

# Comparison of gastric emptying parameters between asymptomatic volunteers and patients with functional dyspepsia in Middle Eastern population

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## ABSTRACT

**الأهداف:** الحصول على القيم المرجعية الطبيعية لفحص خلو المعدة عند الأشخاص الطبيعيين في الشرق الأوسط بطريقة قياسية والتحقق من نتائجها لدى مرضى عسر الهضم الوظيفي.

**الطريقة:** تم إجراء دراسة استطلاعية لقياس مؤشرات خلو المعدة لدى 36 شخص طبيعى سليم. كانت المؤشرات القياسية هي مرحلة الركود، و نصف الوقت، و خلو المعدة في الساعة الأولى، ثم الثانية، ومن ثم الثالثة. تمت بعد ذلك مقارنة النتائج مع 49 مريض مصاب بعسر الهضم الوظيفي. أجريت هذه الدراسة خلال الفترة من يوليو 2005م حتى أغسطس 2009م في مستشفى الجامعة الأردنية – الأردن.

**النتائج:** لم تكن هناك فروق إحصائية بين المجموعتين فيما يتعلق بمرحلة الركود. كان الاحتباس المعدي في الساعة الأولى، والثانية، والثالثة أعلى لدى مرضى عسر الهضم الوظيفي ( $p=0.045$ ,  $p=0.003$ ,  $p=0.002$ ). كان الاحتباس المعدي في الساعة الثالثة أكثر القياسات حساسية لتحري تأخر خلو المعدة، وكان ذلك موجودا لدى 16 مريض (32.6%). كان الاحتباس المعدي في الساعة الأولى أكثر من الطبيعي لدى 3 مرضى فقط (6.1%) و طبيعى في الساعة الثالثة. كان نصف الوقت متأخرا لدى 12 مريض (24.5%)، إلا أن هؤلاء المرضى كان لديهم تأخر خلو المعدة في الساعة الأولى أو الثالثة.

**خاتمة:** لقد حصلنا على قياسات طبيعية لخلو المعدة للأشخاص في الشرق الأوسط. قياس الاحتباس المعدي في الساعة الأولى، و الثانية، و الثالثة كان كافيا للتعرف على تأخر خلو المعدة لدى مرضى عسر الهضم الوظيفي.

**Objectives:** To derive the normal reference values for Middle East population using a standard method, and to validate its performance in functional dyspepsia.

**Methods:** A prospective study was designed to derive gastric emptying parameters in 36 healthy control

subjects. We measured the lag phase, half time, and gastric retention at the first, second, and third hours. Values were compared to 49 patients with functional dyspepsia. This study was carried out between July 2005 and August 2009 at Jordan University Hospital, Amman, Jordan.

**Results:** There were no statistically significant differences between the 2 groups at lag phase. Dyspeptic patients had significantly higher gastric retention at the first, second, and third hours ( $p=0.045$ ,  $p=0.003$ ,  $p=0.002$ ). Gastric retention at the third hour was the most sensitive parameter detecting 16 patients (32.6%). Only 3 patients (6.1%) had increased gastric retention at the first hour and normal retention at the third hour. Twelve patients (24.5%) had delayed half time; these patients had increased gastric retention either at the first or third hour.

**Conclusions:** Measurement of gastric retention at the first, second, and third hour is enough to identify delayed-early and late phases of gastric emptying in functional dyspepsia patients.

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The term “dyspepsia” is derived from the Greek term “bad digestion”. Dyspeptic symptoms are thought to originate from the gastroduodenal region.<sup>1</sup> According to a recent survey, the prevalence of dyspeptic symptoms is

estimated between 10% and 40% in general population.<sup>2</sup> In most subjects with dyspeptic symptoms, no organic abnormality is identified by routine clinical work-up, and these patients are said to have functional dyspepsia.<sup>2</sup> Management of upper abdominal symptoms, when not caused by an organic disorder, is a clinical challenge. Different treatment strategies such as suppressing gastric acid secretion, eradicating *Helicobacter pylori*, prokinetics, and antidepressants have yielded inconsistent results in treating patients with functional dyspepsia.<sup>3</sup> This inconsistent therapeutic efficacy has been attributed to the heterogeneity of patients and to the presence of multiple mechanisms contributing to symptom development.<sup>3</sup> Different pathophysiological abnormalities have been proposed in patients with functional dyspepsia, these include *Helicobacter pylori* infection, impaired gastric accommodation, delayed gastric emptying, hypersensitivity to gastric distension, unsuppressed phasic contractile activity, duodenal lipid or acid hypersensitivity, autonomic or central nervous system disorders, abnormalities of gastric electrical rhythm, and small intestinal dysmotility.<sup>4</sup> To achieve greater therapeutic efficacy, treatment should be addressed towards the underlying pathophysiological process (namely, impaired gastric emptying).<sup>4</sup> Delayed gastric emptying in patients with functional dyspepsia may result from either antral hypomotility or duodenojejunal dysmotility.<sup>5,6</sup> A recent review summarized that 23-59% of dyspeptic patients have significantly delayed gastric emptying; however, most studies failed to find a convincing relationship between delayed gastric emptying and symptom pattern.<sup>7,8</sup> Radionuclide study of gastric emptying and motility is the most physiological study available for evaluating gastric motor function. The study is noninvasive, quantitative, it uses a physiologic meal and it is the most commonly used method for the assessment of gastric emptying.<sup>9</sup> An important limitation of gastric emptying scintigraphy is that different hospitals use test meals that often differ markedly in composition, volume, and caloric content, patient positioning, and frequency of imaging. This lack of standardization limits the clinical utility of the test and presents problems to physicians as they try to interpret study results. Furthermore, it seems that populations of different ethnicities or cultures have different gastric emptying parameters even when using a standardized meal.<sup>10,11</sup>

In this paper, we describe a standardized gastric emptying test, its related reference data, and its performance in patients with functional dyspepsia.

**Methods.** Thirty-six Jordanian control volunteers were prospectively enrolled in the study between July 2005 and August 2007. Volunteers had no history of

gastrointestinal illness, surgery, or other ongoing medical condition, not currently on any medication and all had normal fasting blood glucose level at the day of scan. The Ethical Review Board at the University of Jordan approved the derivation of normal reference data and all volunteers signed informed consent. The scan was also performed to 49 patients with upper gastrointestinal symptoms; nausea, vomiting, belching, bloating, early satiety and vomiting during the period between August 2007 and August 2009. Symptoms were chronic or recurrent for a period of at least one month without clinical, biochemical, endoscopic, or ultrasonic evidence of organic disease that could account to the symptoms. Patients with previously gastroparesis were also excluded from the study. Patients with predominant symptoms of heartburn or acid regurgitation and patients already on prokinetic agents were also excluded from the study. Premenopausal female subjects were imaged in the first 10 days of cycle to minimize hormonal effect on gastric emptying.

The subjects had fasted overnight and asked them not to smoke before the day of the scan. Each subject consumed a standard meal that consisted of 2 scrambled eggs, 4 black olives, 120 ml orange juice and 50 grams of bread. The eggs (60-70 grams each) were first labeled using 18 MBq <sup>99m</sup>Tc-Sulfur colloid, which was mixed with a raw egg. The labeled mixture was then scrambled in a nonstick frying pan for 4-5 minutes. The caloric value of this standard meal was 505 Kcal; it contained 23% protein, 27% fat, and 50% carbohydrates.

Anterior and posterior planar images within one minute after meal ingestion (T<sub>0</sub>). Subsequent anterior and posterior one minute images were obtained every 10 minutes for the first hour and then every 20 minutes for the remaining 2 hours. Patients were not allowed to smoke, eat, or drink anything for the whole duration study.

For each acquired image, a region of interest around the stomach was manually drawn. The geometric mean of anterior and posterior image sets for each time point was then calculated and corrected for decay. Five parameters were individually calculated for each subject, these include the percent gastric emptying at 3 data collecting times (first hour, second hour, and third hour), lag phase, and half time (T<sub>1/2</sub>). The lag phase was defined as the period extending from T<sub>0</sub> to the time at which 5% of gastric content left the stomach. Half time was defined as the time needed by the stomach to empty 50% of its contents. Gastric retention curves, lag phase, and T<sub>1/2</sub> were all generated using a modified power exponential function model describing the

proportion (prop) of retention at time (t): wherein k is gastric emptying rate and  $\beta$  is the intercept on y-axis back extrapolated from the terminal portion of gastric retention curve

$$\text{Prop } t = -(kt)\beta$$

**Statistical analysis.** Mann-Witney U test was used for assessing the effect of gender, body mass index (BMI) and age on gastric emptying parameters within each group and to compare the gastric emptying parameters between both groups. The value of  $p \leq 0.05$  was considered statistically significant. Data were analyzed using SPSS software version 11.5.

**Results.** Thirty-six healthy control subjects were enrolled (22 males and 14 females). The mean age was 31 years (range 19-49 years). Sixteen subjects had a BMI of  $\leq 25$  and 20 subjects had  $>25$ . There were no statistically significant differences between males and females at all parameters examined. No correlation between gastric emptying and age or BMI was found. The dyspeptic group consisted of 49 patients (18 males and 31 females). The mean age was 48 years (range 14-74 years). Sixteen subjects had a BMI of  $\leq 25$  and 33 subjects

had  $>25$ . No correlation between gastric emptying and age, gender, or BMI was found in the control group. Table 1 summarizes the descriptive statistics and Mann-Witney test for lag phase, T1/2, gastric retention at each point in both normal control and dyspeptic groups. Data for healthy control subjects were not normally distributed except for gastric retention at the first and second hours, therefore, it is more appropriate to use the 90th percentile as the upper limit for normal gastric emptying at all parameters examined. Eleven patients (22.4%) had increased gastric retention at the first hour, all patients had prolonged lag phase, and 3 of them normalized gastric emptying at the second hour. Twelve patients had increased gastric retention at the second hour (24.5%) and sixteen patients (32.6%) at the third hour. Twelve patients (24.5%) had delayed T1/2; however, all patients had either increased retention at the first or at the third hour. Data in both groups and at all time points were distributed in a wide range at the first hour (35-93% for control and 23-98% for dyspepsia group), at the second hour (6.7-64% for control and 4.5-93% for dyspepsia group), and at the third hour the range was 0.7-47% for control and 1.0-80% for dyspeptic group.

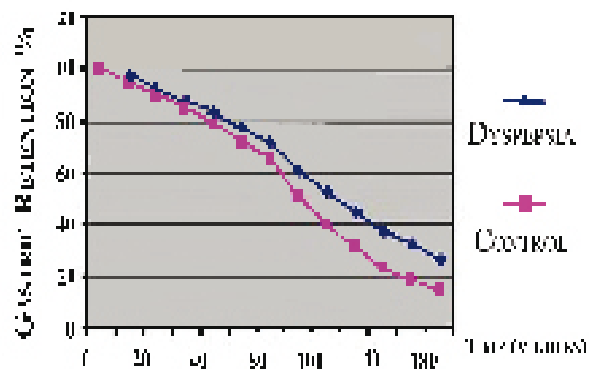
**Table 1** - Descriptive statistics and Mann-Witney test for both groups.

Parameter/groups	Mean $\pm$ standard deviation	Median	90'th percentile
<b>Lag phase (min)</b>			
Control	16.96 $\pm$ 7.49	15.74	28.2
Dyspepsia	23.56 $\pm$ 19.03	16	77.5
P value		0.176	
(95% confidence interval)		(0.171 - 0.186)	
<b>First hour (%)</b>			
Control	0.65 $\pm$ 0.15	0.67	0.82
Dyspepsia	0.71 $\pm$ 0.16	0.74	0.95
P value		0.045	
(95% confidence interval)		(0.041 - 0.049)	
<b>Second hour (%)</b>			
Control	0.31 $\pm$ 0.17	0.3	0.56
Dyspepsia	0.45 $\pm$ 0.2	0.45	0.85
P value		0.003	
(95% confidence interval)		(0.002 - 0.004)	
<b>Third hour (%)</b>			
Control	0.14 $\pm$ 0.12	0.12	0.31
Dyspepsia	0.26 $\pm$ 0.19	0.22	0.66
P value		0.002	
(95% confidence interval)		(0.001 - 0.003)	
<b>T1/2 (min)</b>			
Control	94.84 $\pm$ 39.69	89.4	147.3
Dyspepsia	150.51 $\pm$ 134.6	111	559
P value		0.017	
(95% confidence interval)		(0.013 - 0.018)	

**Discussion.** A considerable proportion of patients in clinical practice present with abdominal symptoms suggesting disordered gastric emptying without identifiable cause.<sup>3-7</sup> Abnormal gastric emptying may cause upper gastrointestinal symptoms due to inappropriate delivery rate of the meal into the small intestine for further digestion and absorption.<sup>4,7</sup> The evaluation of gastric emptying is generally indicated in patients with dyspepsia when morphological investigations fail to reveal the underlying etiology.<sup>9</sup> Scintigraphy is considered the gold standard to assess gastric emptying, it is also the most physiological and the most commonly used methods.<sup>12</sup> An objective and reproducible gold standard should be based on a standardized test meal, imaging technique, and data elaboration. Defining what constitutes normal gastric emptying is an essential step in the clinical assessment of patients with functional dyspepsia. Recently, a consensus for standardized gastric emptying scintigraphy has been published; it has established normative data from North American population using a low-fat egg-white meal.<sup>13</sup> In our region, there are differences regarding lifestyle, type of food consumed as well as racial and genetic variations and it is not commercially available. Data obtained from the western world may not be applicable to our region even if we standardize the methodology.<sup>10</sup> In this study, we provide normal values of gastric emptying in a simple standardized method. We used scrambled egg based meal, this meal represents the average breakfast meal for Middle Eastern population and can be easily prepared in any nuclear medicine facility. Furthermore, the use of egg-based meal (27% fat) may identify a larger number of patients with delayed gastric emptying when compared to a low fat egg-white meal (2% fat) that may not represent an adequate functional challenge to gastric motility.<sup>13,14</sup> As encountered in other studies, data for normal volunteers were not normally distributed; therefore, we preferred to use the 90th percentile to define the upper limit of normal.<sup>11,12</sup> No effect of gender, age and BMI was evident on gastric emptying, this is consistent with findings in other standardized studies and allows the use of our data as reference values for all patients.<sup>11,12,15</sup> Solids are initially retained in the stomach and undergone churning while antral contractions propel particles toward the closed pylorus.<sup>16</sup> The lag phase is the time required for the commencement of gastric emptying of solid particles, it represents the time for solid food to be triturated into small particles that are then passed through the pylorus.<sup>17</sup> There was no statistically significant difference in lag phase between control subjects and dyspeptic patients ( $p=0.176$ ). Gastric retention at the first hour was statistically higher in dyspeptic patients ( $p=0.045$ ); furthermore, all patients who had prolonged

lag phase had also increased gastric retention at the first hour. Therefore, we suggest that measurement of gastric retention at the first hour is enough to estimate the early phase of gastric emptying. The abnormal early phase gastric emptying was the single abnormal parameter in 3 patients (6.1%) suggesting a limited, yet potentially important, role in assessing patients with functional dyspepsia.

The statistical significance between both groups increased by time ( $p=0.03$  second hour and  $p=0.02$  third hour). Gastric retention at the third hour was the most sensitive parameter for abnormal gastric retention detecting 16 patients (32.6%) and missing only the 3 patients (6.1%). This measurement of gastric retention at the late phase of study has been demonstrated as the most useful index to assess gastric motility by few other studies.<sup>11,12</sup> Figure 1 is a time activity curve for overall gastric retention percent in both groups demonstrating better separation of the 2 curves at the third hour. When delayed early and late gastric emptying were considered a total of 19 patients (38.7%) had abnormal emptying. This value is in concordance with other studies regarding the relation between delayed gastric emptying and functional dyspepsia, in the largest of these studies gastric emptying of solids was delayed in approximately 23-59% of the patients with functional dyspepsia.<sup>5,7,8,18</sup> Half time is another parameter frequently reported in gastric emptying studies, it was statistically different between both groups ( $p=0.017$ ) and prolonged in 24.5% of dyspeptic patients. All patients who had delayed T1/2 had either delayed an early phase of gastric emptying or increased gastric retention at the third hour. This is a logical finding since T1/2 depends on gastric emptying rate for the whole duration of study. It has been previously demonstrated that less frequent imaging at 0, 60, 120, and 180 minutes, results in reasonable estimate of both lag phase and T1/2 using power exponential fit



**Figure 1** - Overall measured percent gastric retention curves generated using a power exponential model for healthy control subjects and patients with functional dyspepsia.



function in normal healthy volunteers.<sup>11,12</sup> In this paper, we have demonstrated that the measurement of both lag phase and T1/2 does not contribute to the identification of dyspeptic patients with delayed gastric emptying. We also confirm that the calculation of gastric retention at 4 time points describes accurately gastric emptying in dyspeptic population. This would save both time and money and render the gamma camera available for other studies. Several studies showed that there is poor correlation between gastric emptying, and individual symptoms, severity of symptoms, or symptom categories in dyspeptic patients.<sup>8,19-21</sup> Establishing a correlation between gastric emptying and dyspeptic symptoms was not our goal; therefore, in this study, patients were not divided into symptom subgroups; the selection was focused on patients with dyspeptic symptoms that were severe enough to seek medical care. The poor correlation between dyspeptic symptoms and gastric emptying is frequently explained by the presence of different pathophysiological mechanisms contributing to functional dyspepsia.<sup>4</sup> We suggest that the large variance of gastric emptying parameters in normal subjects and the substantial overlap between gastric emptying parameters in normal and dyspeptic patients may be another plausible explanation (Figure 2).

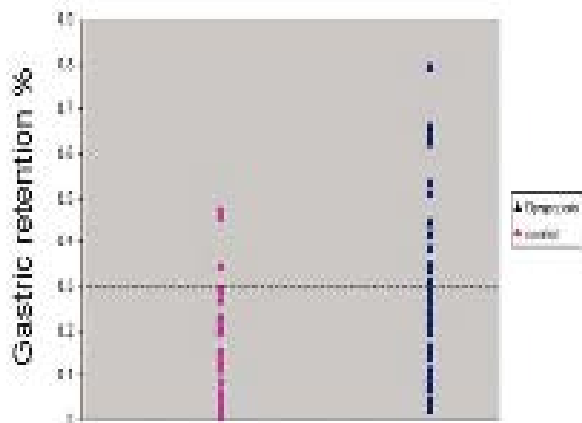
One limitation of this study is that subjects were not classified into habitual smokers versus non-smokers categories. Patients were asked not to smoke on the day of the scan and were not allowed to smoke at the scintigraphic test; however, they were not asked to abstain from smoking for 2 weeks prior to the scintigraphic test as carried out by some standardization studies.<sup>11,12</sup> There have been conflicting results regarding the effect of smoking on gastric emptying; some studies suggested delayed gastric emptying in habitual smokers, others,

on the other hand, demonstrated accelerated gastric emptying.<sup>22</sup>

In conclusion, we provide normal gastric emptying values for Middle East population. Gastric emptying was delayed in 38.7% of the patients with functional dyspepsia and this is consistent with the data obtained from the literature.<sup>7,8,27</sup> Using 4 time points for data collection is enough to identify dyspeptic patients with delayed early and late phases of gastric emptying. Measurement of lag phase and T1/2 is not expected to add clinically useful data in patients with functional dyspepsia. In this paper, we have standardized the test, described reference data in normal control subjects and validated the technique in patients with functional dyspepsia.

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**Figure 2** - Histogram representing overlap between percent gastric retention in both healthy control subjects and patients with functional dyspepsia. Dashed line at the 90th percentile for healthy control subjects.

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#### Related topics

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