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Original article

Diabetes Not an Independent Predictor of Gastroparesis in Symptomatic Patients Referred for Gastric Emptying Studies

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ABSTRACT

Background: It is commonly presumed that diabetics are more prone to gastroparesis when compared to non-diabetics. Objective: To ascertain whether diabetes is an independent predictor of gastroparesis in symptomatic patients who are referred for gastric emptying studies. Methods: This was a cross sectional observational study. The study cohort consisted of 172 consecutive patients who had been referred for gastric emptying studies. Seventy-four of the 172 patients had evidence of diabetes. Results: Gastroparesis was diagnosed in 93 of the 172 patients (54%). Multiple logistic regression analysis did not reveal diabetes to be an independent risk factor (OR 0.77, CI 0.37-1.56, p=0.46). But age >50 years was a significant predictor (OR 3.43, CI 1.62-7.23, p=0.001). The sex of the patient was not a contributing variable (OR 1.47, CI 0.72-2.98, p=0.28). Conclusions: Diabetes is not an independent predictor of gastroparesis in patients with gastrointestinal symptoms referred for gastric emptying studies. Age >50 years was a significant predictor.

Key words: Gastroparesis, Gastric emptying study, Diabetics

INTRODUCTION

Gastroparesis is a chronic disorder of gastric motility that is characterized by delayed emptying of either solids or liquids from the stomach in the absence of any mechanical obstruction. Gastroparesis assumes clinical importance because it can contribute to upper GI symptoms like nausea, vomiting and early satiety.

Delayed gastric emptying *per se* as documented by scintigraphy is present in 25-55% of patients with type 1 diabetes and in 30% of those with type 2 diabetes.[1-4] However, the relevance of these findings to clinical symptoms is unclear as gastrointestinal symptoms correlate poorly with the presence or absence of delayed gastric emptying. Nearly 50% of patients with a marked delay in gastric emptying may exhibit no symptoms while some patients with severe symptoms may have a near-normal or normal emptying pattern.[1,5,6]

Upper gastrointestinal symptoms in diabetics are largely attributed to gastroparesis as it commonly assumed that diabetics are more prone to gastroparesis vis-á-vis the general population. This assumption leads to an increased ordering of gastric emptying studies (GES) among diabetics. We undertook a study to determine whether diabetes is an independent predictor of gastroparesis in symptomatic patients referred for GES.

METHODS AND MATERIAL

Study Population

The study group consisted of ***consecutive*** patients with upper gastrointestinal symptoms referred for a GES over a 5-year period. All, except for one in-patient, were outpatients referred from the primary care clinic and the gastroenterology specialty clinic.

Indication and Referral Pattern

All patients had at least one of the symptoms of ear-

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ly satiety, nausea, vomiting and abdominal discomfort and had undergone either an upper gastrointestinal barium study or an esphagogastroduodenoscopy (EGD) which did not indicate any mechanical obstruction or other findings capable of explaining the patient's symptoms.

Data Acquisition

All data was obtained from review of a state of the art electronic medical record (EMR) system in place at our hospital for more than a decade. Our hospital is the 2002 winner of the Davies award, which recognizes excellence in implementation of EMR among the hospitals of the nation.

Demography

Age in years at time of diagnosis as well as the sex of the patient was documented

Diabetes

The diabetic status of the patients was determined from the electronically documented problem list (ICD-9 code) and confirmed by a review of correlating laboratory studies.

Psychiatric disorders:

The presence of psychiatric disorders in each patient was documented.

Diagnosis:

A diagnosis of symptomatic gastroparesis was made if the patient had any of the clinical symptoms of nausea, vomiting, epigastric pain, bloating or early satiety in association with delayed gastric emptying documented by scintigraphy.

Esphagogastroduodenoscopy and Upper GI series

All symptomatic patients had been evaluated either by an esphagogastroduodenoscopy (EGD) or upper gastrointestinal series (UGIS) to exclude any other pathology or evidence of mechanical obstruction prior to a GES.

Gastric Emptying Study

A solid phase GES was performed as follows. After a fast of 8 hours, the patient was fed a meal consisting of 2 scrambled eggs labeled with 2.5mCi of 99mTc (technetium 99) along with 6 ounces of apple juice or orange juice. The caloric content of this meal was approximately 250 calories. The meal was consumed over a period of 15 minutes. The subject was then placed in the supine position and dynamic images obtained using a gamma camera over a period of 90 minutes.

The gastric emptying technique only utilized the anterior view, because patients frequently moved during the 90-minute acquisition, and the computers utilized did not have motion correction programs. When patients moved, manual processing was performed utilizing region of interest analysis and the frames with the highest and lowest counts in the stomach. Manual processing was also employed when radioactivity in the duodenum abutted the stomach, as this radioactivity could not be separated during automatic processing, and usually resulted in falsely prolonged gastric emptying. Manual processing of the anterior data resulted in better separation, and more accurate results.

Automatic curve fitting by the computer using the gastric emptying data was initially used in all patients to generate a gastric emptying half-time (t½). However, when issues arose due to patient motion or an adjacent duodenum, manual calculation of the disappearance half time was performed using region of interest analysis and the frames with the highest and lowest counts in the stomach. Either of these calculations was used to generate a gastric emptying half time, which was extrapolated as necessary despite the 90-minute acquisition. Even if one were able to anticipate an extremely long gastric emptying half time and would wish to extend the acquisition, most Nuclear Medicine computers would not allow this and retain a continuous gastric clearance curve. Practically, since many patients are already moving during a 90 minute acquisition, extending the acquisition further would guarantee the presence of significant motion artifact, which would then require manual processing.

Delayed gastric emptying was defined as a t½ >90 mins (mean +2SD), the accepted normal in our nuclear medicine department based on historical standards from literature and widely used in clinical practice.

Severity

Patients with a t1/2 >90 but <180 were classified as having mild gastroparesis and patients with a t1/2>180 minutes were designated to have severe disease.

Medication:

The medication list available on the EMR was reviewed to identify any obvious medication that could influence the gastric emptying process.

Exclusion criteria

(1) In patients who had multiple gastric emptying studies, only the index study was included.

(2) Patients with delayed emptying due to esophageal and duodenal causes were excluded.

(3) Patients who did not have EGD or UGIS prior to a GES were also excluded.

Statistical Analysis

The two groups were evaluated for differences using the Chi-Square test. Logistic regression analysis (simple and multiple) was performed to determine the association of different variables with gastroparesis.

RESULTS

A total of 188 consecutive patients had gastric emptying studies done within the study period. Twelve had multiple, indeterminate or un-interpretable results and were excluded. Four other patients had no documentation of a normal EGD or UGIS and were also deleted from the analysis. The final study group consisted of 172 patients.

Gastroparesis

Ninety-three (54%) of the 172 patients had evidence of gastroparesis.

Diabetes

Seventy- four (43%) of the 172 patients had diabetes mellitus. One patient had type 1 diabetes mellitus while the remaining 73 patients were classified as type 2. Of these 74 patients with diabetes mellitus, 42 (57%) had evidence of gastroparesis.

Correlation between diabetic control and gastroparesis

Hemoglobin A1C levels were available in 70 of 74 patients with diabetes and in 60 of these 70 patients, the hemoglobin A1C levels had been measured within 3 months of the date of the GES. In 30 of 32 patients with normal GES, the hemoglobin A1C ranged from 6.1% to 12.4% (median 7.5%, STD 1.53) while in 40 of 42 patients with abnormal GES the range was 5% to 12.5% (median 6.7%, STD 1.76). The Correlation coefficient between gastric emptying values and hemoglobin A1C levels was 0.09.

Duration of Diabetes

Of the 74 patients with diabetes mellitus, 37 patients had diseases duration of at least 5 years and 13 had diabetes of at least 10 years duration. The remaining 37 patients had diseases duration ranging from a minimum of 1 to a minimum of 5 years.

Nineteen of the 32 diabetic patients with normal GES, had a history of diabetes of at least 5 years and 6 had diabetes of at least 10 years duration. Eighteen of the 42 diabetic patients with abnormal GES had diabetes of greater than 5 years and 6 patients greater than 10 years.

Age

The patients ranged in age from 18-88 (median 53). There were 113 patients <50 years of age and 59 patients >50 years of age.

Sex

There were 117 females and 55 males totally in the study group. Of the 93 patients with gastroparesis there were 67 (72%) females and 26 males. Among the 42 diabetic patients with gastroparesis there were 27 females and 15 males compared to 40 female and 11 male in the non-diabetic patients with gastroparesis. These differences were not statistically significant (DF: 1, Chi-Square=2.28, p<0.20)

Medications

Twenty-four of 172 patients were on calcium channel antagonists and 18 of these patients had evidence of gastroparesis. Sixteen patients were taking tricyclic antidepressants and 5 of these patients had gastroparesis.

Severity

The t/1/2 ranged from 18-431 mins (median 97.8) in the non-diabetes patients, while the range was 31.7-560 mins (median 98) in patients with diabetes (see figure1). Of the patients with gastroparesis and diabetes, 29% (12) had severe disease and 71% (30) had mild disease compared to 37% (19) and 63% (32) in the non-diabetic group.

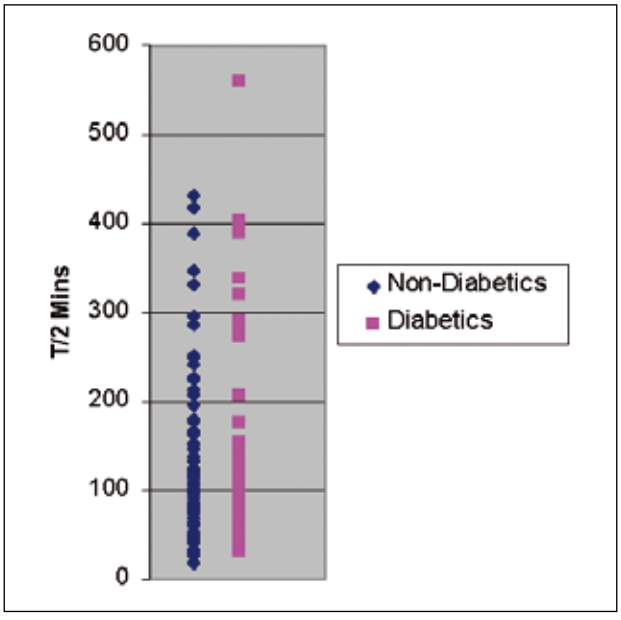

Figure. 1: Range of gastric emptying

Table 1. Characteristics of patients with gastroparesis.

	Diabetics (74)	Non Diabetics (98)
No.with gastroparesis	42(57%)	51 (52%)
Age Range	25-88 (median 58.5)	18-75 (median 54)
Female: Male	1.4:1	3.6:1
Severe gastroparesis	12(28%)	19 (37%)
Psychiatric Disorders	14(33%)	27 (53%)

These differences were not statistically different (DF: 1, Chi-Square=0.78, p>0.05)

Variables

The relationship between gastroparesis and five variables: diabetes, age>50 years, female sex, calcium channel antagonists and tricyclic antidepressants was evaluated by logistic regression. Simple logistic regression analysis (see table 2) revealed an odds ratio of 1.20 for diabetes, but with CI ranging from 0.65-2.2, this was not significant (p=0.54). A clear propensity for diabetics was not confirmed. When multiple logistic regression analysis was done (table 3 and figure 2) to adjust for the other variables, this association became even weaker (OR0.77, CI 0.0.37-1.56, p=0.46).

Age>50 years was an independent determinant (OR3.43, CI 1.62-7.23, p=0.001). We used >50 years as a variable because this cut off level was the most significant (Chi-Square 13.52, DF=1, p=<0.001) as opposed to a cut-off levels of 40 years (Chi-Square=7.45, DF=1, p=>0.005) and 60 years (Chi-Square=8.90, DF=1, p=>0.001).

Sex of the patient was not a significant contributing factor (OR 1.47, CI 0.72-2.98, p=0.28). Medications like calcium channel blockers (OR 1.11, CI 0.42-2.91, p=0.83) and tricyclic antidepressants (OR 0.29, CI 0.08-0.94, p=0.04) did not significantly alter the outcome.

Ordering Physician

Sixty-one (35.5%) of the 172 GES evaluated were ordered by non-GI physicians in contrast to 111 (64.5%) ordered by GI physicians. Diabetics accounted for 67% (41/61) of GES ordered by non-GI physicians. In comparison, diabetics made up only 30% (33 of 111) of GES ordered by GI physicians (see figure 3). These differences were statistically significant (DF: 1, Chi-Square=22.56, p<0.001)

Of 93 positive GES, 62 (66%) were ordered by gastroenterology specialists while the remaining 31 (34%) of tests were ordered by primary care physicians. The GI physicians were successful in accurately predicting gastroparesis in 55.9% (62 of 111) compared to a success rate of 52.5% (31 of 61). These differences were not significant (DF: 1, Chi-Square=0.40, p>0.05)

Co-Morbidities

Co morbidities that had direct effect on gastric motility were evaluated including connective tissue diseases, thyroid disease and psychiatric disease because of frequency

Table 2. Simple Logistic Regression Analysis

Variable	*Coefficient*	*Std. Err.*	*Odds Ratio*	*CI*	*P value*
Diabetes	0.19	0.31	1.20	0.65-2.2	0.54
Age >50	1.18	0.32	3.26	1.72-6.19	0.0003
Gender	0.56	0.33	1.76	0.92-3.37	0.08
CCA	0.61	0.46	1.84	0.74-4.57	0.19
TCA	-1.05	0.56	0.35	0.11-1.05	0.06

Table 3. Multiple Logistic Regression Analysis

Variable	*Coefficient*	*Std. Err.*	*Odds Ratio*	*CI*	*P value*
Diabetes	-0.26	0.36	0.77	0.37-1.56	0.46
Age >50	1.23	0.38	3.43	1.62-7.23	0.001
Gender	0.38	0.36	1.47	0.72-2.98	0.28
CCA	0.10	0.49	1.11	0.42-2.91	0.83
TCA	-1.24	0.60	0.29	0.08-0.94	0.04

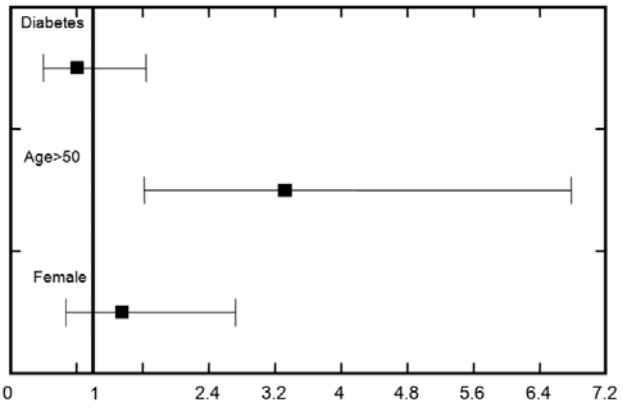

Figure 2. Odds Ratio and Confidence Intervals (Multiple Logistic Regression Analysis) of the three main variables: Diabetes, Age >50 and Female sex.

of occurrence. Six patients had hypothyroidism (4 diabetic and 2 non diabetic) and were controlled on treatment. Three patients had a history of connective tissue disease (Rheumatoid arthritis): all non- diabetic. One patient had fibromyalgia (non-diabetic). Psychiatric disorders (anxiety, depression and schizoaffective disorders) were significantly prevalent in the study population. Out of 42 diabetics with gastro paresis 14(33%) carried an ICD-9 diagnosis of a psychiatric disorder, while 27(53%) out of 51 non- diabetic patients with gastro paresis had a psychiatric disorder. These differences were not statistically significant (DF=1, Chi-Square=3.59, p> 0.05)

DISCUSSION

Studies[7,8] have indicated that diabetic patients tend to have a high incidence of upper gastrointestinal symptoms like nausea, vomiting, early satiety and dyspepsia. In a cohort of 110 patients with type 1 diabetes mellitus, Schvarcz et al [7] found that 27% had early satiety and 23% complained of nausea; these figures were statistically more significant compared to a control population of healthy patients. Enck et al[9] similarly noticed an increased incidence of upper gastrointestinal symptoms like nausea in Type 2 diabetics. Other studies[10,11] however have not been able to validate these findings.

As stated earlier, there is a high incidence (upto 65%) of delayed gastric emptying in patients with both type 1 and type 2 diabetes mellitus,[12] leading physicians in clinical practice to automatically assume that diabetics with upper gastrointestinal symptoms are more likely to have gastroparesis. Our study demonstrated that this is not necessarily the case and is probably the first study to highlight this finding.

Gastroparesis in our study was diagnosed using gastric scintigraphy that remains the gold standard for assessment of gastric emptying. However gastric scintigraphy suffers from a lack of standardized protocol, differing end points and a wide variability in what is considered to be the normal range. We used an egg based meal with a caloric content of 250 calories which is similar to what other centers have used.[13] A detailed discussion of these variabilities is provided by Tougas et al.[13]

Some centers use the percent of gastric retention at 2, 3 or even 4 hours as an index of gastroparesis. Another commonly used measure is the t½, the estimated time required for the stomach to empty one-half of the original meal. The normal range for t½ varies between institutions. In our hospital we have traditionally used a t½ > 90 minutes as indicative of gastroparesis which is in the range quoted by other centers.[14]

Our aim in this study was not to define the overall prevalence of gastroparesis in diabetic patients. Any data

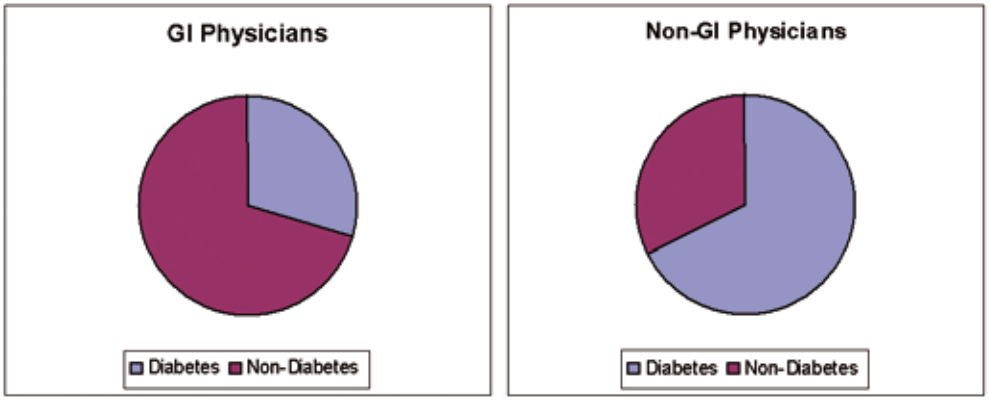

Figure 3. Pattern of ordering of GES by GI specialists compared to others

presented pertains to this select subset of diabetic patients with gastrointestinal symptoms referred for gastric emptying study and is included for the sake of statistical completion. Our goal was to ascertain whether diabetes was an independent risk factor in symptomatic patients referred for gastric emptying study.

Without age-adjustment the odds ratio of 1.20 suggested a slightly increased risk of gastroparesis with diabetes, in our study. When adjusted for age, sex, and medications diabetes was clearly shown not to be a risk factor, with the relationship becoming even weaker (OR 0.77). We have not come across any another systematic study that has attempted to ascertain whether diabetes is an independent determinant of gastroparesis in symptomatic patients.

In a random population of 86 diabetic patients (1) undergoing gastric emptying studies, solid gastric emptying was delayed in 48(56%). Although ours was a select population with upper gastrointestinal symptoms the incidence of 57% with gastroparesis was similar, which reaffirms the poor correlation between delayed gastric emptying and upper gastrointestinal symptoms. Other studies have also hinted that the relationship between symptoms and gastroparesis in diabetic patients may not be strong.[15]

Age greater than 50 was a determining factor in our study. While 3 different studies[16-18] from one center by the same researcher claim that age has no effect on gastric emptying or may even accelerate the process,[18] other researchers have reported results at variance with these findings; these other studies indicate that gastric emptying of both solids and liquids is impaired in elderly subjects.[19-21] The result of our analysis also suggests that increasing age may be a factor in delayed gastric emptying. It is our feeling that correlation between diabetes and gastroparesis made by older studies was obfuscated by the age factor.

Studies have also come up with conflicting results with regard to the effect of gender on gastric emptying. While some studies show no effect,[17,22] other reports[18,23-25] indicate that gastric emptying in females is delayed compared to males. But it is not clear whether the age factor was taken into account in these studies before making the final conclusion.

Seventy –two percent of our patients with gastroparesis were female which is similar to what other studies have reported.[26] Our study, however, indicates that female sex is not an independent risk factor when other factors are adjusted for.

With regard to the duration of diabetes in patients with gastroparesis, the retrospective limitation of our study did not allow us to obtain precise data and hence we cannot make any definitive conclusions. However the data is presented to give an overview of the patient characteristics in the subsets with normal and abnormal GES.

There was poor correlation between gastric emptying and HbA1c levels and our results mirror the findings of Horowitz et al.[5]

Our finding is clinically relevant as a sizable number of physicians are influenced by the diabetic factor in ordering a GES while ascertaining the etiology of upper gastrointestinal symptoms. In our study 67% of GES ordered by non-GI physicians happened to be in diabetic patients.

We conclude that the presence of diabetes must not unduly influence a physician in ordering a gastric emptying study but must be guided by the relevant symptoms. We are fully aware of the limitations of our study because of its retrospective design. However, we feel that the findings are remarkable enough to warrant a prospective study to confirm our findings.

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