therapy, 9(1), S1–S42.
Kumar, M., Chapman, A., Alam, U., Javed, S., Malik, R., & Azmi, S. (2018). The investigation and treatment of diabetic gastroparesis. Clinical Therapeutics, 6 40, 850–861.
Lacy, B., Crowell, M., Mathis, C., Bauer, D., & Heinberg, L. (2018). Gastroparesis: Quality of life and health care utilization. Journal of Clinical Gastroenterology, 52(1), 20–24.
Lacy, B., DiBaise, J., Pimentel, M., & Ford, A. (Eds.). (2019). Essential medical disorders of the stomach and small intestine. Springer International Publishing.
Lam, A., Xin, X., Tan, W. B., Gardner, D., & Goh, S. (2017). Psychometric validation of the hypoglycemia fear survey-II (HFS-II) in Singapore. BMJ Open Diabetes Research and Care, 5, e000329.
Lee, A., & Hasler, W. (2017). Diabetes and the stomach. Current Treatment Options in Gastroenterology, 15(4), 441–459.
Li, X., Reed, N., Li, Q., Hoke, A., & Pasricha, P. (2014). Effects of pre-diabetic obesity on gastric and somatic neuropathy – morphological and functional changes linking obesity to gastroparesis. Gastroenterology, 146(5), 608–609.
Parkman, H., Hallinan, E., Hasler, W., Farrugia, G., Koch, K., Nguyen, L., Snape, W., Abell, T., McCallum, R., Sarosiek, I., Pasricha, P., Clarke, J., Miriel, L., Tonascia, J., & Hamilton, F. (2017). Early satiety and postprandial fullness in gastroparesis correlate with gastroparesis severity, gastric emptying, and water load testing. Neurogastroenterology and Motility, 29, e12981.
Pasricha, P., Camilleri, M., Hasler, W., & Parkman, H. (2017). White paper AGA: Gastroparesis: Clinical and regulatory insights for clinical trials. Clinical Gastroenterology and Hepatology, 15, 1184–1190.
Polonsky, W., Fisher, L., Hessler, D., & Edelman, S. (2017). Investigating hypoglycemic confidence in type 1 and type 2 diabetes. Diabetes Technology and Therapeutics, 19(2), 131–136.
Pop-Busui, R., Boulton, A., Feldman, E., Bril, V., Freeman, R., Malik, R., Sosenko, J., & Ziegler, D. (2017). Diabetic neuropathy: A position statement by the American Diabetes Association. Diabetes Care, 40, 136–154.
Rakan, A., Fulwa, A., Sulaiman, A., & Metab, A. (2016). Prevalence and risk factors of gastroparesis-related symptoms among patients with type 2 diabetes. International Journal of Health Sciences, 10(3), 398–404.
Reddy, S., Ramsubeik, K. P., Federico, J. R., Goodwich, R. B., Palacio, C., & Vega, K. (2009). Do HbA1C levels correlate with delayed gastric emptying in diabetic patients? Gastroenterology, 136(5), 784.
Revicki, D., Camilleri, M., Kuo, B., Szarka, L., McCormack, J., & Parkman, H. (2012). Evaluating symptom outcomes in gastroparesis clinical trials: Validity and responsiveness of the gastroparesis cardinal symptom index-daily diary (GCSI-DD). Journal of Neurogastroenterology and Motility, 24(5), 456–463.
Revicki, D., Lavoie, S., Speck, R., Puelles, J., Kuo, B., Camilleri, M., Almansa, C., & Parkman, H. (2018). The content validity of the ANMS GCSI - DD in patients with idiopathic or diabetic gastroparesis. Journal of Patient-Reported Outcomes, 61(2), 1–10.
Rodrigues, M., & Motta, M. (2012). Mechanisms and factors associated with gastrointestinal symptoms in patients with diabetes mellitus. Jornal de Pediatria, 88(1), 17–24.
Sayyar, M., Edwin, L., Patel, J., Nath, A., Tefera, E., & Cho, W. (2016). The overlooked factors that may lead to delayed gastric emptying. Gastroenterology, 150(4), 728–729.
Syed, A., Calles-Escandon, J., Wolfe, M. (2015). Epidemiology of gastroparesis with and without diabetes mellitus in a large cohort from 340 US hospitals. Gastroenterology, 148(4), 505–506.
Tayupova, D., Valeeva, F., Safiullina, L., & Bareeva, L. (2015). Functional diagnostics of gastrointestinal autonomic neuropathy. Innovative Technologies in Medicine, 89(4), 136–138.
Tkach, S. (2017). Diabeticheskij gastroparez: Jepidemiologija, mehanizmy razvitija, sovremennye podhody k vedeniju bol'nyh [Diabetic gastroparesis: Epidemiology, mechanisms of development modern approaches to the management]. Klinichna Endokrinologija ta Endokrinna Hirurgija, 58(2), 9–18 (in Russian).
Tronko, M., Sokolova, L., Vlasenko, N., & Kostukevich, A. (2015). Dostizhenie celej lechenija pacientami s saharnym diabetom v Ukraine. Rezul'taty Mezhdunarodnogo issledovanija po izucheniju praktiki vedenija saharnogo diabeta (IDMPS) [Achieving the goals in treatment of patients with diabetes mellitus in Ukraine. Results of the International Diabetes Management Practices Study (IDMPS)]. Endokrynologija, 20(4), 658–668 (in Russian).
Valeriani, M., Brock, C., Graversen, C., Frøkjaer, J., Søfteland, E., & Drewes, A. (2013). Peripheral and central nervous contribution to gastrointestinal symptoms in diabetic patients with autonomic neuropathy. Clinical Neurophysiology, 124(11), e193.
Woodhouse, S., Hebbard, G., & Knowles, S. (2017). Psychological controversies in gastroparesis: A systematic review. World Journal of Gastroenterology, 23(7), 1298–1309.
Yu, D., Ramsey, F., Norton, W., Norton, N., Schneck, S., Gaetano, T., & Parkman, H. (2017). The burdens, concerns, and quality of life of patients with gastroparesis. Digestive Diseases and Sciences, 62(4), 879–893.
Yun, H., Honghong, Z., Minxia, Z., Wenya, L., Jinhua, W., & Ji, H. (2017). The association between fasting C – peptide and gastrointestinal symptoms of gastroparesis in type 2 diabetic patients. Journal of Neurogastroenterology and Motility, 23(2), 254–261.
Zhao, L., Ma, J., Wang, S., & Xie, Y. (2015). Relationship between β-cell function, metabolic control, and microvascular complications in type 2 diabetes mellitus. Diabetes Technology and Therapeutics, 17, 29–34.
Zviahintseva, T., & Chernobai, A. (2015). Funkcional'ni zahvoriuvannia organiv travlennia ta jih pojednannia u svitli suchasnyh ujavlen': Vid patogenezu do likuvannia [Functional gastrointestinal diseases and their combinations in view of the modern concepts: From pathogenesis to treatment]. Suchasna Gastroenterologija, 83(3), 61–72 (in Ukainian).