

Delayed Gastric Emptying in Anorexic Adolescents Measured with the ^{13}C Octanoic Acid Breath Test

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ABSTRACT

Many gastrointestinal complaints and motility disorders are described in patients suffering from different eating disorders. These have a negative impact on refeeding. This report evaluated—on admission—gastric emptying of a standardized solid meal with ^{13}C octanoic acid breath test in anorexic adolescents. The results were compared with age and gender matched controls. Gastric emptying data were related to a subjective symptom score. 21 anorexic girls and 3 boys (mean age: $15.6 \text{ y} \pm 1.3 \text{ y}$), body mass index (mean $15.6 \text{ kg/m}^2 \pm 1.6 \text{ kg/m}^2$), weight loss (mean: $22.2\% \pm 10.7\%$) were studied. $T_{1/2}$ of the gastric emptying time exceeded the P95 in 14/24 (58%) patients, classified as having delayed gastric emptying (DGE). One patient (4%) had a $T_{1/2}$ exceeding P75 and was classified as slow (SGE), whereas 9/24 (38%) patients had normal gastric emptying (NGE). In comparison to NGE, subjects with DGE had significantly higher symptom scores ($p = 0.01$) and more weight loss. The DGE and SGE patients lost 25.29% and 21.38% of weight respectively, whereas a weight loss of 17.64% was found in anorexics with NGE. In conclusion, gastric emptying is delayed in patients with anorexia. This is associated with more significant gastrointestinal symptoms and higher weight loss.

Keywords: Anorexia Nervosa; Gastric-Half-Emptying Time; ^{13}C Octanoic Acid Breath Test; Subjective Severity Symptom Score

1. Introduction

Anorexia is commonly associated with gastrointestinal complaints such as bloating, nausea, epigastric discomfort, belching and postprandial fullness [1]. These symptoms have a negative impact on refeeding [2,3]. Delayed gastric emptying has been found in both anorexic and bulimia patients mostly for solids and semi-solids, but not for liquids [4]. It has long been debated whether delayed gastric emptying is influenced by the “fear to eat”—cited by Cannon in 1988 and by Inui in 1995 in their respective papers, or whether primary alterations in gastric motor function are the driving force [5-8]. Gastric dilatation is common in binge-eating [9]. In rare cases dilatation impairs circulation of the gastric wall and mucosa and may lead to gastric perforation.

Gastric emptying of liquids, semisolids and solids can

be measured non-invasively and safely using the ^{13}C octanoic acid breath test [10]. The purpose of the present paper is to evaluate gastric emptying of a standardized solid meal in acutely ill anorexic adolescents and to compare these results with previously obtained normal values [11]. We also investigated whether delayed gastric emptying influenced the patient's subjective symptom score. Gastric emptying was studied in patients suffering from different types of eating disorders (restrictive versus purgatory behaviour).

2. Patients and Methods

2.1. Patient Selection

The study was prospective as all patients with anorexia nervosa (AN) and severe gastrointestinal complaints admitted to our Eating Disorder Unit from 2007 till 2008 were scheduled to undergo a ^{13}C octanoic acid breath test

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on admission. All had gastrointestinal symptoms including gastric fullness, bloating, belching, vomiting, epigastric pain, constipation or nausea. All fulfilled the DMS-IV (Diagnostic and Statistical Manual of Mental disorders, 4th edition DSM-IV) criteria ascertained by a child psychiatrist and a paediatric nutritionist [12]. The patients were recruited according to inclusion and exclusion criteria (**Table 1**). The purpose and methodology of the study were explained to all patients and parents in their native language.

The study was conducted according to GCP guidelines and approved by the Hospital's Ethical Committee (Approval number: 2999). All patients and parents signed informed consent.

2.2. Methods

A clinical examination was carried out by the same paediatrician, specialised in adolescent medicine. A standardized questionnaire was answered concerning gastrointestinal disturbances in their first week of admission, before they had their test meal. The questionnaire was an adapted version of the Likert scale, frequently used in clinical trials to measure dyspepsia [13]. Our symptom score graded from 0 till 5 (0 = no complaints and 5 severe complaints) (**Table 2**), for the following seven signs and symptoms: bloating, gastric fullness, belching, nausea, vomiting, constipation and epigastric pain. Thus the maximum score for each patient was 35 points. Upon completion of the questionnaire with the investigator, patients received a test meal after an overnight fast during the first week, in sitting position and under supervision by a study nurse. Body mass index (kg/m^2) was calculated, curves and percentiles were used as reported by Rolland-Cachera *et al.* [14].

2.3. Test Meal Preparation

The test meal consisted of a pancake enriched with ^{13}C octanoic acid. Preparation was as follows: 50 μL ^{13}C octanoic acid was mixed with 17 g flour, 7 g sugar, 1 egg white, 1 frozen egg yolk and 40 ml half-skimmed milk. The preparation was baked with 5 g margarine. Sugar (5 g) was added for consumption. This meal accounted for 230 calories (12.25 g proteins/27 g carbohydrates/8.8 g fat) [11].

2.4. Breath Sampling

Breath samples were collected in vacutainers: 2 basal breath samples prior to the test meal, followed by one sample every 15 minutes during 4 hr.

2.5. Analysis and Calculation

The medium chain fatty acid ^{13}C octanoic acid is absorbed

Table 1. Inclusion and exclusion criteria of the study patients.

Inclusion criteria
1) Anorexia nervosa adolescent (DMS-IV criteria)
2) Age: 9 - 18 years
3) $\text{BMI} \leq 18 \text{ kg}/\text{m}^2$
4) Gastrointestinal symptoms
Exclusion criteria
1) Connective tissue disease
2) Neuropathic disease
3) Diabetes mellitus
4) Any medication 1 week prior to testing
5) Gastric surgery
6) Food allergies

Table 2. The subjective severity score adapted from the existed likert scale and practically changed for our study population [13].

The subject severity symptom score
1) No problem
2) Minimal problem (can be easily ignored without effort)
3) Mild problem (can be ignored, but does not influence daily activity)
4) Moderate problem (cannot be ignored and occasionally influences daily activity)
5) Severe problem (cannot be ignored and markedly limits daily activity)
6) Very severe problem (cannot be ignored, markedly limits daily activity and requires medication or rest)

and oxidized after being emptied out of the stomach into the duodenum. Measuring the percentage of expired $^{13}\text{C}\text{O}_2$ in the total CO_2 pool using Isotope Rate Mass Spectrometry (IRMS). Mathematical analysis of the percentage of ^{13}C recovery allows calculation of 2 parameters namely the gastric half-emptying time ($T_{1/2}$) calculated in minutes and the gastric emptying coefficient (GEC).

Formulas for both parameters of gastric emptying for solids were formulas have been reported [11].

$$T_{1/2} = [11.83 - 0.59 * \text{gender} - 0.545 * \text{age} + 0.675 * (\text{age} - 6) - 0.635 * (\text{age} - 12)]^2$$

$$\text{GEC} = 1.98 + 0.13 * \text{gender} + 0.18 * \text{age} - 0.18 * (\text{age} - 6)$$

Breath samples were analysed in the Laboratory for Digestion and Absorption, University Hospital Leuven, Belgium.

2.6. Statistical Analysis

The results were compared to previously obtained normal values for gastric emptying (GE) of a similar solid test meal in age matched healthy adolescent girls and boys (**Table 3**). Children were divided into three groups: delayed-, slow- and normal gastric emptying (respectively DGE, SGE and NGE). Children with DGE or SGE were compared to those with NGE. For the subject severity score, the non-parametric Mann-Whitney U-test was applied. As the distribution of weight loss in the normal gastric emptying group allowed for the normality assumption (Kolmogorov-Smirnov, $p > 0.200$), we tested the difference in weight loss by independent t-test (omitting the equal variances assumption). Statistical calcula-

tions were performed using the SPSS statistics version 18.0.

3. Results and Discussion

Out of 56 anorexic patients admitted to our unit from January 2007 till August 2008, 21 anorexic girls and 3 anorexic boys participated [mean age: $15.65 \text{ y} \pm 1.32 \text{ y}$, mean body mass index (BMI) $15.56 \text{ kg/m}^2 \pm 1.62 \text{ kg/m}^2$, mean weight loss mean: $22.25\% \pm 10.66\%$ (range 7.9% - 49.5%)]. Fourteen (58%) anorexic patients with a $T_{1/2}$ exceeding P95 were classified as having delayed gastric emptying (DGE), in 1/24 (4%) the $T_{1/2}$ exceeded P75 (SGE). 9/24 (38%) Patients had normal gastric emptying (NGE) (**Table 3**). An average symptom severity score of

Table 3. Study results of the patients; the results of the symptom score and the gastric emptying measured with the ¹³C octanoic acid breath test are compared with a control population of the same age and gender [11] (R = restrictive and P = purgative).

Pat.	Gender	Age (y)	BMI (kg/m ²)	Weight loss (%)	T _{1/2} GE (min)	T _{1/2} GE controls (min) (perc)	Interpretation	Symptom score (total: 35 pt)	R/P
1	F	15.9	16.0	20.4	162	122 (P99)	DGE	18	R
2	F	16.7	17.9	7.9	99	99 (P97)	DGE	15	R
3	F	14.2	15.6	20.0	66	67 (P45)	NGE	19	R
4	F	16.6	18.2	18.5	66	69 (P85)	NGE	28	P
5	F	16.2	12.7	21.4	81	83 (P90)	SGE	29	R
6	F	16.0	16.7	25.2	143	112 (P99)	DGE	32	P
7	F	14.4	14.4	49.8	186	134 (P99)	DGE	27	R
8	F	14.2	15.0	27.7	70	70 (P50)	NGE	24	P
9	F	14.0	12.9	23.0	166	134 (P99)	DGE	27	R
10	F	15.9	14.3	25.4	92	93 (P95)	DGE	19	R
11	F	13.0	14.8	9.4	250	146 (P99)	DGE	28	R
12	F	17.3	14.5	37.2	141	103 (P99)	DGE	27	R
13	F	16.1	16.4	15.8	54	54 (P50)	NGE	22	R
14	F	17.0	15.3	22.9	153	103 (P99)	DGE	28	R
15	F	16.2	17.1	20.0	137	112 (P99)	DGE	24	R
16	M	16.3	16.3	48.4	117	101 (P99)	DGE	30	R
17	F	15.8	15.1	20.4	126	112 (P99)	DGE	19	P
18	M	13.3	12.6	10.2	70	71 (P55)	NGE	19	R
19	F	14.2	15.9	21.7	73	72 (P55)	NGE	16	R
20	F	13.0	16.2	11.3	70	69 (P35)	NGE	20	R
21	F	13.6	14.8	10.5	59	59 (P20)	NGE	12	R
22	M	16.7	16.7	27.2	106	91 (P99)	DGE	32	P
23	F	15.2	23.2	23.3	67	67 (P60)	NGE	16	R
24	F	18.9	17.0	17.0	124	123 (P99)	DGE	24	R

25/35 (71.4%) was found in the groups with DGE and SGE while a severity score of 19/35 (54.3%) was found in the normal group ($p = 0.029$). The delayed group (DGE and SGE) had 25.0% weight loss whereas a weight loss of 17.6% was found in the group with NGE ($p = 0.059$). 19/24 (79%) patients had a restrictive character of their eating disorder and 5/24 (21%) have a purging type eating disorder. In the purging group we found 3/5 DGE and 2/5 NGE; in the restrictive group we found 12/19 (63%) DGE. 7/19 (37%) Anorexic adolescents had NGE.

Delayed gastric emptying (DGE + SGE) was thus recorded in 62%, with an average severity score of 25/35. The majority of these anorexic patients had a restrictive character of their eating disorder with an average weight loss of 25%.

Observations in “the biology of human starvation” by Keys *et al.* in 1950 indicate that in the starving man the nutritional state plays a key role in gastric emptying. Hence the hypothesis that severe malnutrition by atrophy of the smooth muscles of the gastro-intestinal tract can explain delayed gastric emptying, especially in restrictive anorexic behaviour, seems plausible [15-17]. Other muscle dysfunctions are on record in anorexia. Myocardial muscular atrophy is seen in the acute state of starvation, with thinning of the left ventricular wall and a reduced left ventricular mass index [18]. Atrophy of type two fibers in skeletal muscle explains functional disturbances in daily life [19]. Therefore the possibility exists that gastric muscle function may be altered in emotional disturbances. The fear to eat has induced a depreciation of these gastrointestinal symptoms: “anorexics will complain of feeling full after a few bites” [2]. In one study where oesophageal motility is investigated with manometry, there was no improvement of oesophageal symptoms like dysphagia, belching and heartburn after a prolonged rehabilitation program with return to normal weight. An improvement, only for gastric and colonic symptoms, was observed. The authors found no association between frequency and severity of oesophageal symptoms and major motor disturbances of the oesophagus [20].

This is the first report comparing the results of the GE breath test with a subjective symptom score; we observed that a significantly higher symptom score of 25/35 was found in the groups with DGE and SGE. Thus the presence of a 25% weight loss and a symptom severity score of $\geq 25/35$ in an anorexic adolescent are objective components of delayed gastric emptying demonstrated by the ¹³C octanoic acid breath test. This is probably due to the fact that delayed GE is caused by wasting of the smooth muscle fibers of the gastrointestinal wall resulting in dysmotility. Other observations mentioned malnutrition as a cause of dysmotility: acute gastric dilatation in pris-

oners of war during refeeding and slow gastric emptying in normal volunteers during starvation [15]. That gastric emptying is correlated with body weight is confirmed in obese subjects who evacuate gastric contents more rapidly [21].

To our knowledge there are no data on the use of the ¹³C octanoic acid breath test in anorexic adolescents for measuring gastric emptying time. The gold standard for measurements of oesophageal and gastric emptying in patients with eating disorders has been radioscintigraphy with technetium 99 labelled triethylenetetraamine polystyrene resin [22]. Gastric emptying times have been studied in the same patient without and with the use of metoclopramide [10,22]. In our view, for anorexic adolescents with gastrointestinal complaints the ¹³C octanoic acid breath test is better, easier, cheaper and safer than radioscintigraphy with technetium 99 labelled triethylenetetraamine polystyrene resin (^{99m}Tc TETA) and the electrogastrogram to confirm gastric dysmotility disorders [22-24]. With this breath test technique follow-up studies become easier and safer.

4. Conclusion

Our observations point to one of the main reasons why it is difficult to refeed some anorexic patients. It is probably useful to choose more digestible diets for refeeding: namely meals and nasogastric feeding containing more whey and soy proteins and less casein and carbohydrate. The latter digest faster in these patients and therefore facilitate refeeding. It is important to plan refeeding with specialized nutrition teams for every severely anorexic patient, to prevent or minimize these gastrointestinal complaints. Future gastric emptying studies should be compared with gastric biopsy, in the acute stage and after refeeding, to document atrophy and subsequent recuperation of smooth muscle fibers.

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Abbreviations

AN: anorexia nervosa

GE: gastric emptying

GI: gastrointestinal

DMS IV: Diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV)

IRMS: Isotope rate mass spectrometry

IGF-1: Insulin growth factor-1

NGE: normal gastric emptying

SGE: slow gastric emptying

DGE: delayed gastric emptying