

# Pilot Trial on the Efficacy and Safety of a Natural Mineral Water Rich in Hydrogen Carbonate on Functional Dyspepsia and Heartburn

Ute Pohl, Annegret Auinger, Gordana Bothe\*, Ralf Uebelhack

Analyze & realize GmbH, Berlin, Germany

Email: \*GBothe@a-r.com

Received 10 February 2016; accepted 27 March 2016; published 30 March 2016

Copyright © 2016 by authors and Scientific Research Publishing Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

---

## Abstract

**Background:** Dyspepsia and heartburn are among the most frequent complaints of the upper gastrointestinal tract impacting quality of life. The present study aimed to investigate the impact of drinking a natural mineral water (medicinal product category “Heilwasser” in Germany) high in hydrogen carbonate (Staatl. Fachingen STILL) on functional dyspeptic complaints and heartburn. **Methods:** 56 men and women with self-reported heartburn were enrolled to this one-arm pilot study. They had to drink 1.5 L of a hydrogen carbonate rich mineral water each day over a course of six weeks. Participants reported the number and duration of heartburn episodes in a daily diary. The Reflux Disease Questionnaire (RDQ), Quality of Life in Reflux and Dyspepsia questionnaire (QOLRAD) and the Gastrointestinal Quality of Life Index (GILQI) were used to assess the therapeutic course of the treatment and the Short Form Health Survey (SF-12) to assess general quality of life. Mean  $\pm$  standard deviation were calculated and pre- and post-treatment changes were compared using the Wilcoxon test. **Results:** The consumption of a hydrogen carbonate rich mineral water decreased the number of heartburn episodes per week significantly by  $4.8 \pm 8.2$  at the end of the study ( $p < 0.001$ ). The duration of episodes was also significantly reduced by 25.7 minutes after six weeks of intervention ( $p < 0.001$ ). Accordingly, the subjectively perceived severity of heartburn, regurgitation and dyspeptic complaints as well as the GERD dimension as assessed by Reflux Disease Questionnaire improved significantly. There was a significant improvement in the disease-specific quality of life as measured by the Gastrointestinal Quality of Life Index ( $p < 0.001$ ) and by the Quality Of Life in Reflux and Dyspepsia ( $p < 0.001$ ) questionnaires and the general health-related quality of life as assessed by SF-12 ( $p < 0.007$ ). **Conclusions:** The present pilot study provides evidence that supplementation with natural mineral water rich in hydrogen

---

\*Corresponding author.

**carbonate may improve heartburn and dyspeptic symptoms, which finally resulted in an improvement of the subjectively perceived quality of life. Drinking mineral water rich in hydrogen carbonate may be an alternative remedy for the treatment of dyspeptic symptoms and heartburn. Trial Registration: Eudra CT No 2013-001256-36.**

## Keywords

**Heartburn, Dyspepsia, Natural Mineral Water, “Heilwasser”, Pilot Study, Hydrogen Carbonate**

## 1. Introduction

Functional gastrointestinal (GI) disorders are described as a group of GI disorders including different combinations of chronic or recurrent symptoms that cannot be explained by structural or biochemical abnormalities [1]. Among the functional GI disorders, functional dyspepsia, which presents as epigastric pain or burning, early satiety during normal-sized meals, or postprandial fullness without an organic disease in the upper GI tract, is one of the most prevalent functional GI disorders with a reported prevalence rate of 7% - 20% [2]-[4]. The underlying pathophysiology of functional dyspepsia is still not fully understood, but there are indications that delayed gastric emptying, impaired gastric accommodation to a meal, visceral hypersensitivity to distension, hypersensitivity of the duodenal bulb to acid, or central nervous system dysfunction may play an important role [5]-[8].

Various dyspeptic symptoms are frequently associated with reflux and heartburn. Gastro-esophageal reflux is a cluster of symptom frequencies and/or severities with occasional or mild symptoms experienced by a large proportion of the population [9] [10]. Indeed, in the Western World, a prevalence rate of 17% - 42% was reported [10] [11], with 6% - 27% of the general population experiencing symptoms once a week. Reflux symptoms, even mild ones, are one of the most common gastro-intestinal complaints and have been shown to reduce well-being and quality of life [12]. In general, heartburn comprises symptoms of gastro-oesophageal discomfort such as retrosternal discomfort or pain that can radiate toward the neck, throat, or angle of the jaw and is often worse postprandially, during exercise, or while lying recumbent [13]. It is usually associated with regurgitation of gastric acid, and it may be accompanied by dyspeptic complaints such as bloating, distension, nausea, or lack of appetite.

The aetiology of heartburn is very complex and is mainly induced by acidic esophageal reflux, but non-acidic or duodeno-gastroesophageal reflux or motor abnormalities are also causes for heartburn [14]. Moreover, certain types of food and beverages but also lifestyle factors can induce postprandial heartburn [15]. Based on the numerous mechanisms and influencing factors, the spectrum of heartburn comprises functional complaints, an acid-hypersensitive esophagus, and gastroesophageal reflux disease (GERD) with or without endoscopically visible lesions.

As diverse as the pathophysiology of heartburn is, so also do the pharmacological therapy options vary. Usually, antacids, prokinetics, antispasmodic drugs, or gastroprotective agents are recommended, with antacids being one of the most popular over-the-counter treatments for occasional heartburn episodes. However, the different remedies are not always satisfactory, especially for patients with functional complaints [16]. As the exact causes of functional dyspepsia remain unclear, a similar picture can be drawn for the therapy of functional dyspepsia.

Natural water rich in minerals has been used for decades in the treatment of heartburn and dyspeptic symptoms. As yet, only a small number of clinical studies have been conducted investigating the efficacy of natural waters on dyspepsia and heartburn [17]-[19].

The therapeutic water Staatl. Fachingen STILL, is a medicinal product (category therapeutic water “Heilwasser”) in Germany on the market and is rich in hydrogen carbonate, calcium and magnesium. For simplicity reasons within this publication the water is called a “mineral water”. Staatl. Fachingen STILL, has been known for centuries for its positive effects on heartburn, acid regurgitation, abdominal fullness and gastric discomfort. In the early 50s, cures with the mineral water showed an improvement of different forms of gastritis after drinking the water for several weeks [20]. The aim of the present open label pilot trial was to systematically investigate the effects of a natural mineral water rich in hydrogen carbonate on dyspeptic syndrome and heartburn in

patients with self-reported heartburn.

## 2. Methods

### 2.1. Study Design

The trial was conducted as a mono-centric, single arm pilot study in patients with heartburn. The study was approved by the Ethics Committee (Office for Health and Social Affairs, Berlin, Germany). It was conducted in compliance with the Declaration of Helsinki as well as the German Pharmaceuticals Act, the principles of ICH-GCP, and the German GCP-V. The trial was registered in the European Clinical Trials Database (EudraCT) as EudraCT No 2013-001256-36. Participants gave written informed consent prior to the study.

### 2.2. Study Participants

A total of 56 subjects aged 18 - 65 who had self-reported heartburn for at least two times a week for a duration of at least 3 months (the frequency was additionally checked in patient's diary during a run-in phase between the screening and the baseline visit) and did not receive prescribed treatment for heartburn, gastro-esophageal reflux or other disorders of the upper gastro-intestinal system were enrolled to the study site in Berlin. The subjects were recruited from the subject database and via advertising. They were asked not to change their dietary habits and had to be accustomed to drinking at least 1300 ml of water daily, incl. tea and mineral water (the quantity was also evaluated per patient's diary during the run-in phase). Women of childbearing potential had to agree to use contraception methods. Subjects were excluded if they presented with weight loss of  $\geq 6$  kg in the last 6 months prior to the study, gastrointestinal bleeding within 12 months prior to the study, dysphagia, Zollinger–Ellison syndrome, oesophageal or gastric malignancy, gastric or duodenal ulcer, pernicious anaemia, Barrett's oesophagus or systemic sclerosis, coronary disease, anorexia, irritable bowel syndrome, previous surgery of the oesophagus, stomach, or small intestine, acute or chronic intestinal diseases, endocrine disorders, severe renal impairment, iron deficiency anemia, persistent vomiting, a family history of gastrointestinal tract malignancy, clinically relevant deviations of laboratory parameters, use of antacids, H<sub>2</sub> receptor antagonists, motility stimulants, prokinetics, or other treatment for the relief of reflux within 2 days, or proton-pump inhibitors or psychiatric medication within 14 days prior to study start and during the study, use of treatment for *Helicobacter pylori* eradication or bismuth compounds within 3 months prior to study start and during the study, use of acetylsalicylic acid and nonsteroidal anti-inflammatory drugs during the study, intake of mineral water other than the investigational product during the study. Further exclusion criteria were: pregnancy or nursing (women of childbearing potential), drug, alcohol or medication abuse, participation in another clinical trial during the last 30 days prior to study start and during the study, persons that are in relationship or dependence to the sponsor or the investigator, evidence that the subject would not be able to comply with clinical trial and requirements (e.g. limited willingness to cooperate).

### 2.3. Intervention

During the treatment period of six weeks ( $\pm 5$  d), the subjects were asked to consume 1.5 L of the mineral water throughout the day. Each glass should be sipped within 5 - 10 minutes. Subjects were instructed to drink 1 - 2 glasses (200 - 500 ml) 15 - 30 minutes prior to breakfast. The remaining volume should be taken between meals and 15 - 30 minutes before each main meal and, when required, with the meal. Over the course of the study a total of four visits were performed including a screening visit, a baseline visit 8 - 12 d after the screening visit, a control visit  $21 \pm 3$  d, and a final visit  $42 \pm 5$  d after the baseline visit. The following drugs were allowed in case of urgent need: antacids, H<sub>2</sub> receptor antagonists, motility stimulants, prokinetics, proton-pump inhibitors or other treatment for the relief of reflux, new psychiatric medication, use of treatment for *Helicobacter pylori* eradication or bismuth compounds, use of acetylsalicylic acid and nonsteroidal anti-inflammatory products.

The investigational product, Staatl. Fachingen STILL, contains mainly hydrogen carbonate, sodium, magnesium and calcium (**Table 1**). The mineral water was produced by Fachingen Heil- und Mineralbrunnen GmbH and was derived from a spring in the Lahn valley, Germany.

Compliance was checked by quantifying (ml) returned mineral water and assessing the trial duration. The accepted compliance rate was defined as 75% - 125% of the correct quantity of investigational product and max. five days deviation from the 6-week study period.

**Table 1.** Composition of the therapeutic water Staatl. Fachingen STILL.

Composition	mg/L
Lithium	0.77
Sodium	564.00
Potassium	16.1
Rubidium	0.026
Caesium	0.005
Magnesium	59.2
Barium	0.13
Ammonium	0.48
Calcium	98.70
Iron	0.007
Manganese	0.4
Fluoride	0.3
Chloride	139.00
Iodide	0.014
Bromid	0.17
Sulphate	39.0
Hydrogen Carbonate	1846
Nitrate	1.5

## 2.4. Outcome Measures

Patients had to document the frequency and duration of heartburn episodes in a daily diary including information on the use of rescue medication. The Reflux Disease Questionnaire (RDQ) [21], Quality of Life in Reflux and Dyspepsia questionnaire (QOLRAD) [22] and the Gastrointestinal Quality of Life Index (GILQI) [23] were used at the baseline, control, and final visit to assess the therapeutic course of the treatment over the course of the study. In addition, the subjective perception of well-being was assessed using the SF-12 questionnaire [24]. Eating and drinking habits were recorded in a daily diary.

Liver function, lipid parameters, safety blood parameters, blood pressure and heart rate as well as body weight were assessed at screening and at the end of the intervention. Adverse events were monitored throughout the study. Patients and investigators had to independently perform a global assessment of efficacy and safety of the investigational product at the end of the study by means of a globally scaled evaluation with “very good”, “good”, “moderate” and “poor”.

## 2.5. Statistics

As the study was performed as a pilot study without a confirmatory statistical hypothesis testing, there was no formal sample size calculation performed. However, a sufficient subject number to observe positive changes with respect to the study endpoints was estimated. Based on the assumption of expected changes in about 70% of subjects and in compliance with the requirements of the significance level (5.0%, two-sided) and power (80%) and according to Dixon and Mood, 56 subjects were considered required for the analysis by taking a drop-out rate of 10% into account.

Outcome parameters were presented descriptively using their statistical key data and frequency distribution, respectively. The pre- and post-treatment changes were calculated and compared using the non-parametric Wilcoxon test. The Mann-Whitney U-test was used to test for between-group comparisons. All statistical analyses were carried out on both the ITT (intention-to-treat)/FAS (full analysis set) and PP (per-protocol)/VCAS (valid case analysis set) collective. Only results for the FAS population are presented. Statistical analyses were performed with SPSS (SPSS for windows, Release 22, LEAD Technologies Inc.).

### 3. Results

56 patients were randomized (safety population). Of these, 3 subjects were excluded from the FAS population and further 13 from the VCAS population resulting in 53 and 40 participants in the FAS and VCAS population, respectively.

Out of the 56 Caucasian participants, 26 were men and 30 were women. The mean age of the study patients was  $36 \pm 12$  years.

The mean number of heartburn per week as assessed by patient's diary decreased by 67% after drinking the mineral water for six weeks (**Table 2**;  $p < 0.001$ ). As soon as after three weeks, patients reported about 57% less episodes ( $p < 0.001$ ). In addition, the duration of heartburn episodes was significantly reduced by about 26 minutes at the end of the study (**Table 2**;  $p < 0.001$ ) and by about 19 minutes after three weeks of intervention ( $p < 0.001$ ). Six weeks of daily consumption of the mineral water reduced the frequency of heartburn episodes in 81% of patients and the duration in 89% of participants; at three weeks the frequency was reduced in 74% and the duration in 76% of subjects.

The RDQ was used to assess the frequency and severity of heartburn, regurgitation and dyspeptic complaints and GERD dimension. In accordance with the reduced frequency and severity of heartburn, patients experienced an improvement in all RDQ dimensions (**Table 3**). Complementary to these results, the QOLRAD sub-scores (emotional distress, sleeping disturbance, food and drink problems, physical and social functioning and vitality), also improved after six weeks of drinking the mineral water ( $p < 0.001$  each, **Table 3**). Moreover, the GILQI sum score (**Table 3**) as well as the sub-scores (symptoms, emotions, physical and social function) improved significantly from baseline to week six. Lastly, there was a significant improvement regarding changes in the SF-12 sum score throughout the study.

**Table 2.** Mean  $\pm$  SD number of heartburn per week and duration of episodes during a 6-week intervention.

	Baseline	Week 3	Week 6	$\Delta$ week 6-baseline	$p^a$
Frequency	$7.09 \pm 7.49$	$3.02 \pm 2.64$	$2.32 \pm 3.44$	$4.77 \pm 8.24$	$<0.001$
Duration (min)	$35.2 \pm 41.4$	$16.3 \pm 17.4$	$9.4 \pm 11.6$	$25.7 \pm 36.4$	$<0.001$

<sup>a</sup> $p$  values (Wilcoxon) for pre- and post-treatment differences (at six weeks).

**Table 3.** Mean  $\pm$  SD scores of the RDQ, QOLRAD, GILQI and SF-12.

	Baseline	Week 3	Week 6	$\Delta$ week 6-baseline	$p^a$
<b>RDQ</b>					
Heartburn	$6.36 \pm 4.56$	$4.23 \pm 3.85$	$1.92 \pm 2.49$	$4.43 \pm 4.11$	$<0.001$
Regurgitation	$7.46 \pm 4.25$	$4.08 \pm 3.58$	$2.60 \pm 2.96$	$4.86 \pm 4.21$	$<0.001$
GERD	$13.79 \pm 6.32$	$8.23 \pm 5.36$	$4.56 \pm 3.93$	$9.23 \pm 6.69$	$<0.001$
Dyspepsia	$6.24 \pm 4.16$	$3.86 \pm 3.30$	$2.47 \pm 3.05$	$3.76 \pm 4.35$	$<0.001$
<b>QOLRAD</b>					
Emotional distress	$5.74 \pm 1.17$	$6.36 \pm 0.77$	$6.57 \pm 0.72$	$0.83 \pm 1.06$	$<0.001$
Sleeping disturbance	$5.75 \pm 1.12$	$6.27 \pm 0.78$	$6.57 \pm 0.70$	$0.82 \pm 1.05$	$<0.001$
Food/drink problems	$5.22 \pm 1.17$	$6.07 \pm 0.75$	$6.38 \pm 0.72$	$1.16 \pm 1.02$	$<0.001$
Physical/social functioning	$6.20 \pm 0.80$	$6.56 \pm 0.61$	$6.77 \pm 0.47$	$0.57 \pm 0.74$	$<0.001$
Vitality	$5.48 \pm 1.14$	$5.94 \pm 0.93$	$6.37 \pm 0.79$	$0.89 \pm 1.00$	$<0.001$
<b>GILQI</b>					
Sum Score	$108.3 \pm 16$	$115.8 \pm 13.9$	$121.5 \pm 14$	$13.15 \pm 12.51$	$<0.001$
<b>SF-12</b>					
Sum Score	$38.17 \pm 5.02$	$39.12 \pm 4.55$	$40.17 \pm 4.57$	$2.00 \pm 5.10$	$0.007$

<sup>a</sup> $p$  values (Wilcoxon) for pre- and post-treatment differences (at six weeks).

93% of patients and 94% of the physicians rated the global evaluation of efficacy as “very good” or “good” at the end of the six weeks intervention.

Throughout the study period of six weeks, four adverse events occurred, with one case (light meteorism) possibly being associated with the intervention. None of the adverse events was classified as serious.

Neither liver enzymes nor triglycerides, cholesterol, HDL-C, LDL-C, blood pressure, or heart rate values changed significantly over time. Moreover, there was no significant difference in body weight at the end of the study.

At baseline, a total of six patients reported the intake of warm water, camomile tea or “over-the-counter” drugs with occurring heartburn, while at the end of the study none of the subjects took any remedy during a heartburn episode. All subjects were compliant with regards to the actual intake of the mineral water and the study duration.

#### 4. Discussion

This is the first pilot study to evaluate the efficacy of the hydrogen carbonate rich mineral water Staatl. Fachingen STILL on functional dyspepsia and heartburn. The study shows that the daily consumption of a mineral water rich in hydrogen carbonate for six weeks reduced the frequency and duration of heartburn episodes. In addition, drinking mineral water significantly decreased dyspeptic symptoms and GERD as assessed by changes in RDQ scores. Regarding the results of the QOLRAD assessing the reflux/dyspepsia disease specific quality of life, the most concise change was observed for the dimension “problems with eating and drinking”, which is in accordance with the observation that heartburn is often associated with consumption of food and beverages. In line with the relief of dyspeptic symptoms and heartburn, participants reported a subjectively perceived improvement of disease-related and health-related quality of life as assessed by the GILQI and SF-12, respectively.

Our findings that drinking a mineral water rich in hydrogen carbonate promotes the relief of dyspeptic symptoms and heartburn are in line with previous studies showing the efficacy of mineral water to improve gastro-esophageal symptoms. Bertoni *et al.* [18] investigated the effect of drinking a bicarbonate-alkaline mineral water (683.2 mg bicarbonate/L) on various digestive symptoms in subjects with functional dyspepsia. At the end of the four weeks open label intervention study, subjects experienced a relief in postprandial fullness, gastric distension, retrosternal pyrosis and epigastric pain. Another study reported on the improvement of heartburn in subjects with gastro-esophageal reflux after drinking a mineral water containing 1750.7 mg/L hydrogen carbonate and 482.6 mg/L calcium [25].

The acid neutralizing capacity of hydrogen carbonate is well known and is assumed to be one of the relevant mechanisms of action of mineral rich water. Within the stomach, hydrogen carbonate neutralizes gastric acid leading to a faster increase of gastric pH preventing subsequent acidic gastro-oesophageal reflux [26]. Indeed, a study in subjects with gastro-esophageal reflux investigating the effect of a mineral water rich in calcium and hydrogen carbonate showed a significant and constant increase of esophageal and gastric pH [25]. This is in line with a study conducted in 12 healthy subjects showing that drinking Staatl. Fachingen STILL increased gastric acidity in the fasting phase as well as the postprandial phase as compared to tap water [27].

Moreover, there is evidence from a human study that exposure of the proximal duodenum to gastric acid increases proximal gastric relaxation and sensitivity to gastric distension resulting in the reduction of gastric emptying [28]. Indeed, an increased duodenal acid exposure has been associated with a higher severity of various dyspeptic symptoms in patients with dyspepsia [17] but also in healthy subjects [5]. Provided that impaired gastric motility or delayed emptying is considered one of the underlying pathophysiological mechanisms of dyspeptic symptoms [8], the regular consumption of alkaline mineral water may contribute to the relief of these symptoms. A preclinical study in rats revealed an increase in the gastric emptying rate as compared to control after four weeks of regular intake of the mineral water [18]. Moreover, the secretion of gastric acid and pepsinogen without changes in bound mucus indicates that motor and secretory gastric functions are improved with drinking hydrogen carbonate rich water. Other studies in humans used scintigraphic techniques to show that the consumption of hydrogen carbonate rich waters enhanced gastric emptying after the intake of a labelled test meal [19] [25] [29].

In summary, the observed effect of Staatl. Fachingen STILL on upper GI complaints can probably be attributed to its naturally high content of hydrogen carbonate. However, other minerals contained in the mineral water such as calcium, which is crucial for muscle tone, are also thought to prevent heartburn by improving the induc-

tion of peristalsis and acid clearance [30].

Some limitations of the study should be mentioned. The present study was designed as an explorative pilot study without a control group as clinical data on the efficacy of the mineral water on dyspepsia and heartburn was not available. Although the outcome of the pre-post study design allows the assumption that the hydrogen carbonate rich mineral water reduces dyspeptic symptoms and heartburn, a large-scale, randomized, placebo-controlled clinical trial is necessary to confirm the outcomes of the present study. Moreover, the patients were selected on the basis of self-reported heartburn. In future trials, standardized diagnostic criteria such as e.g. endoscopy findings, the ROME III criteria etc. should be used as proper inclusion criteria.

The presented pilot study in patients with self-reported heartburn provides the first clinical evidence of the beneficial effect of drinking 1.5 L of Staatl. Fachingen STILL on dyspeptic symptoms and heartburn. The water was demonstrated to be safe and tolerable. Although there is need for further randomized, placebo-controlled trials, drinking the mineral water might be recommended for patients with dyspepsia and heartburn and may help reduce accompanying symptoms and thereby improve quality of life. Given the fact that functional dyspepsia and heartburn impact work productivity and lead to substantial healthcare costs [31], hydrogen carbonate rich natural mineral water such as Staatl. Fachingen STILL might be a safe and tolerable alternative remedy helping to reduce direct and indirect treatment costs of functional dyspepsia and heartburn.

### Conflict of Interests

The study was funded by Fachingen Heil- und Mineralbrunnen GmbH. The authors declare no other competing interests regarding this study.

### Acknowledgements

All authors would like to thank Norman Bitterlich, PhD (Medizin & Service GmbH) for his support in statistical analysis of the data.

### References

- [1] Drossman, D.A. (2006) The Functional Gastrointestinal Disorders and the Rome III Process. *Gastroenterology*, **130**, 1377-1390. <http://dx.doi.org/10.1053/j.gastro.2006.03.008>
- [2] Kim, S.E., Park, H.K., Kim, N., Joo, Y.E., Baik, G.H., Shin, J.E., Seo, G.S., Kim, G.H., Kim, H.U., Kim, H.Y., *et al.* (2014) Prevalence and Risk Factors of Functional Dyspepsia: A Nationwide Multicenter Prospective Study in Korea. *Journal of Clinical Gastroenterology*, **48**, e12-e18. <http://dx.doi.org/10.1097/MCG.0b013e31828f4bc9>
- [3] Matsuzaki, J., Suzuki, H., Asakura, K., Fukushima, Y., Inadomi, J.M., Takebayashi, T. and Hibi, T. (2012) Classification of Functional Dyspepsia Based on Concomitant Bowel Symptoms. *Neurogastroenterology & Motility*, **24**, 325-e164. <http://dx.doi.org/10.1111/j.1365-2982.2011.01859.x>
- [4] Aro, P., Talley, N.J., Ronkainen, J., Storskrubb, T., Vieth, M., Johansson, S.E., Bolling-Sternevald, E. and Agreus, L. (2009) Anxiety Is Associated with Uninvestigated and Functional Dyspepsia (Rome III Criteria) in a Swedish Population-Based Study. *Gastroenterology*, **137**, 94-100. <http://dx.doi.org/10.1053/j.gastro.2009.03.039>
- [5] di Stefano, M., Vos, R., Vanuytsel, T., Janssens, J. and Tack, J. (2009) Prolonged Duodenal Acid Perfusion and Dyspeptic Symptom Occurrence in Healthy Volunteers. *Neurogastroenterology & Motility*, **21**, 712-e40. <http://dx.doi.org/10.1111/j.1365-2982.2009.01274.x>
- [6] Kindt, S. and Tack, J. (2006) Impaired Gastric Accommodation and Its Role in Dyspepsia. *Gut*, **55**, 1685-1691. <http://dx.doi.org/10.1136/gut.2005.085365>
- [7] Sarnelli, G., Vandenbergh, J. and Tack, J. (2004) Visceral Hypersensitivity in Functional Disorders of the Upper Gastrointestinal Tract. *Dig Liver Dis*, **36**, 371-376. [http://dx.doi.org/10.1016/S1590-8658\(04\)00082-9](http://dx.doi.org/10.1016/S1590-8658(04)00082-9)
- [8] Stanghellini, V., Tosetti, C., Paternico, A., Barbara, G., Morselli-Labate, A.M., Monetti, N., Marengo, M. and Corinaldesi, R. (1996) Risk Indicators of Delayed Gastric Emptying of Solids in Patients with Functional Dyspepsia. *Gastroenterology*, **110**, 1036-1042. <http://dx.doi.org/10.1053/gast.1996.v110.pm8612991>
- [9] Bolling-Sternevald, E., Carlsson, R., Aalykke, C., Wilson, B.V., Junghard, O., Glise, H. and Lauritsen, K. (2002) Self-Administered Symptom Questionnaires in Patients with Dyspepsia and Their Yield in Discriminating between Endoscopic Diagnoses. *Digestive Diseases*, **20**, 191-198. <http://dx.doi.org/10.1159/000067482>
- [10] Dent, J., El-Serag, H.B., Wallander, M.A. and Johansson, S. (2005) Epidemiology of Gastro-Oesophageal Reflux Disease: A Systematic Review. *Gut*, **54**, 710-717. <http://dx.doi.org/10.1136/gut.2004.051821>

- [11] Pehl, C. and Schepp, W. (2002) Wie entsteht Sodbrennen? *Deutsches Ärzteblatt*, **44**, A2941-A2949.
- [12] Wiklund, I., Carlsson, R., Carlsson, J. and Glise, H. (2006) Psychological Factors as a Predictor of Treatment Response in Patients with Heartburn: A Pooled Analysis of Clinical Trials. *Scandinavian Journal of Gastroenterology*, **41**, 288-293. <http://dx.doi.org/10.1080/00365520500292970>
- [13] Kumar, A.R. and Katz, P.O. (2013) Functional Esophageal Disorders: A Review of Diagnosis and Management. *Expert Review of Gastroenterology & Hepatology*, **7**, 453-461. <http://dx.doi.org/10.1586/17474124.2013.811028>
- [14] Fass, R. and Tougas, G. (2002) Functional Heartburn: The Stimulus, the Pain, and the Brain. *Gut*, **51**, 885-892. <http://dx.doi.org/10.1136/gut.51.6.885>
- [15] Oliver, K., Davies, G. and Dettmar, P. (2011) Diet and Lifestyle as Trigger Factors for the Onset of Heartburn. *Nursing Standard*, **25**, 44-48. <http://dx.doi.org/10.7748/ns2011.05.25.36.44.c8516>
- [16] Lacy, B.E., Talley, N.J., Locke3rd, G.R., Bouras, E.P., DiBaise, J.K., El-Serag, H.B., Abraham, B.P., Howden, C.W., Moayyedi, P. and Prather, C. (2012) Review Article: Current Treatment Options and Management of Functional Dyspepsia. *Alimentary Pharmacology & Therapeutics*, **36**, 3-15. <http://dx.doi.org/10.1111/j.1365-2036.2012.05128.x>
- [17] Lee, K.J., Demarchi, B., Demedts, I., Sifrim, D., Raeymaekers, P. and Tack, J. (2004) A Pilot Study on Duodenal Acid Exposure and Its Relationship to Symptoms in Functional Dyspepsia with Prominent Nausea. *Alimentary Pharmacology & Therapeutics*, **99**, 1765-1773. <http://dx.doi.org/10.1111/j.1572-0241.2004.30822.x>
- [18] Bertoni, M., Olivieri, F., Manghetti, M., Boccolini, E., Bellomini, M.G., Blandizzi, C., Bonino, F. and Del Tacca, M. (2002) Effects of a Bicarbonate-Alkaline Mineral Water on Gastric Functions and Functional Dyspepsia: A Preclinical and Clinical Study. *Pharmacological Research*, **46**, 525-531. <http://dx.doi.org/10.1016/S1043661802002323>
- [19] Stanghellini, V., Corinaldesi, R., Raiti, C., Rea, E., Salgemini, R., Paparo, G.F., Dominici, G. and Barbara, L. (1987) Effect of Alkaline-Earth Water on Gastric Emptying Time in Patients with Anorganic Dyspepsia. *La Clinica terapeutica*, **121**, 63-74.
- [20] Reichel, H. and Pola, H. (1952) Hastrinkuren mit Natriumhydrogencarbonathaltigem Brunnen (alkalischer Säuerling) —Drinking Cures at Home with a Mineral Water Containing Sodium Hydrogen Carbonate. *Fortschritte der Medizin*, **70**, 115-116.
- [21] Nocon, M., Kulig, M., Leodolter, A., Malfertheiner, P. and Willich, S.N. (2005) Validation of the Reflux Disease Questionnaire for a German population. *European Journal of Gastroenterology & Hepatology*, **17**, 229-233. <http://dx.doi.org/10.1097/00042737-200502000-00015>
- [22] Kulich, K.R., Malfertheiner, P., Madisch, A., Labenz, J., Bayerdorffer, E., Miehle, S., Carlsson, J. and Wiklund, I.K. (2003) Psychometric Validation of the German Translation of the Gastrointestinal Symptom Rating Scale (GSRs) and Quality of Life in Reflux and Dyspepsia (QOLRAD) Questionnaire in Patients with Reflux Disease. *Health and Quality of Life Outcomes*, **1**, 62. <http://dx.doi.org/10.1186/1477-7525-1-62>
- [23] Eypasch, E., Williams, J.I., Wood-Dauphinee, S., Ure, B.M., Schmullig, C., Neugebauer, E. and Troidl, H. (1995) Gastrointestinal Quality of Life Index: Development, Validation and Application of a New Instrument. *The British Journal of Surgery*, **82**, 216-222. <http://dx.doi.org/10.1002/bjs.1800820229>
- [24] Gandek, B., Ware Jr., J.E., Aaronson, N.K., Alonso, J., Apolone, G., Bjorner, J., Brazier, J., Bullinger, M., Fukuhara, S., Kaasa, S., et al. (1998) Tests of Data Quality, Scaling Assumptions, and Reliability of the SF-36 in Eleven Countries: Results from the IQOLA Project. International Quality of Life Assessment. *Journal of Clinical Epidemiology*, **51**, 1149-1158. [http://dx.doi.org/10.1016/S0895-4356\(98\)00106-1](http://dx.doi.org/10.1016/S0895-4356(98)00106-1)
- [25] Grassi, M., Fraioli, A., Pappalardo, G., Messina, B., Belardinelli, L. and Guadalaxara, A. (1993) Alkalizing Activity of a Calcium-Bicarbonate-Containing Water, Evaluated for pH, in Patients with Gastroesophageal Reflux. *La Clinica Terapeutica*, **143**, 131-136.
- [26] Graham, D.Y. and Patterson, D.J. (1983) Double-Blind Comparison of Liquid Antacid and Placebo in the Treatment of Symptomatic Reflux Esophagitis. *Digestive Diseases and Sciences*, **28**, 559-563. <http://dx.doi.org/10.1007/BF01308159>
- [27] Schmidt-Kessen, W.W.P. (1983) Die intragastrale Azidität beim Trinken von Hydrogencarbonat-Mineralwässern. *Zeitschrift für Physikalische Medizin. Balneologie Medizinische Klimatologie*, **12**, 199-209.
- [28] Lee, K.J., Vos, R., Janssens, J. and Tack, J. (2004) Influence of Duodenal Acidification on the Sensorimotor Function of the Proximal Stomach in Humans. *Am J Physiol Gastrointest Liver Physiol*, **286**, G278-G284. <http://dx.doi.org/10.1152/ajpgi.00086.2003>
- [29] Bortolotti, M., Turba, E., Mari, C., Lopilato, S., Scalabrino, A. and Miglioli, M. (1999) Effect of a Mineral Water on Gastric Emptying of Patients with Idiopathic Dyspepsia. *International Journal of Clinical Pharmacology Research*, **19**, 53-56.

- [30] Rodriguez-Stanley, S., Ahmed, T., Zubaidi, S., Riley, S., Akbarali, H.I., Mellow, M.H. and Miner, P.B. (2004) Calcium Carbonate Antacids alter Esophageal Motility in Heartburn Sufferers. *Digestive Diseases and Sciences*, **49**, 1862-1867. <http://dx.doi.org/10.1007/s10620-004-9584-1>
- [31] Lacy, B.E., Weiser, K.T., Kennedy, A.T., Crowell, M.D. and Talley, N.J. (2013) Functional Dyspepsia: The Economic Impact to Patients. *Alimentary Pharmacology & Therapeutics*, **38**, 170-177. <http://dx.doi.org/10.1111/apt.12355>