



## The consumption of snacks and soft drinks between meals may contribute to the development and to persistence of gastro-esophageal reflux disease<sup>☆</sup>



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### ABSTRACT

**The hypothesis:** The habit of snacking and drinking soft beverages between breakfast, lunch and dinner, which is very widespread in the western world, could be a *primum movens*, thereby contributing to the development and subsequent persistence of gastroesophageal reflux disease (GERD).

**What does the proposed hypothesis based on?:** The high prevalence of GERD suggests that it is very probably caused by factors, which are intrinsic and widespread in a western lifestyle. Ingesting snacks or imbibing soft drinks between breakfast, lunch and dinner causes additional gastric acid secretion, acid pocket formation, and additional transient lower esophageal sphincter relaxations (TLESRs) with acid reflux; the latter are proportional to the number of ingestions. Moreover, there is increased esophageal acid exposure, which can last up to several hours in a 24-h period. The majority of patients with GERD do not have a hiatal hernia, and TLESRs are the main pathophysiological factor, resulting in an increase in esophageal acid exposure and, therefore, symptoms and the disease. Overweight/obese people very frequently consume snacks and imbibe soft drinks between breakfast, lunch and dinner and they would, therefore, share according to the hypothesis of the authors of this paper. That is, the same eating habit can cause the two conditions obesity and GERD.

**The hypothesis unfolded:** Every time a snack is ingested or a soft drink imbibed between the three daily meals, gastric acid is re-secreted, the acid pocket reforms, the TLESRs are triggered again and acid reflux events recur. The greater the number of snacks and/or soft drinks consumed, the greater the esophageal engagement of the cleaning system with, over time, increasing impairment. This mechanism may account for disease onset. According to the hypothesis outlined in this paper, GERD patients should consume moderate portions constituting three meals a day, thereby limiting the quantity of acid reflux from TLESRs.

### Introduction

GERD is a worldwide phenomenon and the most common problem of the alimentary tract in western countries where up to 40% of people regularly experience heartburn [1]. From the early 1970s onwards, much has been understood regarding GERD, and major therapeutic breakthroughs have been made to control its symptoms and complications.

GERD occurs when the number, duration or quality of physiological gastro-esophageal reflux (GER) events becomes pathological. The latter are more frequent and/or more durable and/or more acidic: thus, total daytime esophageal acid exposure increases and symptoms result. TLESR is the main mechanism, which is responsible for reflux episodes in healthy subjects and GERD patients. Furthermore, the presence of an acid pocket, close to the esophago-gastric junction during digestion, predominantly accounts for the ease with which the gastric acid flows back into the esophagus during TLESR. The latter are related to the distension of the proximal stomach on consuming food, beverages and gas. It cannot be, therefore, ignored that ingested food and beverages could have a role in the development and persistence of this disease. It has already been hypothesized that the excessive consumption of

carbonated beverages, which are usually consumed between meals, is a factor in the modern diet contributing to the development of GERD [2]. This latter data has had the effect of advising patients with GERD not to consume carbonated drinks. As far as is known, it has never been hypothesized that the consumption of snacks and soft drinks between meals can contribute to the development of GERD, and the current opinion is that of advising patients to consume smaller but more numerous meals.

The purpose of this article is to suggest an innovative counter-current hypothesis, according to which the habit of snacking and drinking soft beverages between main meals, very widespread in the western world, could be a *primum movens*, thereby contributing to the development and subsequent persistence of GERD.

This hypothesis has been based on tendencies from subsequent claims regarding the scientific evidence of GERD, which are outlined in this paper: the prevalence of the disease, the TLESRs mechanism, the gastric acid secretion, the gastric acid pocket, and from what is currently known regarding the known risk factors of GERD, that is, hiatal hernia and overweight/obesity.

<sup>☆</sup> This work has never been peer-reviewed previously.

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**Prevalence of GERD**

Whilst on the increase in recent decades, the prevalence of GERD, when defined by heartburn and regurgitation at least once a week, is approximately 20% for North America, Europe and the Middle East and below 8% for East Asia [3,4,5]. This wide difference in prevalence is most likely related to a different lifestyle and, specifically, to different eating habits. This in turn regards different socio-economic and cultural conditions, where there is also a reduced consumption of snacks and soft drinks. However, recent reports have suggest that the pattern of GERD in Asia is changing, most likely due to the socio-economic development and to an increasing spread of a western lifestyle in the Far East [6]. Moreover a recurrence of the GERD symptoms is common after suspension of Proton Pump Inhibitors, the class of drugs most widely used in these patients; lifelong treatment is often required. This would imply that GERD is probably maintained by a factor, which cannot be controlled by drugs, such as, for example, eating habits.

GERD is related by prevalence and causality association to overweight/obesity, a condition arising and developing from inappropriate eating habits [7]. There is evidence that GERD and overweight/obesity in the Asia-Pacific region has been on the increase due to an ever-widespread adoption of western eating habits in the last decade [8,9]. The reported data, which reveal a marked occurrence of GERD, suggest that the disease can very well be caused by factors, which are engrained and widespread in the western lifestyle, such as the habit of consuming food and soft drinks between meals.

**Transient lower esophageal sphincter relaxations**

TLESR is a sudden fall in lower esophageal sphincter (LES) pressure, which is triggered by proximal gastric distension due to a gaseous, solid and/or liquid content stretching the cardia. TLESR is the main pathophysiological factor in the reflux event in healthy subjects and GERD patients [10,11]. Reflux events in healthy, awake subjects almost always occur during TLESRs, whose frequency is greater in the postprandial, two-hour period and in an upright position. TLESR is also the prevalent mechanism of reflux events in GERD patients, with no more than 20% of reflux events usually occurring in cases of a more advanced or a longer-lasting disease for a reduced or absent LES pressure or straining [12,13,14]. The postprandial TLESRs rate in healthy subjects and GERD patients ranges from 1 to 7 for 60/min, and it is affected by posture, being more frequent in an upright or sitting position [15]. Whether or not the TLESRs rate is increased in GERD patients is a matter of controversy. However, there is general agreement that patients have an increased TLESRs rate, which is associated with acid reflux events, and that TLESRs are the major contributor to increased esophageal acid exposure during the day [16,17]. An increase during two postprandial hours of the total TLESRs rate, which is associated with acid reflux events, has also been documented in overweight/obese subjects when compared to normal weight subjects, all in the absence of GERD [18]. The greater the volume of gastric distension, the greater the number of TLESRs leading to a significant correlation between meal size and TLESRs rate [19]. This correlation has been demonstrated after an infusion of 200 ml of a liquid test meal [20,21], and it was already evident at volumes of approximately 150 ml. This means that TLESRs in daily life do not only occur after breakfast, lunch and dinner, but also post-ingestion of any foodstuff, such as a snack or a cup of coffee.

Typically, TLESRs have been and are always evaluated after test meals, standardized by caloric power and/or volume. This is optimal but perhaps an unrealistic condition when compared to the habit of consuming food and beverages throughout the day. If a healthy subject has an average of twenty-four TLESRs for their three main, daily and regular meals (breakfast, lunch and dinner), of which 40% probably occurs with acid reflux [15] (Fig. 1), it can be logically and consequentially assumed that ingesting snacks or soft drinks between the three main meals will cause an increase in TLESRs with acid reflux rate.

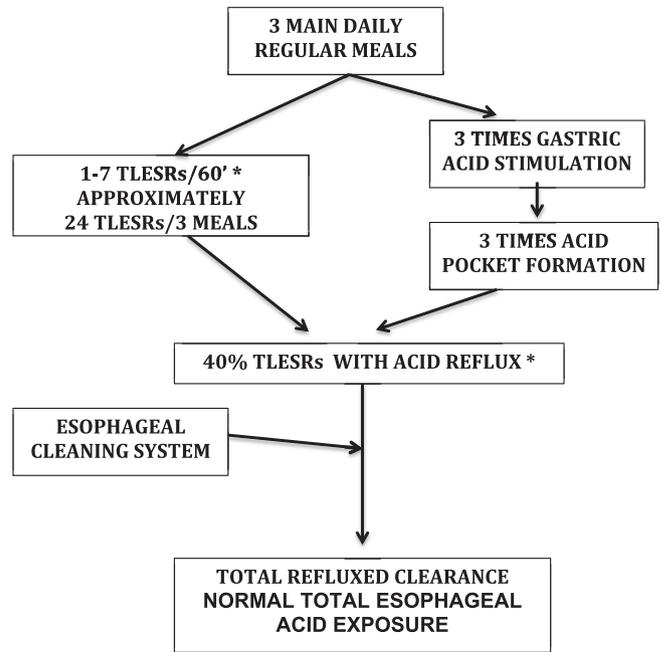


Fig. 1. The mechanism of physiological acid refluxes consuming only three main daily regular meals. \* (Ref. [15]).

There will also be an increase in total esophageal acid exposure, which is proportional to the number of ingestions. This increased acid exposure will initially be balanced by the esophageal cleaning system which, however, over the time will be impaired and eventually lead the way to GERD (Fig. 2).

**Gastric acid secretion and gastric acid pocket**

Gastric acid secretion is always stimulated by any ingested food or beverage. Protein foods and milk are the strongest stimulants of acid secretion, as are carbonated beverages, alcoholic drinks and coffee,

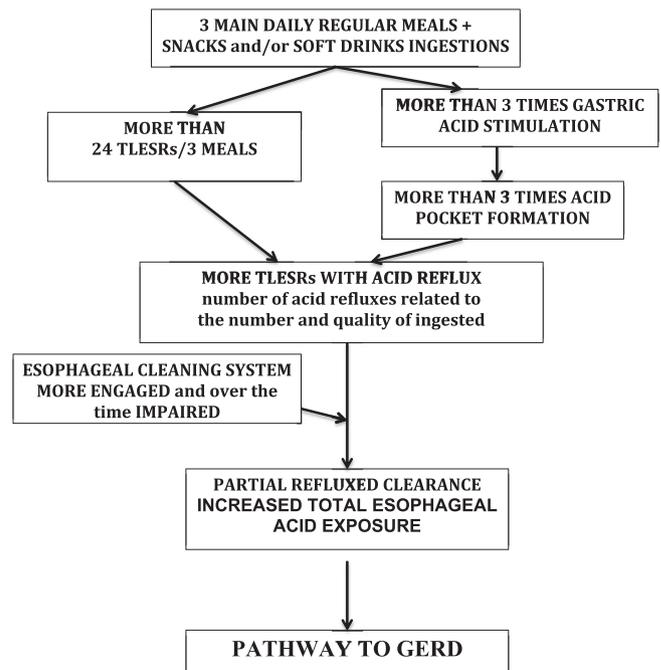


Fig. 2. Hypothesis of the origin of GERD: what happens consuming snacks and/or soft drinks between the three main daily regular meals.

while fruits and vegetables are among the weakest. Tap water also stimulates acid secretion, albeit in minimal quantities [24,25]. All of these are mostly consumed between meals.

It has been demonstrated in healthy young subjects that acid secretion, in response to an inert liquid meal, is volume-dependent; it is already conspicuously present for a volume of 330 ml, which is the usual volume of a soft drink [22]. Increasing the meal size raises the maximal acid response while frequent, smaller meals, even if they cause a more uniform stimulation of acid production, are responsible for almost continuous gastric acid secretion [23,24,25]. The smallest volume of gastric contents capable of stimulating acid secretion is unknown but the existence of the cephalic phase can lead us to speculate that any volume, even minimal, can stimulate acid secretion. It should also be remembered that acid secretion, reacting with the bicarbonates of the gastric mucosa surface, gives rise to carbon dioxide, which contributes to the distension of the proximal stomach, thereby triggering TLESRs. Furthermore, the greater the acid secretion, the greater is the formation of carbon dioxide, and the latter further increases gastric distension.

The gastric acid pocket is a physiologic phenomenon, always caused by gastric acid secretion, which does not mix with ingested food but instead floats on top of it [26]. It is a highly acidic zone, which is localized in the proximal stomach just below the LES, where unbuffered gastric juice is always present after the ingestion of any food or soft beverages. Acid pocket onset occurs approximately 15 min after ingestion, it lasts for more than 80 min after food or beverage intake, and its mean volume exceeds more than 120 ml of acidic juice [27,28]. The acid pocket is the acid source for postprandial reflux episodes, which are correlated to TLESRs, as well as an important mechanism of distal esophageal acidification in healthy subjects and GERD patients. Indeed, it has also been well documented that healthy subjects, who ingested food without any limitations except acidic foods and alcohol, displayed up to 25 min of  $\text{pH} < 4$  in the nine postprandial hours of pH-metric recording and up to 35 reflux episodes/hour in the distal esophagus, although the majority of these episodes were of a short duration, typically 0.3/min. [29]. It has been demonstrated that, after the ingestion of a liquid test meal, the acid pocket is the cause of esophago-gastric junction acid exposure in healthy subjects for approximately 35 min [30]. Therefore, it can be stated from reported data that the consumption of any type of snack or soft drink between the three main meals is the cause of: additional and the more frequent secretion of gastric acid, the additional formation of the gastric acid pocket, and additional increased esophageal acid exposure, which can last for several hours a day, thereby increasing the engagement of the esophageal cleaning system (Fig. 2). This is also proportional to the quantity and quality of food and/or beverage ingestion.

### Hiatal hernia

A sliding hiatal hernia is believed to be a risk factor of GERD, being strongly associated with the disease and contributing to its progression. The prevalence of sliding hiatal hernia in the general population is approximately 25% [31], and it is believed that a physiological herniation of the esophago-gastric junction  $\geq 1$  cm is related to breathing and swallowing [32]. Recent data have shown that 57% of GERD patients either do not have or have a 1 cm long hiatal hernia, 23% have a 2 cm long hiatal hernia, and only when the hiatal hernia is  $\geq 2$  cm long does the association with regurgitation and heartburn become significant [33]. In patients in which the hiatal hernia is  $> 3$  cm long, there will be an intra-thoracic localization of the LES and, therefore, almost always the hernia will be of clinical relevance [34]. A strong correlation exists between a hiatal hernia and the presence and severity of erosive esophagitis and Barrett's esophagus. The reason for this correlation is variously supported by numerous studies adopting a univariate and multivariate approach, deploying endoscopy, radiology, manometry and 24 h pH-metry. Moreover, general agreement exists regarding the finding that the greater the hiatal hernia size, the greater

the reduction in LESP, the number of reflux events, the impairment in refluxate clearance, esophageal acid exposure time and, therefore, the severity of GERD and its complications [35,36,37]. This leads us to believe that only when the hiatal hernia is 3 or more cm long is GERD also supported by a reduction in LESP.

However, when the hiatal hernia is less than 3 cm long, the main pathophysiological mechanism, which sustains the disease, continues to be that of TLESRs. The latter are more frequent and more prolonged in patients with a hiatal hernia due to a lowering of the triggering threshold during gastric distension. Furthermore, the post-prandial acid pocket is larger and trapped in the herniated stomach, thereby acting as a reservoir of acid, ready to reflux [17,28]. TLESRs and acid pocket are two factors underpinning the hypothesis presented in this paper.

A hiatal hernia is an alteration of the morphological factors supporting natural, anti-reflux mechanisms. It is also the cause of the disappearance of the intra-abdominal LES, LESP reduction and an impairment of esophageal clearance. The presence of a hiatal hernia does not affect, but rather facilitates, the only pro-reflux mechanism, the TLESRs.

Up to this point, the hypothesis presented in this paper can be said to be 'reasonable', even in the presence of hiatal hernias up to 2 cm in length. This occurs where the intra-abdominal localization and the LES competence are maintained [33], and the origin and the persistence of the GERD can be induced by the consumption of snacks and soft beverages between main meals. In the presence of hiatal hernias  $\geq 2$  cm long or in any way associated with partial or total intra-thoracic localization and LES incompetence [34], any ingestion of snacks and soft beverages between main meals adds periods of acid secretion stimulation and acid pocket formation, which is related to a greater availability of acid to reflux, a greater total time of esophageal acid exposure and more severe GERD.

It could be assumed that, in patients with GERD associated with hiatal hernia, the latter, compromising anti-reflux mechanisms, gives rise to more severe GERD but a doubt may persist: which comes first, the hiatal hernia or GERD? Presumably the hiatal hernia begins as physiological herniation [32] and develops gradually as GERD does. Often associated with perhaps already-established GERD, the hiatal hernia aggravates GERD with the former leading to complicating conditions of the latter. According to this point of view, a hiatal hernia should be considered as an aggravating factor rather than a risk factor for GERD. On the other hand and as previously stated, the majority of patients with GERD, approximately 80% [33], do not have a hiatal hernia or have a  $\leq 2$  cm long hiatal hernia. This leads to the assumption that TLESRs in these patients, as triggered by gastric distension caused by the ingestion of foodstuffs and drinks, even between meals, remain the most important factor causing an increase in esophageal acid exposure and, therefore, the symptoms and the disease.

### Overweight and obesity

The relationship between weight gain and GERD has been widely demonstrated and even a moderate weight gain in normal weight subjects may cause the development or exacerbation of GERD symptoms [38]. The prevalence of obesity in recent decades has increased hand in hand with the prevalence of GERD [39,40]. GERD is more frequent among overweight and obese subjects than those of normal weight, and for this reason overweight and obesity are considered conditions predisposing to the disease, that is, as risk factors [41]. Moreover, the risk for GERD symptoms, erosive esophagitis, and esophageal adenocarcinoma seem to progressively increase with increasing weight [42,43]. However, some studies have also evaluated the relationship between various types of foods, caloric intake and GERD in obese subjects. Regrettably, the results are conflicting: the effect of an increased Body Mass Index (BMI) has been also considered to be independent of dietary intake [44,45]. There are also conflicting results regarding the relationship between weight reduction and improvement

in GERD symptoms and complications, even if weight reduction is recommended as a component of the first-line management of the disease [46,47].

It is believed that the positive correlation between BMI and intra-esophageal acid exposure is mediated by waist circumference, which results in an increased mechanical pressure on the stomach. Obesity has been positively associated with a significant increase in the number of reflux episodes and in the percentage time with a pH < 4, especially in the postprandial period. The positive association with postprandial reflux episodes also indicates diet-related effects [48]. During a two-postprandial-hour period, a standard meal causes a greater number of total TLESRs and TLESRs with acid reflux in overweight and obese when compared to the normal weight subjects, all without GERD. This increase in TLESRs is believed to be related to a proportional increase in the gastro-esophageal pressure gradient [18], but it could also be related to a frequent ingestion of snacks and soft drinks, which can characterize overweight and obese as normal weight subjects. All these, therefore, share the same mechanism of risk regarding the development of GERD. Moreover, it has been demonstrated that being overweight or obese is significantly associated with night meals and larger portions of main meals, as well as frequent snacking [49,50]. Weight gain in overweight subjects is related to an increased intake of food and beverages, with greater size portions, which are more frequent and higher in calories. Snacking and drinking soft beverages, in addition to the three main meals, results in a continuous postprandial condition, which implies: continuous secretion of acid, a continuous presence of the acid pocket, an increased number in TLESRs with acid reflux episodes and longer exposure of the esophago-gastric junction to acid for up to several hours a day. And the result is GERD (Fig. 2). On the other hand, weight reduction, which regularizes and reduces food and beverage intake, reduces the number of postprandial conditions. The exposure of the esophago-gastric junction to acid is reduced and this could lead to an improvement in GERD symptoms and complications.

According to the hypothesis outlined in this paper, the relationship between being overweight/obese with GERD, as well as in the mechanism of an increase in the gastro-esophageal pressure gradient, regards sharing the same eating habits, that is, the consumption of snacks and soft drinks between main meals. Evidently, obese subjects ingesting greater size portions, an increased number of calorie-laden snacks, and imbibing an increased number of higher calorie-laden soft drinks leads to a greater caloric load and overweight. This is not the case with normal weight subjects.

## Discussion

GERD is a chronic disease, whose diffusion around the world is always on the increase. The drugs, currently in use, only control the symptoms and heal the esophagitis, not the disease; medication is, therefore, life-long. In the management of GERD, some modifications in dietary habits have traditionally been and are still part of first-line therapy, despite conflicting results regarding their efficacy. The following are invariably recommended to patients: an avoidance of alcohol, soft drinks, carbonated beverages, acidic and fatty foods, chocolate and carminatives, large and late-evening meals, and a reduction in body weight. However, the latter also involves substantial changes in eating habits [51,52,53,54].

The few, large-scale studies on GERD patients have all demonstrated that overweight/obesity and irregular dietary habits, especially irregular meal patterns, are associated with a high risk of disease [55,56,57]. Moreover, soft drinks, tea and fast foods, which, as is known, are usually, consumed between main meals, have been highlighted as risk factors [58,59].

Two studies have also suggested that large meals should be replaced by smaller and more frequent meals. In the study by Wu et al. [60], the sample size (five patients for each of the three groups) in opinion of the authors of this paper was insufficient to apply the results of this

research to the huge predominance of GERD worldwide. Furthermore, even the regime, proposed by Wu et al., of smaller and more frequent meals caused reflux symptoms and abnormal acid exposure, albeit lower but with large standard deviation values, compared to a regime of large meals. In the study by Jarosz et al. [61], an association between GERD and eating habits was demonstrated, specifically for patients who consumed large evening meals or only two meals a day. However, a lack of data meant that the study groups could not be differentiated by eating or not between meals.

The current view is that the eating habits of GERD patients should include not large but frequent smaller meals because these would guarantee lower daily acid exposure of the esophagus. The authors of this paper recommend that oversized meals should be replaced by three regular moderate-sized meals, but not by more frequent and smaller meals.

Relatively little regarding the possible etiological role of eating habits in GERD development has been investigated in a healthy population. In recent decades the consumption of food and soft drinks, especially that consumed between meals, has increased enormously, in line with the occurrence of GERD and rates of overweight/obesity. It has been already hypothesized that carbonated drinks, given their enormous consumption in the western world, could potentially contribute to the development of GERD. The mechanism could be the distension of the gastric fundus, which thereby triggers TLESRs [62,63]. Furthermore, it has been shown that the median rate of TLESRs after the ingestion of 200 ml of a carbonated beverage in healthy subjects was ten times higher when compared to the baseline, as well as after ingesting the same quantity of water [64]. It should be emphasized that carbonated drinks as well as snacks are usually consumed in between the meals.

Randhawa et al. were the first to propose that a two-meal regimen with only fluids in between the two meals improved reflux symptoms in patients with esophagitis [65,66]. And the authors of this contribution generally concur with these findings. However, they would prefer to suggest three main meals a day of a moderate quantity and these findings regarding the consumption of fluid between the two meals cannot be shared with those of Randhawa et al. This is due to the fact, as previously stated in this paper, the rate of TLESRs and acid secretion stimulation also increase after ingesting beverages of 150–200 ml such as a cup of coffee or tea or any other soft drink [20,21]. The authors of this paper, therefore, hold that, where necessary, only natural water should be consumed between meals.

In conclusion the hypothesis of the authors of this paper, whilst in sharp contrast with current opinion, is speculative but logical and, therefore, we believe probable: every time a snack or a soft drink is ingested between the three main daily meals, acid is once again secreted to reform the acid pocket. TLESRs are triggered again and acid reflux episodes reoccur. The greater the volume of liquid ingested, the greater the stimulating power of gastric acid, the more frequent consumption of snacks and/or soft drinks ingested, the greater the esophageal acid exposure and the greater the impairment over time to the esophageal cleaning system. This could be the pathway by which the disease originates (Fig. 2). According to the hypothesis outlined in this paper, patients with GERD who modify their eating habits by consuming two or three main meals a day, which are moderate in quantity, will thus limit the number of acid reflux episodes from TLESRs and they could contribute to controlling symptoms, especially during periods when anti-secretory drugs are not used. In order to verify this speculative hypothesis, regarding the etiological role of the current and excessive consumption of snacks and soft drinks between meals in the development of GERD large-scale population studies, possibly on young people, would be necessary. These studies are very challenging to conduct but they may well illuminate the *primum movens* of GERD and, therefore, point to a strategy of GERD prevention for future generations.

## Conflict of interest statement

No financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

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