

# The Effectiveness of Calcium Supplement as Orally Contrast Media for Gastric Magnetic Resonance Imaging

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## Abstract

The objective of the present work aims to find an alternative oral contrast agent that could be used in magnetic resonance imaging (MRI) of the gastrointestinal system and satisfy the following criteria: it should be safe, it has no or few side effects, it is inexpensive, and it produces the highest imaging quality. The method: We prepared samples (solutions) as oral contrast agents by separately dissolving calcium and magnesium supplements (taken daily dose) in varied quantities of distilled water. In order to identify the sample with the lowest concentration and best quantitative image, the samples were examined in MRI by phantoms. After that, the best sample was tested by ten healthy individuals. The image result is measured by the signal value to calculate signal to-noise-ratio (SNR), relative signal to noise ratios (RSN) and contrast (C) and then a different test is performed. There were significant variations in stomach signal values between pre and post contrast (p-value 0,05). The results: The results showed that the magnesium supplement has essentially no effect on the water signal intensity in T1-weighted and T2-weighted, whereas the calcium supplement enhances the signal intensity of the water in T2-weighted. The conclusion: The magnesium mineral solution with all concentrations has relatively little impact on the water's hydrogen signal, making it impossible to distinguish this impact with the naked eye. Therefore, it is neglected in the clinical study. The calcium supplement can be employed as a positive contrast agent on T2-weighted images for gastrointestinal imaging.

**Keywords:** Contrast agent, Contrast media, Magnetic Resonance Imaging, Oral contrast agent, Safe contrast agent.

## Introduction

One imaging technique that can distinguish between diseased and healthy tissues of organs without utilizing ionizing radiation is magnetic resonance imaging (MRI). It has proven challenging to identify the gastrointestinal (GI) tract from intra-abdominal masses and normal organs when using

MRI for gastrointestinal imaging. So, some oral materials have been employed as contrast agents to aid this problem <sup>1</sup>. Contrast agent (CA) enhances the quality of images by enhancing the visibility of particular organs, blood vessels, and tissues, which are crucial for making a precise diagnosis.

The first use of gadolinium-based contrast agent (CA) for magnetic resonance imaging (MRI) is established in the late 1980s<sup>2</sup>, the gadolinium-based solution (Gd) acts as a positive contrast agent while the barium dilute (2%) acts as a negative contrast agent on T2 weighted these solutions have been used as oral contrast agents<sup>3</sup>. Like any medicine, MRI oral contrast media can result in mild allergic reactions, nausea, flushing, headache, rash, and nephrogenic systemic fibrosis is one of the most severe side effects of the gadolinium-based solution contrast agent<sup>4</sup>. Conventional radiographic gastrointestinal examinations employ barium sulphate, but there is a chance that some may leak into the respiratory tract or perforation. For MR imaging of the gastrointestinal, high-density barium has been employed as an oral contrast agent, but this method often requires large quantities of contrast to be consumed, which is not advisable for small children, and neonates<sup>5</sup>.

Numerous investigations have been done to discover contrast agent substitutes that are less harmful to patients and to reduce the adverse effects of chemical contrast agent allergies during MRI exams. In these substances are either paramagnetic such as manganese complex<sup>6</sup>, manganese oxide nanoparticles<sup>7</sup>, magnesium chloride ( $MgCl_2$ )<sup>8</sup>, magnesium chloride nanoparticles<sup>9</sup> or ferromagnetic substances such as iron oxide nanoparticles<sup>10</sup>. All these studies have been done in vitro, while some studies have used iron supplement<sup>11</sup>, and medlar fruit (Containing *Fe*, *Cu*, and *Mn*) in vivo<sup>12</sup>. In our research, we will use phantoms to find low concentration sample that has high contrast. After that, this sample tested by ten healthy individuals

The objective of this study is to investigate the use of calcium and magnesium supplements as oral contrast agents for magnetic resonance imaging of the gastrointestinal system, Calcium and magnesium supplements are available in pharmacies and are cheap, safe, and also calcium and magnesium are paramagnetic metal that may be

## Materials and Methods

### MRI examination protocol

The images of examinations were accomplished by 1.5Tesla-MRI machine (Siemens) and the imaging conditions are as follows:

changed local magnetic field surrounding proton of hydrogen in water. Additionally, this study has been accomplished on phantoms in vitro and healthy volunteers in vivo.

### Basic equations

The effect of the contrast agents used in MRI on the proton relaxation process modifies the MRI signal intensity, increasing the contrast and informative value of the images<sup>13</sup>. The qualitative and quantitative evaluation of images was conducted by calculating the anatomical signal to noise ratio (SNR) value, relative signal to noise ratio (RSN), and contrast value.

The signal to noise ratio (SNR) is the measurement of the difference between the signal intensity (SI) obtained in the region of interest (ROI) and the standard deviation of the signal intensity in a region outside the object being scanned<sup>14</sup>. SNR is calculated by the following formula.

$$SNR = \frac{\text{mean}(SI) \text{ of solution} - \text{mean}(SI) \text{ of background}}{\text{standard deviation}(SD) \text{ of background}} \dots \dots 1$$

The relative signal to noise ratio (RSN) is measurements of the amount of change that occurs as a result of dissolving the contrast material in water (SNR of solution) to SNR of water.

The formula for calculating relative signal to noise ratios (RSN) is as follows<sup>15</sup>:

$$RSN = \frac{SNR \text{ of solution}}{SNR \text{ of water}} \dots \dots \dots 2$$

Contrast describes the difference in signal intensity between two neighboring areas, including those between tissues as well as between contrast agents and surrounding tissues.

$$C = SI_A - SI_B \dots \dots 3$$

$SI_A, SI_B$  are signals of two adjacent tissues or contrast agent and surrounding tissues<sup>1,16,17</sup>.

- T1-weighted:- 2-dimensions, Gradient echo sequences, flip angle=65 degree, repetition time=6.16msec, echo time=2.15msec.

- T2-weighted:- 2-dimensions, turbo spin echo sequence, flip angle=140 degree, repetition time=2400msec, echo time=689msec.

Average signal intensity was calculated on each phantom and the stomach area by drawing a region of interest (ROI) with an area 300 mm<sup>2</sup>.

### The phantom study

The special type of tubes is used from polymer that not affected in MRI as figure below



**Figure 1. The phantoms**

We dissolved two tablets of calcium supplement (content 1000 mg of calcium carbonate  $CaCO_3$ ) in each (240,360,480 ml) of distilled water (TDS=0ppm) (TDS is an abbreviation for Total Dissolved Solids, which is a measure of the total charged mineral content of water. The total amount of dissolved solids (ppm) is commonly displayed by TDS meters), and also two tablets of magnesium supplement (content 400 mg of magnesium hydroxide  $Mg(OH)_2$ ) in each (240,360,480 ml) of distilled water to obtain six samples that have

### Results and discussion

After dissolving the calcium supplement in each (240,360,480 ml) of distilled water, the

different concentrations which can be used as contrast agents. The six samples and distilled water (TDS=0ppm) as control have been tested by phantoms for finding the sample that has the lowest concentration with the best quantitative image, after that, this sample was tested by healthy volunteers.

### In vivo study

Healthy adult individuals participated in the study (5 females and 5 males ranging in age from 25 to 35 years, with an average of age 27 years, with an average body mass index 26, and range 24.43–34.73).

The ten healthy volunteers were tested by two MRI examinations following an eight-hour fasting period; the imaging was done on them before and after three minutes of drinking the best solution of supplement. Ten volunteers provided their information, which was tallied for two groups (before and after taking the best solution of supplement). The data were examined using the SPSS (Statistical Package for Social Science) program, version 22.0. The mean and standard deviation (SD) were used to estimate the quantitative data. The t-test for quantitative data was used to compare attributes between two groups, and a P-value of 0.05 on both sides was deemed statistically significant. The MR images underwent qualitative analysis after being reviewed by a radiologist.

The study protocol was authorized by the medical research committee, Training and Human Development Center, Karbala Health Department, Iraqi Ministry of Health. This research was conducted out at the Imam Zain El Abidine hospital's MRI unit in Karbala, Iraq.

concentration of calcium is measured in each sample by TDS meter as shown in table 1.

**Table 1. The concentration of calcium in each sample**

	$H_2O$ (240 ml) + $CaCO_3$ (1000mg)	$H_2O$ (360 ml) + $CaCO_3$ (1000mg)	$H_2O$ (480 ml) + $CaCO_3$ (1000mg)	The distilled water without calcium supplement
The concentration of calcium (ppm)	24	19	15	0

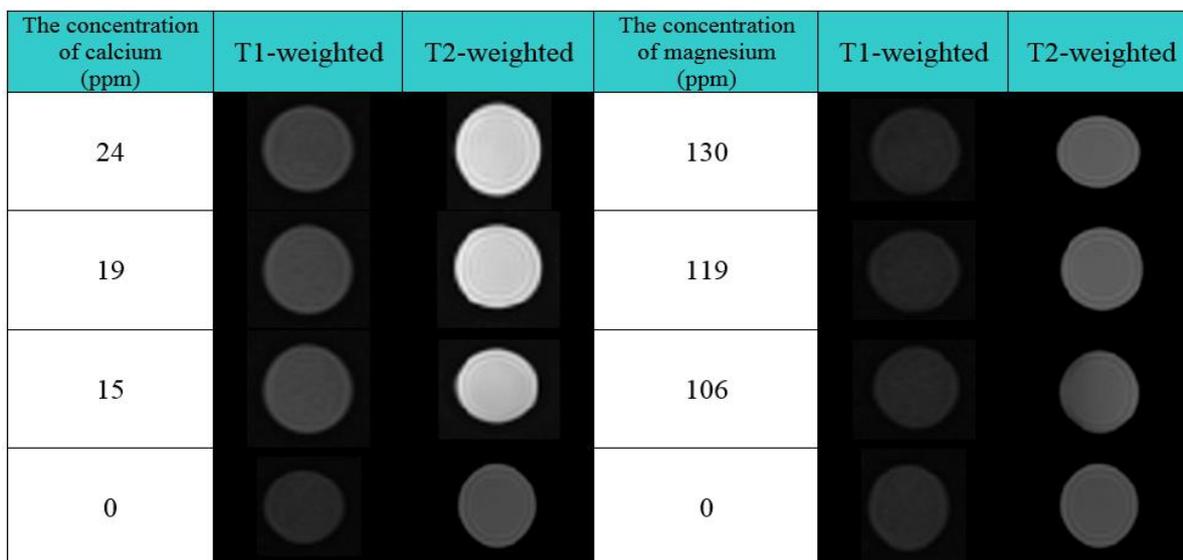
The table 2 shows concentration of magnesium in each sample that are measured by TDS meter.

**Table 2 . The concentration of magnesium in each sample**

	$H_2O(240\text{ ml})$ $+ CaCO_3(400\text{mg})$	$H_2O(360\text{ ml})$ $+ CaCO_3(400\text{mg})$	$H_2O(480\text{ ml})$ $+ CaCO_3(400\text{mg})$	The distilled water without magnesium supplement
The concentration of magnesium (ppm)	130	119	106	0

After that, the samples and water (control) were examined by phantoms in MRI to obtain T1-

weighted and T2-weighted at temperature=30°C as shown in Fig.2.



**Figure 2. MRI images of phantoms, T1-weighted (2-dimensions, Gradient echo sequences), and T2-weighted (2- dimensions, turbo spin echo sequence)**

The section on optimal sample concentration for use as an oral contrast agent involved, quantitative image assessment by calculating signal intensity,

signal to noise ratio, and relative signal to noise ratios (RSN), as illustrated in table 3 and table 4.

**Table 3 .The values of signal intensity(S), standard deviation (SD), and signal to noise (SNR) of each calcium sample forT1-weighted and T2-weighted**

The concentration of calcium (ppm) in sample	T1-weighted			T2-weighted		
	$SI \pm SD$	SNR	RSN	$SI \pm SD$	SNR	RSN
<b>24</b>	195.54±9.74	192.83	2.25	988.86±27.38	988.32	2.18
<b>19</b>	194.98±7.79	192.27	2.24	974.19±33.87	973.65	2.14
<b>15</b>	192.63±6.78	189.92	2.22	871.97±40.21	871.43	1.92
<b>0</b>	88.41±3.37	85.70	1.00	454.78±9.41	454.24	1.00

**Table 4. The values of signal intensity(S), standard deviation (SD), and signal to noise (SNR) of each magnesium sample for T1-weighted and T2-weighted**

The concentration of magnesium (ppm) in sample	T1-weighted			T2-weighted		
	<i>SI ± SD</i>	SNR	RSN	<i>SI ± SD</i>	SNR	RSN
<b>130</b>	92.55±4.90	89.84	1.05	495.16±9.71	494.62	1.09
<b>119</b>	91.25±4.69	88.54	1.03	492.41±7.09	491.87	1.08
<b>106</b>	91.03±4.63	88.32	1.03	491.47±6.17	490.93	1.08
<b>0</b>	88.41±3.37	85.70	1.00	454.78±9.41	454.24	1.00

The calcium mineral has a trivial effect on the hydrogen signal (the water) on T1-weighted, whereas T2-weighted imaging and quantitative image assessment displayed a significant increase in signal intensity of hydrogen and SNR, it is noted that the water signal (RSN) is doubled by the presence of calcium. The presence of calcium ions in the water generated a local magnetic field that increased the hydrogen signal on T2-weighted.

The sample with a calcium content of 24 ppm (2 calcium supplement tablets + 240 ml of water) may be regarded as an optimum oral contrast agent to be investigated inside the human body.

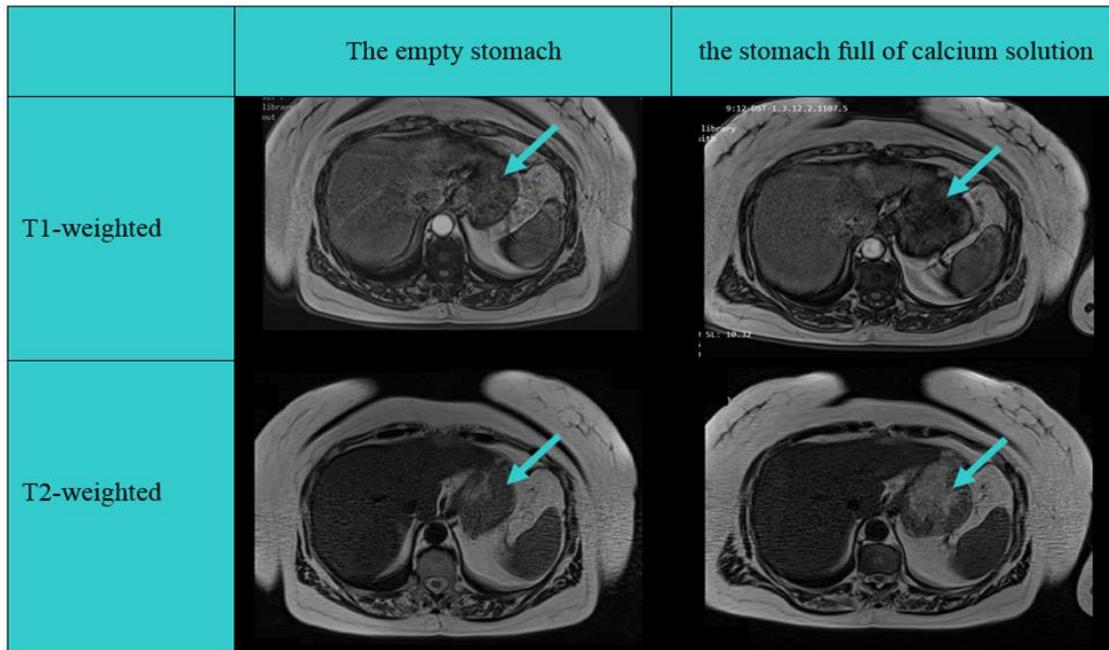
The magnesium mineral solution with all concentrations has relatively little impact on the water's hydrogen signal, making it impossible to distinguish this impact with the naked eye. The presence of magnesium ions in the water generated a weak local magnetic field that not affected the hydrogen signal. Therefore, it is neglected in the clinical study.

The images information of volunteers was evaluated before and after the oral administration of the

calcium supplement solution (2 calcium supplement tablets + 240 ml of water) to compare MRI images for an empty stomach with a stomach full of calcium solution as Fig. 3

The signal intensity (SI), Signal-to-noise ratio (SNR), relative signal to noise ratios (RSN) and contrast (C) have been used to assess the magnetic resonance device's image quality of all two examinations obtained from each volunteer. Measurements were performed to calculate signal intensities by drawing the area of anatomical (ROI) 300 mm<sup>2</sup> in the stomach area for each volunteer.

Data from ten volunteers were collected and tabulated for a two-group (before and after taking a calcium supplement solution). Version 22.0 of the SPSS (Statistical Package for Social Science) application was used to analyze the data. The estimations of the quantitative data were the mean and standard deviation (SD). For a two-group comparison, differences in attributes were examined using the t-test for quantitative data. The P-value < 0.05 on both sides was considered statistically significant, as shown table 5 and table 6



**Figure 3. MRI images of phantoms, T1-weighted (2-dimensions, Gradient echo sequences), and T2-weighted (2- dimensions, turbo spin echo sequence)**

**Table 5. signal intensity (SI), signal to-noise-ratio (SNR), relative signal to noise ratios (RSN) and contrast (C) in the stomach before and after taking a calcium supplement solution on T1-weighted.**

	The empty stomach	the stomach full of calcium solution	correlation	P-value
$SI_{mean} \pm SD$	96.18 ± 2.92	188.51 ± 4.17	0.762	2.56*10 <sup>-15</sup>
$SNR_{mean} \pm SD$	94.02 ± 2.93	186.38 ± 4.12	0.757	2.46*10 <sup>-15</sup>
$RSN_{mean} \pm SD$	1.17 ± 0.04	2.32 ± 0.05	0.757	2.46*10 <sup>-15</sup>
$C_{mean} \pm SD$	32.99 ± 4.33	125.32 ± 3.69	0.783	2.56*10 <sup>-15</sup>

Table 6 demonstrates that the signal intensity (SI), signal-to-noise ratio (SNR), relative signal to noise ratios (RSN), contrast(C) in the stomach values rise

following the administration of a calcium supplement solution with p-value <0.05

**Table 6. Signal intensity (SI), signal-to-noise ratio (SNR), relative signal to noise ratios (RSN), and contrast(C) in the stomach before and after taking a calcium supplement solution on T2-weighted.**

	The empty stomach	the stomach full of calcium solution	correlation	P-value
$SI_{mean} \pm SD$	291.89 ± 4.45	828.67 ± 10.16	0.909	7.76*10 <sup>-19</sup>
$SNR_{mean} \pm SD$	290.12 ± 4.45	826.95 ± 10.22	0.907	8.48*10 <sup>-19</sup>
$RSN_{mean} \pm SD$	0.68 ± 0.01	1.94 ± 0.02	0.907	8.48*10 <sup>-19</sup>
$C_{mean} \pm SD$	145.96 ± 1.58	682.72 ± 7.80	0.875	8.50*10 <sup>-19</sup>

Five notes are displayed by the data that are presented by our assessment:

1. The T2-weighted imaging and quantitative image analysis of calcium solution showed a notable rise in hydrogen signal intensity, we

illustrate that the presence of calcium supplement resulted in a doubling of the relative signal to noise ratios (RSN). However, T1-weighted imaging showed little impact on the hydrogen signal (the water).

2. There were high statistically significant differences in MRI images for an empty stomach and the stomach full of calcium solution.
3. The calcium supplement solution is an effective as oral contrast agent for gastrointestinal tract magnetic resonance imaging. Where it appears white color as a positive contrast agent on T2-weighted.
4. A safe daily intake of calcium supplements was determined by the European Scientific Committee for Food (SCF) to be between 500 and 1500 mg<sup>18</sup>. In this study, two tablets of calcium supplement (1000mg) were utilized to ensure that it is safe and has few side effects, and it is non-expensive
5. The magnesium mineral has a negligible impact on the hydrogen signal in water, making it unable to identify this impact on MRI images with the human eye. This contradicts previous research results on the viability of utilizing magnesium components as a contrast agent in magnetic resonance imaging<sup>8, 9</sup>. The previous research used the voltammetry technique in vitro.

## Conclusion

Our results indicate that calcium supplement solution is an effective oral contrast agent for gastrointestinal tract magnetic resonance enterography, with good image quality, no image

artifacts, and minimal gastrointestinal problems. The magnesium mineral has a negligible impact on the hydrogen signal in water, limiting its significance to identify this impact on MRI images.

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## Author's Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Besides, the Figures and images, which are not ours, have been given the permission for re-publication attached with the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee in Training, and Human Development Center, Karbala Health Department, Iraqi Ministry of Health. the code number of the search is (2022020/ Karbala)

## Author's Contribution

Z. A. M., contributed to the implementation of the research, to the analysis of the results and to the writing of the manuscript.

K. I. R., and A. M. A. contributed to the design of the research, and to the analysis of the results.

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## فعالية مكملات الكالسيوم كوسيط تباين في تصوير الجهاز الهضمي بواسطة جهاز الرنين المغناطيسي

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### الخلاصة

العمل الحالي يهدف لإيجاد عامل تباين فموي يمكن استخدامه في تصوير الجهاز الهضمي بالرنين المغناطيسي (MRI) وكذلك خاضع للمعايير التالية: يجب أن يكون أمثًا، ليس له آثار جانبية أو أقل ما يمكن من الآثار الجانبية، إنه غير مكلف وينتج عنه أعلى جودة تصوير.

الطريقة: تم إعداد العينات (المحاليل) كعوامل تباين فموية عن طريق إذابة مكملات الكالسيوم والمغنيسيوم بشكل منفصل (مقدار الجرعة اليومية المسموحة) بكميات مختلفة من الماء المقطر. ولأجل تحديد العينة ذات أقل تركيز وأفضل تباين في صورة لذلك تم فحص العينات في جهاز التصوير بالرنين المغناطيسي بواسطة الأنابيب اختبار. بعد ذلك، تم اختبار أفضل عينة بواسطة عشرة متطوعين أصحاء. والصور الناتجة يتم تقييمها بواسطة قياس شدة الإشارة لحساب نسبة الإشارة الى الضوضاء (SNR)، ونسبة الإشارة إلى الضوضاء النسبية (RSN) والتباين (C) في المعدة قبل وبعد تناول محلول مكمل الكالسيوم. والقيم الحسابية الناتجة تعالج احصائياً (p-value 0,05).

النتائج: أظهرت النتائج أن مكمل المغنيسيوم ليس له أي تأثير جوهري على شدة إشارة الماء في T1-weighted و T2-weighted، بينما مكمل الكالسيوم يعزز شدة إشارة الماء في T2-weighted. الاستنتاج: يمكن استخدام مكمل الكالسيوم كعامل تباين إيجابي على الصور T2-weighted للتصوير الجهاز الهضمي بالرنين المغناطيسي (MRI).

**الكلمات المفتاحية:** عامل التباين، وسائط التباين، التصوير بالرنين المغناطيسي، عامل التباين الفموي، عامل التباين الآمن.