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# Gastrointestinal motility in elderly patients with well-controlled type 2 diabetes mellitus

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**ABSTRACT – Background** – Gastrointestinal (GI) motility disorders in type 2 diabetes mellitus (T2DM) are common. However, the endpoints in well-controlled T2DM in elderly patients are barely understood. **Objective** – To evaluate GI transit and gastric myoelectric activity in elderly patients with T2DM who were undergoing treatment with metformin and to compare them with non-diabetic healthy controls. **Methods** – A total of thirty participants were enrolled in this study: young non-diabetic (n=10), elderly non-diabetic controls (n=10), and patients with T2DM managed with metformin (n=10). After fasting overnight, the participants ingested a standard meal and magnetic markers for non-invasive monitoring of GI transit and gastric contractility using the alternating current biosusceptometry and electrogastrography techniques. **Results** – Mean gastric emptying time, mean colon arrival time, and mean intestinal transit time were determined. There were no significant differences between the groups and in the parameters evaluated ($P$>0.05). The frequency and amplitude of gastric myoelectric activity were not different between groups; however, abnormal rhythmic index and the half-bandwidth were slightly higher for both elderly diabetic and non-diabetic groups compared with the young adults ($P$<0.01 and $P$<0.05, respectively). **Conclusion** – Our study showed unaltered gastric emptying and intestinal transit in T2DM patients with good glycemic control, and suggest changes in the gastric electrical activity can be a part of aging.

**Keywords** – Elderly, gastrointestinal motility, glycemic control, metformin, type 2 diabetes mellitus.

## INTRODUCTION

Type 2 Diabetes mellitus (T2DM) is one of the most prevalent chronic diseases worldwide and its complications demand significant public health expenditure[1,2]. In addition, the prevalence of gastrointestinal (GI) disorders in T2DM is relatively common and generally includes motor and functional changes affecting different segments[3]. Gastroparesis and enteropathy, and their classical symptoms, are typically associated with abnormal GI motility, but little is known concerning the GI function in elderly patients with well-controlled T2DM[3-5].

Both dietary and pharmacological approaches have been employed for the management of T2DM[6,7]. Metformin is a biguanide which acts to decrease blood glucose concentration and has been used as the first-line drug in the management of T2DM[8]. Studies have reported several effects caused by metformin within the gut, but little is known about its effects on GI motility[9].

The evaluation of GI functional disorders remains a clinical challenge and motility testing is used to identify physiological abnormalities and to guide a more effective management[10]. However, the lack of standardized protocols, ionizing exposure, and costs have been encouraging new noninvasive techniques as alternative methods for such evaluations. The issue with these methods is that most are not able to evaluate transit times and contractility abnormalities simultaneously, also requiring bowel preparation.

Alternating current biosusceptometry (ACB) has been developed and validated as a research tool to evaluate GI motility and transit in cases of physiological and altered conditions[11-14]. ACB is radiation-free, noninvasive, and does not require a magnetically shielded environment or prepared bowel. It can be used to evaluate different GI tract segments without any interference on physiological parameters[15]. Electrogastrography (EGG) is also a non-invasive technique used to record gastric myoelectric activity by means of cutaneous electrodes[16]. Currently, EGG is employed to evaluate normal and altered activity of slow waves in different conditions, such as gastroparesis and functional dyspepsia[17].

Despite the wide range of current techniques available for clinical practice, the results concerning GI motility are not fully comparable. Age, gender, diseases, and treatment should be also taken into consideration with any protocol. Particularly in T2DM, the comparison with healthy subjects is essential to provide a more accurate analysis since the baseline motility can already be impaired.

The goal of this study was to evaluate GI transit and gastric myoelectric activity in elderly T2DM patients undergoing treatment with metformin and to compare with non-diabetic healthy controls.

## METHODS

### Alternating current biosusceptometry

ACB is a non-invasive biomagnetic technique used towards monitoring GI transit and motility parameters in both human and animal models[18,19]. ACB uses a set of sensors consisting of two

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pairs of excitation and detection coils arranged in a first-order gradiometric configuration to monitor the displacement of magnetic markers throughout the GI tract[15,20]. Ferrites ($MgFe_2O_3$, 53≤ ø ≤75 µm) are widely used as magnetic markers since they have high magnetic susceptibility and strongly respond to the applied field. Besides, this material is non-toxic, insoluble, and is not absorbed by the GI mucosa[21].

### Electrogastrography

Electrogastrography (EGG) is a non-invasive method that uses Ag/AgCl electrodes placed on the abdominal surface to measure gastric electrical activity[17]. In EGG, the spontaneous rhythmic electrical activity recorded determines the timing and the frequency of the contractile activity.

### Ethics

This study was approved by the Institutional Ethics Committees at the Alagoas State University of Health Sciences (CAAE 89359018.3.0000.5011) and the Federal University of Alagoas (CAAE 89359018.3.3001.5013). It was conducted in accordance with the latest revised Declaration of Helsinki and all participants gave their informed consent before entering the study.

### Participants

Thirty participants were recruited from the community and from five medical centers for diabetes management. They were separated into three groups: a) young non-diabetic volunteers aged 40 years or less; b) elderly non-diabetic volunteers; and c) elderly T2DM volunteers. Both elderly groups were over 60 years of age. T2DM patients had been diagnosed at least a year earlier and had their glycemic levels well controlled since starting metformin monotherapy. All subjects had no symptoms of GI diseases, none had undergone GI surgery or had taken medication that affected GI function during the evaluation period. They were also asked to keep to their usual dietary habits and medications during the week before the study.

### Study protocol

GI transit time of the ingested magnetic markers was evaluated on a single-day study, following a protocol developed by our research group[19,22]. After fasting overnight, all participants had their capillary blood glucose measured with a portable blood glucose meter (ACCU – CHEK Active, Roche, Brazil). Afterwards, the participants received a standardized meal with a total caloric content of 550 kcal (white bread, cheese, and orange juice). Immediately after this meal they swallowed four hard gelatin capsules (size 00, Capsugel, Brazil) with 200 mL of water. Each capsule contained 1,000 mg of ferrite powder.

With the subjects in an upright position, the magnetic measurements were started 5 min afterward. Magnetic measurements were performed using the single-sensor ACB equipment (Br4-Science, Brazil) to monitor the square-point matrices (5 x 5) drawn around the gastric and colonic regions (FIGURE 1 A). Each biomagnetic monitoring session lasted 2 min and was repeated every 15 min for 8h.

EGG recorded gastric contractility during 15 min using surface electrodes with a bipolar configuration and connected to an amplifier system (Biopac EGG100C amplifier; set to 1000 gain, low-pass filter at 1 Hz, high-pass filter at 0.005 Hz) (FIGURE 1 B). Electrical signals were captured at the sampling rate of 20 Hz/channel, stored in ASCII, and digitized using a multi-channel recorder (MP100 System; Biopac Inc., Santa Barbara, CA, USA).

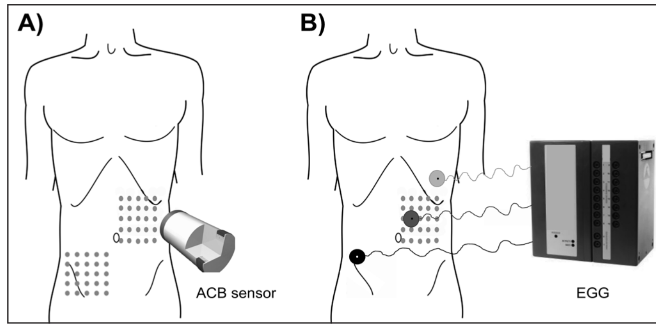


FIGURE 1. (A) Square-point matrices designed in the gastric and colonic projection regions of the participants for gastrointestinal transit monitoring using ACB sensor. (B) EGG electrodes for the recording of the gastric electrical activity.

All the participants remained moderately active during the day and were given lunch 5 h after the standardized meal.

### Data analysis

GI transit parameters were quantified using the sequential images obtained from the magnetic measurements[22,23]. The location of the magnetic material was obtained by plotting data on coordinate systems and in accordance with external anatomical references. The variation of the area of the magnetic image vs. time was used to generate the curve representing the GI transit profile for each participant.

The following parameters were calculated by applying statistical moment[24]: mean gastric emptying time (MGET), which represents the amount of magnetic material that empties from the stomach as a function of time t (min); mean colon arrival time (MCAT), which indicates the amount of magnetic material reaching the proximal colon region as a function of time t (min), and mean intestinal transit time (MSITT), which is the difference between MCAT and MGET[19].

Frequencies were expressed in cycles per minute (cpm). The contractility signals from EGG were analyzed using Butterworth filters with a cutoff frequency between 0.003 and 0.03 Hz (1.8–18 cpm). The frequency of gastric myoelectrical activity (GMA) was calculated using the fast fourier transform (FFT). The highest peak of frequency for each FFT was established as the gastric dominant frequency and the lowest peak was stated as the intrinsic noise of the signal. The amplitude of contraction was determined by the ratio between the intensity of intestinal peak (P) and noise peak intensity (P') and expressed in decibels (dB) as follows: $A = 10 \log10 (P/P')$[25].

Frequencies ranging from 2.4 to 3.6 cpm, which correspond to two standard deviation of the average gastric frequency obtained in the young non-diabetic group (3.06 0.35 cpm), were considered as normal. The abnormality rhythmic index (ARI) was calculated as the percentage of the peak frequency outside the range defined as normal[26]. Gaussian curves were plotted on the gastric frequency distribution obtained by the FFT. Half bandwidth (mHz) was defined as the bandwidth at 1/2 peak height and was quantified using the two points on the curve where the intensity was half the maximum intensity (y-axis). At these two points, the corresponding frequencies (x-axis) indicate the morphology of spectral distribution[13]. Such an analysis allows for the observing of narrow spectral profiles due to the single peak and wide spectrum represented by several peaks resulting from EGG recordings.

Data analysis and quantification were performed using MatLab® (Mathworks Inc., USA), Origin® (OriginLab, Co., USA), and GraphPad Prism 8 (GraphPad Software Inc, USA) softwares. The results were presented as mean ± standard deviation. A comparative statistical analysis between the groups was performed using one-way ANOVA with Bonferroni post-test. Differences were considered significant for a *P*-value <0.05.

## RESULTS

All the participants tolerated the protocol well and no adverse effects were observed. No differences in age and BMI for the elderly non-diabetic patients and for elderly with T2DM were found out. Fasting capillary blood glucose concentrations were moderately higher in the patients with T2DM than in the young group (*P*=0.007) or in the elderly participants without diabetes (*P*=0.001) (TABLE 1).

FIGURE 2 depicts the magnetic images (A) obtained for one representative subject from each group and the respective GI transit time curves (B). The gastric and colonic regions shown in this figure illustrate the regional transit of the magnetic markers.

TABLE 2 shows the mean gastric emptying time (MGET), the mean intestinal transit time (MSITT), and the mean colon arrival time (MCAT) for all the groups evaluated. Overall, gastric emptying, small intestinal transit, and colon arrival for the three groups of participants ranged from 50.0 to 154.1 min, 75.8 to 409.2

**TABLE 1.** Characteristics of the study participants.

| | Young non-diabetic (n=10) | Elderly non-diabetic (n=10) | Elderly T2DM (n=10) |
|---|---|---|---|
| Age (y) | 25.0±3.3[a] | 67.0±5.4 | 67.0±12.6 |
| Gender (M/F) | 5 M/5 F | 5 M/5 F | 3 M/7 F |
| BMI (Kg/m²) | 23.4±1.2 | 23.0±1.3 | 26.1±4.0 |
| Capillary blood glucose (mg/dL) | 93.7±14.4[b] | 86.4±9.3[c] | 125. 5±33.2 |
| Duration of T2DM (y) | N/A | N/A | 8.1±7.0 |
| Metformin treatment (y) | N/A | N/A | 8.0±6.1 |

Values are mean ± SD. BMI: body mass index; T2DM: type 2 diabetes mellitus; M: male; F: female; N/A: not applicable. [a]*P*<0.0001 compared with elderly non-diabetic and T2DM patients. [b]*P*=0.007 compared with T2DM patients. [c]*P*=0.001 compared with T2DM patients.

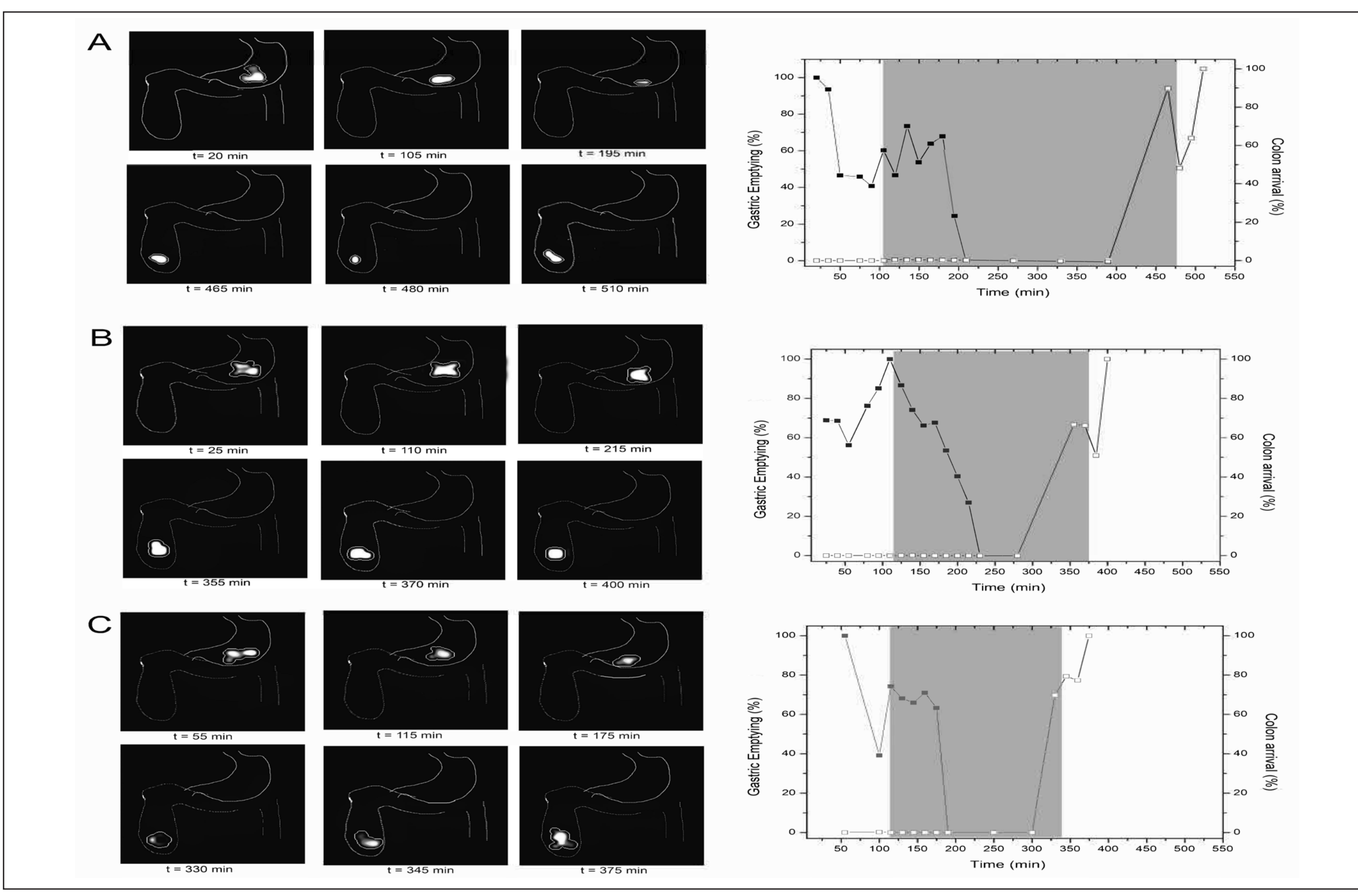


**FIGURE 2.** Magnetic images acquired for a representative (A) young non-diabetic participant, (B) elderly non-diabetic participant, and (C) elderly T2DM participant with their respective gastrointestinal transit time curves. Gray areas indicate the small intestinal transit.

**TABLE 2.** Gastrointestinal transit parameters assessed by ACB technique.

| | Young non-diabetic (n=10) | Elderly non-diabetic (n=10) | Elderly T2DM (n=10) |
|---|---|---|---|
| MGET (min) | 95.0±32.8 | 84.0±36.2 | 84.2±19.0 |
| **CV inter (%)** | 34.5% | 46.1% | 22.6% |
| **MSITT (min)** | 291.7±159.7 | 203.4±99.0 | 252.0±96.1 |
| **CV inter (%)** | 54.7% | 48.7% | 38.1% |
| **MCAT (min)** | 321.6±175.5 | 287.4±106.8 | 333.4±95.4 |
| **CV inter (%)** | 54.5% | 37.2% | 38.1% |

Values are mean ± SD. MGET: mean gastric emptying time; MSITT: mean intestinal transit time; MCAT: mean colon arrival time; CV inter: interindividual variation coefficient.

min, and 125.7 to 530.2 min, respectively. In view of the expressive intersubject variability, no significant differences among the groups studied were found.

FIGURE 3 illustrates the electrogastrograms obtained for the frequency analysis for a representative young non-diabetic participant (A), an elderly non-diabetic participant (B), and an elderly T2DM patient (C). Interestingly, spectral analysis revealed different patterns regarding signal morphology.

EGG analysis demonstrated that the frequency and amplitude of gastric myoelectrical activity among groups were not different (TABLE 3). Meanwhile, half-bandwidth and abnormal rhythmic index were slightly higher for both elderly non-diabetic and elderly diabetic participants when compared with the young group.

## DISCUSSION

In this study, we reported that GI transit in elderly patients taking metformin and with well-controlled T2DM was not different from that seen in elderly non-diabetic and young non-diabetic subjects. However, the analysis of the electrogastrograms revealed marked differences in signal morphology for both elderly groups. Age, gender, diseases, and treatment should be also taken into consideration in any protocol. In the case of T2DM, the comparison with age-matched healthy subjects is essential to provide a more accurate analysis since baseline motility can be already impaired. It is also interesting to point out that such an analysis and comparisons are barely discussed when considering elderly patients.

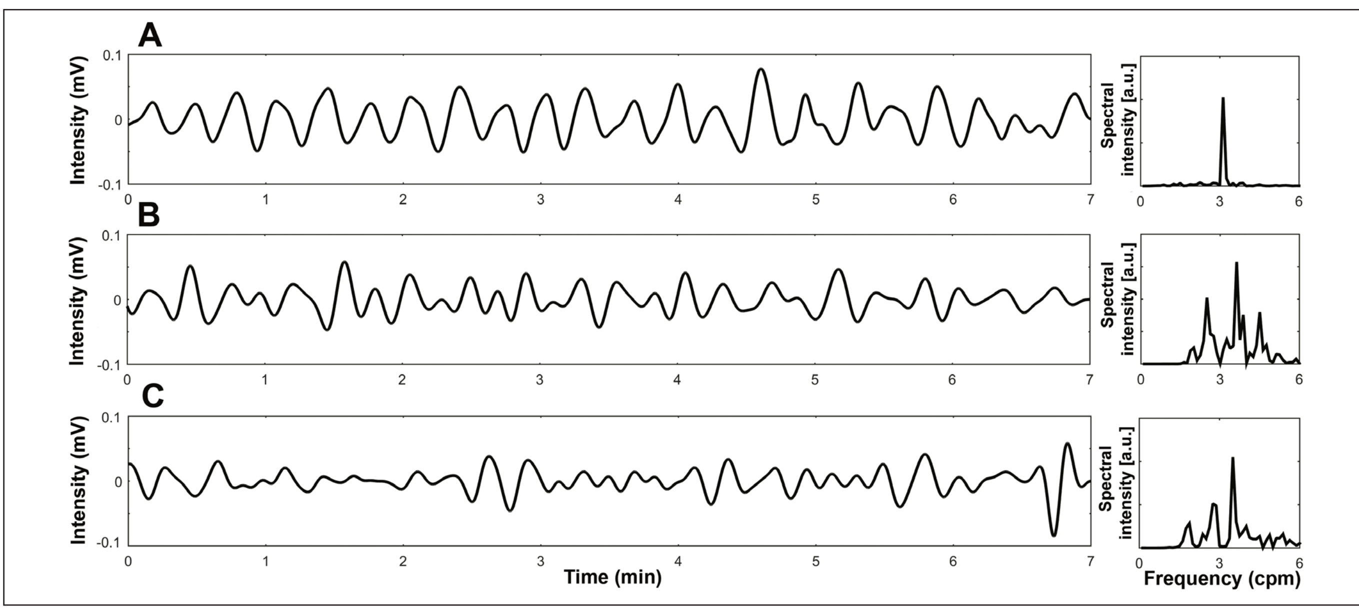


**FIGURE 3.** Gastric contractility signals recorded by EGG and their respective gastric dominant frequency in a young non-diabetic participant (A), an elderly non-diabetic participant (B), and a T2DM patient (C).

**TABLE 3.** Gastric myoelectric activity evaluated by EGG technique.

| | Young non-diabetic (n=10) | Elderly non-diabetic (n=10) | Elderly T2DM (n=10) |
|---|---|---|---|
| Frequency (cpm) | 3.1±0.4 | 3.3±0.2 | 3.5±0.8 |
| **Amplitude (mHz)** | 44.0±4.9 | 45.7±17.2 | 51.9±6.6 |
| **Half-bandwidth (mHz)** | 0.0023±0.0018[ab] | 0.0214±0.014[ac] | 0.047±0.026[bc] |
| **ARI** (%) | 24.0±19.6[a] | 32.0±16.6[b] | 57.8±26.4[ab] |

Values are mean ± SD ($P<0.05$, ANOVA, Tukey post hoc test). ARI: abnormal rhythmic index; T2DM: type 2 diabetes mellitus. For half-bandwidth, [a]$P<0.05$ compared with elderly non-diabetic; [b]$P<0.001$ compared with T2DM patients; [c]$P<0.01$ compared with T2DM patients. For ARI, [a]$P<0.01$ compared with elderly T2DM; [b]$P<0.05$ compared with elderly T2DM.

It is understood that uncontrolled diabetes mellitus can affect every GI segment and lead to several complications referred to as diabetic gastroenteropathy, a multifactorial and poorly understood condition[27]. Such alterations can especially impair gastric emptying, which becomes slower over time[2,28].

Metformin is an antidiabetic drug used in the management of blood glucose levels. It can cause GI symptoms and acutely slow gastric emptying, in part due to its stimulation of GLP-1 secretion[7]. In our study, gastric emptying in T2DM patients taking metformin as a monotherapy was not altered when compared with non-diabetic controls (TABLE 2). A recent report suggests that gastric emptying in patients with long-term T2DM treated with insulin or anti-hyperglycemic medication does not become abnormally slow and may even be improved, corroborating our data[29].

A study performed in a type 1 diabetes animal model showed that early and continuous therapeutic intervention was essential to recovering GI motility since even small increases in serum glucose levels significantly altered GI parameters, which may become irreversible in the course of the disease[30]. Such findings reinforce the notion that proper glycemic control in long-term T2DM has a protective effect on the GI tract against the damages caused by the disease.

GI transit can also be altered in patients with diabetes especially in those with gastroparesis[31]. GI transit has substantial effects on glucose absorption and therefore plays an important role in its regulation[34]. Slow or accelerated small intestinal and colonic transit time can be partially explained by myenteric neuronal loss caused by long-standing changes in blood glucose and can be a result of adverse effects brought on by antidiabetics drugs[32]. In our present study, we demonstrated that small intestinal transit and colon arrival were not changed in T2DM patients (TABLE 2).

In severe cases of T2DM, the stomach is unable to empty properly and the absorption of carbohydrates and glycemic control are impaired[35]. The lack of correlations between symptoms and GI transit reinforces the need for complementary studies.

It is also emphasized that non-treated T2DM impairs gastric contractility and consequently gastric emptying[35]. Gastric contractility is the result of rhythmic and spontaneous gastric electrical activity which determines the time and the frequency of contractile activity[16]. In fact, abnormal spatial parameters detected by cutaneous EGG correlated with the severity of upper GI symptoms, regardless of gastric emptying[36]. The electrogastrogram obtained for both elderly non-diabetic and T2DM patients evidenced differences in signal morphology when compared with the young control group (FIGURE 3).

Surprisingly, mean frequency and amplitude did not change despite the significantly abnormal gastric electrical activity registered for the T2DM patients (TABLE 3). A study performed on a long-standing diabetic model showed substantial impairment in gastric electrical and mechanical activities[13], even though the average frequency was not different from the control; similar changes were also seen in patients[37].

Accordingly, these findings can be the result of a well-controlled diabetes since none of our patients had reported relevant GI symptoms during the recruiting and study periods. As shown by several studies, the treatment for diabetic gastroenteropathy helps to delay its progression, relieves symptoms, manages complications, and contributes to restoring function[27,28].

In general, changes in electrical rhythm do not impact mechanical activity[37], which could explain our findings, since the gastric emptying was not impaired by the disease. On this basis, the combined results from EGG and gastric emptying may provide higher specificity and sensitivity for selecting patients for specific treatments[36].

As discussed above, diabetic gastroenteropathy can affect the entire GI tract and has often a poor correlation with symptoms which are caused by a multitude of factors. Despite the wide range of current techniques available for clinical practice, results regarding GI motility are not fully comparable. The lack of correlations between symptoms and GI transit reinforces the need for complementary studies. Hence, GI motility tests can be used as a tool to diagnose disturbances associated with diabetic gastroenteropathy. There is a plethora of standard methods capable of evaluating GI function, but some of them are limited by radiation exposure, lack of protocol standardization, costs, and invasiveness[10].

In addition, there are few techniques that can assess the whole GI transit without the need of prior preparation. Emerging techniques, such as alternating ACB, were developed for research use and make it possible to evaluate the multi-segmental transit times in a single test[11,13]. The role of electrogastrography in clinical practice is still under-recognized and this technique is only used to detect abnormal slow wave activity[16].

Considering that its clinical usefulness has been questioned due to insufficient correlation with the diagnoses made by means of gastric emptying scintigraphy and antroduodenal manometry, the importance of its use associated with different instruments is highlighted. There is still a lot to understand about EGG, and its association with ACB is a promising approach. Thus, simple, non-invasive techniques were used to obtain different and complementary records without exposing the participants to any risk.

Our study has limitations. First, the sample size was relatively small and larger cohorts must be studied to confirm our findings. However, based on previous studies, comparisons between the groups were meaningful. Second, the patients with T2DM showed no complications and their disease had been well controlled with long-term use of metformin. In this case, our study does not provide information regarding baseline data prior to the treatment. Besides, any extrapolation of our findings to those with obesity and/or poorly controlled T2DM deserves caution.

Our study points to unaltered gastric emptying and intestinal transit in T2DM patients with good glycemic control and that changes in gastric electrical activity may be a part of aging. Although the GI function assessed is not compromised in the elderly groups, a more detailed analysis showed detectable gastric myoelectric abnormalities that would indicate the need for further studies.

## Authors' contribution

Sena EMAB, Silva DVL and Corá LA performed the data collection; Americo MF, Corá LA and Miranda JRA conceptualized and designed the manuscript; Sena EMAB, Silva DVL, Américo MF, Miranda JRA, and Corá LA carried out the analysis; Americo MF, Sena EMAB, and Nascimento JWG drafted the initial manuscript; all authors reviewed and approved the final manuscript as submitted.

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Sena EMAB, Silva DVL, Américo MF, Nascimento JWG, Miranda JRA, Corá LA. Motilidade gastrintestinal em pacientes idosos com diabetes mellitus tipo 2 bem controlado. Arq Gastroenterol. 2022;59(2):231-7.

**RESUMO – Contexto** – As desordens da motilidade gastrintestinal (GI) no diabetes mellitus tipo 2 (DM2) são comuns. No entanto, os desfechos em pacientes idosos com DM2 bem controlado são pouco compreendidos. **Objetivo** – Avaliar o trânsito GI e a atividade mioelétrica gástrica em idosos com DM2 em tratamento com metformina e compará-los com controles saudáveis não diabéticos. **Métodos** – Trinta participantes foram incluídos neste estudo: adultos jovens não diabéticos (n=10), idosos não diabéticos (n=10) e pacientes com DM2 tratados com metformina (n=10). Após jejum noturno, os participantes ingeriram uma refeição padrão e marcadores magnéticos para monitoramento não invasivo do trânsito GI e da contratilidade gástrica usando as técnicas de biosusceptometria de corrente alternada e eletrogastrografia. **Resultados** – Foram determinados o tempo médio de esvaziamento gástrico, o tempo médio de chegada ao cólon e o tempo médio de trânsito intestinal. Não houve diferenças significativas entre os grupos e nos parâmetros avaliados ($P$>0,05). A frequência e amplitude da atividade mioelétrica gástrica não foram diferentes entre os grupos; entretanto, o índice rítmico anormal e a meia largura de banda foram ligeiramente maiores para os grupos idosos diabéticos e não diabéticos em comparação com os adultos jovens ($P$<0,01 e $P$<0,05, respectivamente). **Conclusão** – Nosso estudo mostrou esvaziamento gástrico e trânsito intestinal inalterados em pacientes com DM2 com bom controle glicêmico, sugerindo que as alterações na atividade elétrica gástrica podem fazer parte do envelhecimento.

**Palavras-chave** – Idosos, motilidade gastrintestinal, controle glicêmico, metformina, diabetes mellitus tipo 2.

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