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Osteopathic treatment in addition to standard care in patients with Gastroesophageal Reflux Disease (GERD) – A pragmatic randomized controlled trial

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ABSTRACT

Background: Long-term Proton Pump Inhibitor use is associated with low response rates and the risk of adverse events.
Objective: The objective of this study was to assess the effectiveness of Osteopathic Treatment in patients with Gastroesophageal Reflux Disease (GERD).
Methods: This study was a randomized controlled trial with a series of osteopathic interventions and an untreated control group. Patients in the osteopathic group (OG) received 4 osteopathic treatments within a time of eight weeks. The control group (CG) did not receive any osteopathic treatment. Primary outcome parameters were gastrointestinal symptoms, assessed by means of the Reflux Disease Questionnaire (RDQ). Secondary outcome parameters were Quality of life with regards to GERD symptoms, assessed by means of the Quality of Life in Reflux and Dyspepsia (QUOLRAD) questionnaire, medication use and osteopathic dysfunctions.
Results: Seventy patients were randomized. RDQ mean scores decreased statistically significantly in the OG but did not change in the CG; however, these data cannot be interpreted due to a large number of incorrectly completed questionnaires. The between group difference of the changes for the QOLRAD score was statistically significant 0.69 [95%CI = 0.35 to 1.0]. At week 20, changes in the QOLRAD of the OG were sustainable. Medication use decreased substantially in the OG whilst it remained the same in the CG.
Conclusion: A series of osteopathic treatments might potentially be beneficial for patients suffering from GERD. Future studies should include longer follow-up times and establish the clinical significance of results by introducing a global rating of change measurement.

1. Introduction

Gastro-Oesophageal Reflux Disease (GERD), also known as acid reflux, is a chronic condition experienced by 18–28% of the population in North America, 9–26% in Europe and 3–8% in East Asia (El-Serag et al., 2014), demonstrating a negative effect on health-related quality of life (HRQoL) in adults, children and adolescents (Wiklund 2004a,b; Revicki et al., 1999; Talley et al., 2001; El-Dika et al., 2005; Tolia et al., 2004). Two main phenotypes of GERD have been described, non-erosive oesophageal reflux disease (NERD) and erosive oesophagitis (EE), which both represent different pathophysiological and clinical features and differences in response to anti-reflux therapy (Hershcovici and Fass 2010; Dickman et al., 2015; Fass 2007). GERD has been associated with substantial costs, both directly in terms of health care costs but also indirectly with regards to productivity loss (Brook et al., 2007; Joish et al., 2005; Peery et al., 2012; Wahlqvist et al., 2008).

Common symptoms include heart burn and regurgitation, which were reported by 44% of the US adult population at least once a month and by 20% at least once a week, respectively (Peery et al., 2012). Other, atypical extra-oesophageal symptoms may

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include chronic cough, dental erosion, or asthma (Vakil et al., 2006). Common risk factors for the development of GERD include various lifestyle factors including diet, smoking, alcohol and change in Body Mass Index (NIDDK 2015).

Commonly applied treatment modalities for GERD include lifestyle modifications, pharmacological agents such as antacids, H_2 receptor blockers or Proton pump inhibitors (PPI), and sometimes surgery if other measures are not effective (NIDDK 2015; Hershcovici and Fass 2011; Katz et al., 2012).

Relief of GERD -related symptoms, prevention of complications, and improvement of HRQoL are the goals of anti-reflux therapy (Dickman et al., 2015). Currently, PPI are the cornerstone of GERD treatment (Dickman et al., 2015). However, response rates to PPI remain as low as 37% and 56% for both patients with NERD and EE, respectively (Dean et al., 2004). Available evidence indicated the occurrence of adverse events (AEs) of chronic PPI therapy, manifesting in an increased risk of fractures, vitamin/mineral/electrolyte deficiencies, *Clostridium difficile* colitis, microscopic colitis, bacterial overgrowth, and community-acquired pneumonia (Yang et al. 2010, Keszthelyi et al., 2010; Lombardo et al., 2010; McColl 2009; Dial et al., 2004; Laheij et al., 2004). Whilst the risk of acquiring these AEs is considered low, safety concerns about long-term PPI therapies have been raised, calling for identification of and need for effective alternative treatment modalities (Dickman et al., 2015).

According to the 2012 National Health Interview survey of 13 505 US adults with a gastro-intestinal (GI) condition, 42% (n = 5629) reported to have used Complementary and Alternative Medicine (CAM) in the last year for any reason, and 3% (n = 407) used at least one CAM modality to address their GI condition (Dossett et al., 2014). The top three modalities among those using CAM for their GI condition were herbs and supplements, mind body therapies and manipulative therapies including chiropractic and osteopathy, with over 80% feeling it was helpful in addressing the GI condition and important in maintaining health and well-being (Dossett et al., 2014). Out of 7903 patients experiencing acid reflux and heartburn and reporting to have used CAM in the last year for any reason, 1689 patients (21.5%) used herbs and supplements, 1392 patients (17.5%) used manipulative therapies including chiropractic and osteopathy, and 967 (12.4%) used mind body therapies (Dossett et al., 2014). Despite its popularity, the evidence on the effectiveness of osteopathic interventions in patients with GERD is scarce and remains unclear.

Bjornaes and colleagues (2016) performed a single-centre, one armed interventional trial, investigating the effects of an osteopathic intervention on GERD symptoms in 22 patients recruited from one single osteopathic practice. The prevalence and total number of GERD symptoms were significantly reduced ($p < 0.01$) and only two patients reported an unchanged situation. A “moderate” or “good” effect of treatment was reported by 77.3% of the patients. No differences were detected between patients using and not using additional GERD pharmaceuticals (Bjornaes et al., 2016).

An unpublished study by Nerreter et al. (2006) explored the effect of an osteopathic intervention in a one-armed study. Twenty-five patients with GERD underwent a run-in phase of four weeks to establish baseline parameters, then received eight osteopathic treatments at weekly intervals (Nerreter et al., 2006). During the treatment phase, frequency and intensity of the reflux decreased by 26% and the use of drugs decreased by 18%, compared to the run-in phase which remained stable (Nerreter et al., 2006). The authors of this study concluded that eight osteopathic treatments showed a positive influence on GERD symptomology.

None of the above cited studies testing the effects of osteopathy on GERD symptoms used a randomized controlled study design, making judgements on the true effects of the intervention difficult, since the natural history of the disease has not been considered and controlled for by introducing a no intervention control.

The aim of this current study, therefore, was to investigate the effectiveness of an osteopathic intervention in patients with GERD by means of a pragmatic randomized controlled trial.

2. Methods

2.1. Study design and time period

This study was a pragmatic randomized controlled trial (RCT). Patients with GERD were randomly allocated to an osteopathic intervention group (IG) (n = 35), receiving four osteopathic treatments, or a control group (CG) that received no osteopathic intervention (n = 35). Patients in the control group were reimbursed for their time by offering two osteopathic treatments after the study was finished. All treatments were provided free of charge. Patients in both groups received usual care, consisting of medication therapy on demand. Recruitment for this study started on October 01, 2014, and the last follow-up questionnaire was received in February 2016.

2.2. Setting, subjects, and recruitment

This study was conducted at three osteopathic practices in Germany. Patients of both sexes were included into the study if they suffered from reflux symptoms for the last six months, at least once or twice per week, and who have been diagnosed with GERD by their General Practitioner (GP). Participants had to be 18 and 75 years old, as research indicates that GERD affects all age groups (Yamasaki et al., 2018). Additionally, patients had to present with an endoscopic test result that was not older than one year and did not present severe pathological findings.

Patients were excluded if they presented with one of the following: malignant tumours, Barrett syndrome, severe reflux symptoms (Grade II, III, IV after Savary/Miller), reflux in pregnancy, Coronary heart disease, varicose veins of the oesophagus, neuropathies due to diabetes mellitus and alcoholism, and surgery of the gastrointestinal tract within the last six months.

Patients were recruited via their GPs or other relevant clinics specialised in the treatment of this patient group. Diagnosis and assessment of eligibility was performed by the GP of the patient.

All eligible patients were permitted to enter the study, regardless of any concomitant care or other intervention.

Three osteopathic practitioners performed case history taking, physical assessment and treatment, all of them being fully trained over a six-year period with a minimum of 1500 h of patient contact. All osteopaths had similar amount of working experience.

2.3. Randomization and allocation concealment

Randomization of the participants with an allocation ratio of 1:1 was performed by external computerized block randomization of 4 and 8 for each practitioner. The randomization was kept by the academic office at Still Academy, Germany, and group allocation was revealed by telephone once initials and date of birth of participants were disclosed by the practitioners.

2.4. Blinding

Practitioners and participants were not blind to group allocation. Except for the osteopathic dysfunctions, which were assessed by the practitioners, outcomes were patient-reported. Each time a participant entered the osteopathic practice, the questionnaires were filled out and placed in a sealed envelope which was then collected in a dedicated box, assuring that the treating osteopath did not become aware of the outcomes. Questionnaires filled out by

patients in the control group were sent to the study team by post. Data entry was performed by an independent person who was not aware of group allocation.

2.5. Intervention and control

To facilitate adherence to the study protocol, a study-specific training was undertaken. A standardised examination form was used by all three osteopathic practitioners. Individual osteopathic treatment was performed according to clinical findings, only those structures were treated with structural (high-velocity thrust, muscle energy, and myofascial release techniques as well as functional techniques and balanced ligamentous tension technique), visceral and/or craniosacral techniques for which osteopathic dysfunctions were present. These techniques are standard osteopathic techniques and are commonly described in the osteopathic literature (AACOM 2020).

Participants of the control group did not enter the osteopathic practice.

For participants in both groups, at the first consultation the diagnosis, eligibility assessment and informed consent were performed by their GPs, followed by randomization into one of the two groups. Participants in the osteopathic intervention group then received four osteopathic assessments and treatments in a timeframe of six weeks, resulting in a treatment approximately once every two weeks. For each patient in the osteopathic treatment group, the treatment period was completed at 8 weeks, with a follow-up assessment at week 20.

After week 8, participants in the control group received two osteopathic treatments free of charge.

2.6. Outcomes and measures

As a primary outcome parameter, gastrointestinal symptoms were assessed by means of the Reflux Disease Questionnaire (RDQ) (Shaw et al. 2001, 2008), which was validated in German by Nocon et al., (2005). The RDQ assesses frequency and intensity of GERD symptoms (heartburn, regurgitation, and dyspeptic complaints), with the German version being modified to assess these symptoms over the last week, compared to the original questionnaire which uses 4 weeks as assessment period (Shaw et al. 2001, 2008, Nocon et al., 2005). It consists of a total of 12 questions. The Heartburn scale consists of four items on the severity and frequency of pain and burning behind the breastbone, the Regurgitation scale asks four questions on the severity and frequency of acid taste in the mouth and movement of acid upwards from the stomach, and the Dyspepsia scale consists of four items on the severity and frequency of pain or burning in the upper stomach. Responses are scored on a Likert-type scale, ranging from 0 (not present) to 4 (daily) for frequency and 0 (not present) to 5 (severe) for severity (Nocon et al., 2005). Each participant's scores for dyspepsia, heartburn and regurgitation are calculated as the sum of item responses, ranging from 0 to a maximum of 18 points (Nocon et al., 2006). Higher scores indicate more severe or frequent symptoms.

For the osteopathic treatment group, the RDQ questionnaire was filled at baseline and every two weeks, immediately before the osteopathic treatments, resulting in five completed questionnaires per patient during the treatment period. Additionally, follow-up assessment occurred at week 20. The control group filled this questionnaire at baseline and at 8 weeks (Table 1).

As secondary outcome parameters, Quality of life with regards to GERD symptoms by means of the Quality of Life in Reflux and Dyspepsia (QUOLRAD) questionnaire, osteopathic dysfunctions as part of the case history taking and medication use by a medication diary were assessed. The QOLRAD is a disease specific instrument containing 25 questions about gastrointestinal symptoms based on five areas: emotional distress (six questions), vitality (three questions), food/drink problems (six questions), sleep disturbance (five questions), and physical/social functioning (five questions) (Wiklund et al., 1998). Responses are assessed over the last week and are rated on a 7-point Likert-type scale, with lower values indicating a more severe impact on daily functions. This instrument has been validated in a German translation (Kulich et al., 2003).

The QOLRAD questionnaire was filled in at baseline, after 4, 8 and 20 weeks for the osteopathic intervention group, and at baseline and week 8 for the control group.

For participants in both groups, the medication diary was completed daily by the patients until week 8. Osteopathic dysfunctions were assessed by the osteopaths at baseline and at each treatment session, resulting in four assessments for the osteopathic intervention group and two assessments (at baseline and at week 8) in the control group.

All patients were monitored for the occurrence of adverse events.

2.7. Discontinuation of the study

Discontinuation occurred if patients withdrew from the study after randomization, either by withdrawing consent or dropping out of the study. Where possible, the reasons for withdrawal were ascertained. All demographic or outcome data were included in the analysis until the date of discontinuation. After discontinuation, the available data of the participant were intended to be analysed within the framework of the Intention-to-treat analysis by last observation carried forward.

Participants were planned to be removed from the study if an adverse event made it inadvisable to continue with the study.

2.8. Data analysis

The sample size calculation was based on an estimated effect size of 0.7 in the study of Nerreter et al., (2006). Type I error was set at 0.05 and type II error at 0.2 (80% Power). Thirty-four participants per group (total of 68) were needed, and due to potential drop-outs, a sample size of 70 was aimed for in this study.

Descriptive and summary statistics were calculated including means, standard deviations and 95% confidence intervals (CIs). In the confirmatory analysis, longitudinal changes were compared between both groups by unpaired, two-sided t-tests. A p-value of <0.05 was considered statistically significant, and 95% CIs were calculated for all point estimates.

2.9. Research ethics approval

The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the institutional review board of the German Academy of Osteopathy (EK002, September 2014).

This manuscript has been prepared according to the CONSORT 2010 Statement: updated 229 guidelines for reporting parallel group randomised trials recommended by the Enhancing the Quality and Transparency of Health Research (EQUATOR) network (Schulz et al., 2010).

3. Results

A total of 172 participants were assessed for eligibility, of which 70 were randomized into either the osteopathic intervention group ($n = 35$) or the control group ($n = 35$) (Fig. 1). There were no drop-outs. Only 23 patients in the osteopathic group and 18 patients in

Table 1
Demographic and baseline data.

Characteristics	Osteopathic group (n = 23) [Mean (SD)]	Control group (n = 18) [Mean (SD)]	p-value
Age	48.8 (14)	50.5 (13.4)	0.7
Gender (F/M)	14/9	14/4	0.2
RDQ - Heartburn scale			
Total score: 0 - 18	7.2 (4.4)	4,5 (4,6)	0.06
Frequency: 0 - 8	3.1 (2.1)	2 (2.2)	0.1
Severity: 0 - 10	4.1 (2.5)	2.5 (2.6)	0.05
RDQ - Regurgitation scale			
Total score: 0 - 18	6.7 (4.4)	5.7 (4.7)	0.5
Frequency: 0 - 8	3 (2.1)	2.4 (1.9)	0.4
Severity: 0 - 10	3.7 (2.4)	3.3 (2.8)	0.6
RDQ - Dyspepsia scale			
Total score: 0 - 18	6 (4.8)	4.4 (5.3)	0.3
Frequency: 0 - 8	2.6 (2.3)	1.8 (2.2)	0.2
Severity: 0 - 10	3.3 (2.5)	2.6 (3.2)	0.4
QOLRAD	**(n = 35)**	**(n = 35)**	
Total score	5.1 (1)	5.3 (0.9)	0.4
Emotional distress	5 (1.4)	5.1 (1)	0.7
Sleep disturbance	5 (1.2)	5.4 (1.2)	0.2
Food/Drink Problems	4.7 (1.2)	4.9 (1.2)	0.6
Physical/Social functioning	6.1 (1.1)	6.2 (0.8)	0.6
Vitality	4.8 (1.3)	5.2 (1.3)	0.4

Abbreviations: F – Female; M – Male; QOLRAD – Quality of Life in Reflux and Dyspepsia; RDQ – Reflux Disease questionnaire, SD – Standard Deviation.

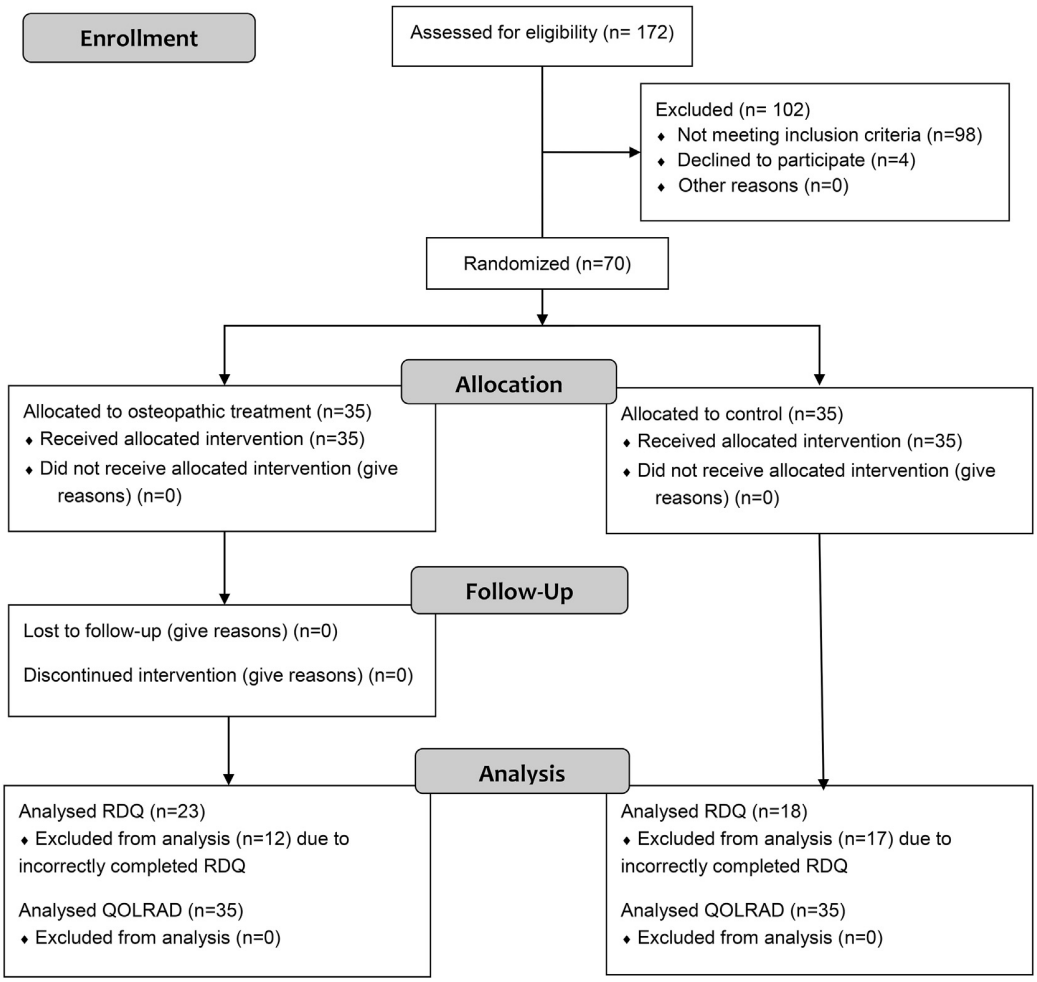

Fig. 1. CONSORT Flow diagram.
Abbreviations: QOLRAD – Quality of Life in Reflux and Dyspepsia; RDQ – Reflux Disease questionnaire.

the control group completed the RDQ correctly. Hence, only data of those 41 patients were analysed. All 70 patients completed the QOLRAD questionnaire correctly and were analysed. No patients were lost to follow-up.

3.1. Baseline data

Baseline characteristics of both groups are shown in Table 1. In terms of sociodemographic and baseline outcome data, the assessment of correctness of randomization was successful, as differences between groups were not significant.

3.2. Primary outcome – GERD symptoms (Dyspepsia, Heartburn, Regurgitation)

Data of only 41 patients could be analysed due to incorrect completion of the RDQ by 29 patients. Between group differences of the scores for heartburn, regurgitation and dyspepsia were statistically significant, with total scores and scores for frequency and severity improving in the osteopathic group and remaining almost unchanged in the control group (Table 2).

Within group differences in the total scores for heartburn, regurgitation and dyspepsia in the osteopathic group indicated an improvement in symptoms by 40%, 28% and 31%, respectively at week 8 and were statistically significant. These changes were sustainable through week 20. In contrast, the control group did not exhibit any statistically significant changes in total scores from baseline to end of treatment (Fig. 2).

3.3. Secondary outcome – Quality of life

All 70 patients completed the QOLRAD correctly. The total QOLRAD score of the osteopathic intervention group improved by 0.64 (SD 0.7) after 8 weeks, whereas the total score of the control group slightly decreased (−0.05 (SD 0.8)) at the same timepoint. The between group difference of the changes was statistically significant (0.69; 95% CI 0.35 to 1.0; $p < 0.005$) (Table 3).

Within group analysis showed that the individual domain scores in the osteopathic intervention group improved statistically significantly by more than 0.5 in all domains except the physical/social function domain and were sustainable through week 20, but remained either fairly constant or improved only slightly in the control group (Fig. 3).

3.4. Use of medication

The number of tablets taken per day in the osteopathic group has decreased by 33%, from n = 18/day in week 1 to n = 12/day in week 8, whereas the number of tablets taken per day in the control group remained constant (n = 11/day at baseline, n = 12/day at week 8). However, the average dose of medication taken by those who remained on medication, was the same in both groups (Table 3).

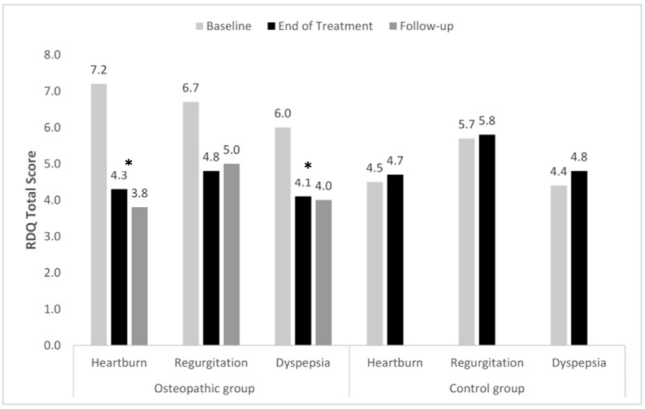

Fig. 2. Longitudinal changes RDQ Total scores.
Abbreviations: RDQ – Reflux Disease questionnaire*Changes between Baseline and End of Treatment (Week 8) were statistically significant ($p < 0.05$).

3.5. Osteopathic dysfunctions

The most common osteopathic dysfunctions that responded the most to treatment were at the sacrum, upper and middle cervical spine (C3-5, C0/1), and at the upper end of the thoracic spine (T1/T2), at the respiratory diaphragm and around the pylorus (Fig. 4).

3.6. Adverse events

No adverse events were reported by the patients.

4. Discussion

The aim of this study was to assess the effectiveness of a series of osteopathic interventions in addition to usual care in patients with GERD. Reflux symptoms, assessed by means of the RDQ appeared to be sustainably reduced by at least 28% in the osteopathic group, compared with no change in the control group. However, due to incorrect completion of a high number of RDQ questionnaires and subsequent removal of these data from the analysis, the results are to be interpreted with extreme caution and in the light of potential risk of bias, which does not allow to draw any conclusions of the

Table 2
Between group changes RDQ scores.

	DifferenceEnd of treatment – Baseline [(Mean (SD)]		**Difference of Means (95% CI)**	**p-value**
	Osteopathic group (n = 23)	**Control group (n = 18)**		
RDQ - Heartburn scale				
Total score: 0 - 18	−2.9 (3.9)	0.2 (3.9)	3.1 (0.6–5.5)	0.01
Frequency: 0 - 8	−1.5 (1.7)	0 (2.2)	1.5 (0.2–2.7)	0.02
Severity: 0 - 10	−1.4 (2.3)	0.2 (2)	1.6 (0.2–3)	0.03
RDQ - Regurgitation scale				
Total score: 0 - 18	−1.9 (4.6)	0.1 (3.6)	2 (−0.7 - 4.7)	0.1
Frequency: 0 - 8	−0.9 (2.1)	0.2 (1.6)	1.1 (−0.07 - 2.3)	0.06
Severity: 0 - 10	−0.9 (2.8)	−0.1 (2.1)	0.8 (−0.8 - 2.5)	0.3
RDQ - Dyspepsia scale				
Total score: 0 - 18	−1.9 (2.9)	0.4 (3.6)	2.3 (0.2–4.4)	0.03
Frequency: 0 - 8	−1 (1.4)	0.2 (1.6)	1.2 (0.3–2.2)	0.01
Severity: 0 - 10	−0.9 (2)	0.1 (2.2)	1 (−0.3 - 2.4)	0.1

Abbreviations: CI – Confidence Interval; RDQ – Reflux Disease questionnaire, SD – Standard Deviation.

Table 3
Between group changes QOLRAD scores and medication use over the study period.

Difference Baseline - End of treatment QOLRAD score [Mean (SD)]			
Osteopathic group (n = 35)	Control group (n = 35)	Difference of Means (95% CI)	p-value
0.64 (0.7)	−0.05 (0.8)	0.69 (0.35–1.0)	<0.005

Medication use over the study period Number of tablets per day	**Osteopathic group**	**Control group**
Week 1 (number of tablets per day)	18	11
Week 8 (number of tablets per day)	12	12

Abbreviations: CI – Confidence Interval; QOLRAD – Quality of Life in Reflux and Dyspepsia; SD – Standard Deviation.

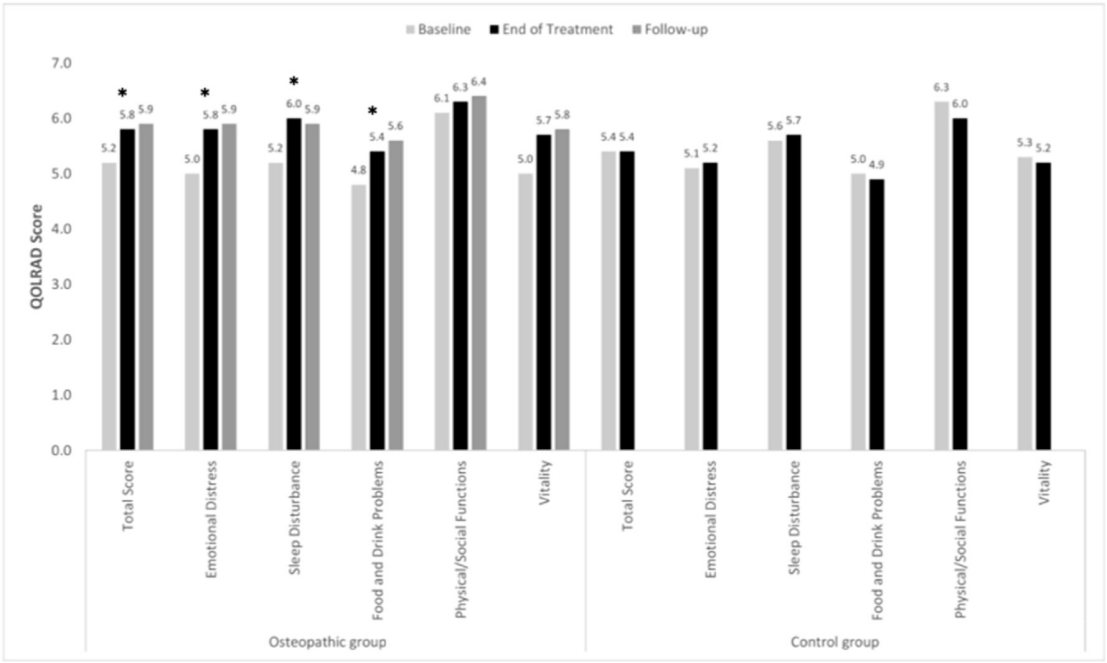

Fig. 3. Longitudinal changes QOLRAD scores.
Abbreviations: QOLRAD – Quality of Life in Reflux and Dyspepsia*Changes between Baseline and End of Treatment (Week 8) were statistically significant ($p < 0.05$).

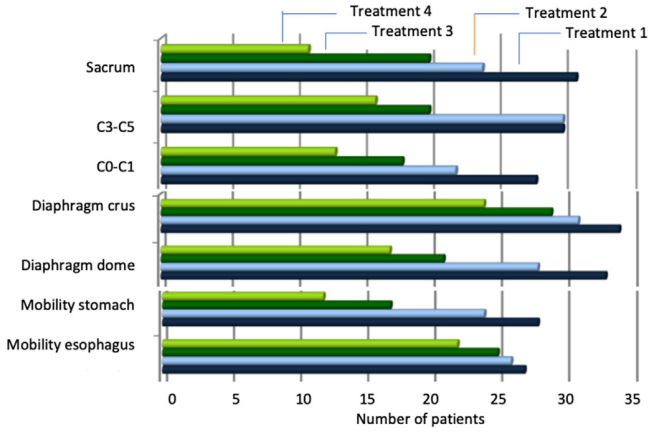

Fig. 4. Osteopathic dysfunctions in the intervention group.

effects of osteopathic treatment on GERD symptoms. On the other hand, the Quality of Life-data of this study show a lasting improvement in QoL domains of the QOLRAD disease-specific assessment tool and a reduction in medication use in the osteopathic group, but not in the control group. All study participants were able to correctly fill in the QOLRAD questionnaire, hence the data of all these patients were analysed.

The RDQ instrument used in the present study was validated in German (Nocon et al., 2005), however, the scoring is slightly different from the one used in the original publications of Shaw et al. 2001, 2008. Although the RDQ was judged applicable for the evaluation of oesophageal symptoms in response to treatment (Bolier et al., 2015), it may be difficult to compare scorings from German studies with international studies which assess osteopathic treatment with the RDQ score. Additionally, it appears that the correct completion of the RDQ by the German study subjects was problematic. Patients had to rate how often they had symptoms in the last week and how severe these were. There often was a discrepancy in that patients either responded that there were no symptoms, but then rated the severity as mild or other, or they said that there were symptoms, but then rated the severity as of 0 on the Likert scale (no symptoms). Future German studies should either put heavy emphasis on explaining to study participants how to correctly fill out the Questionnaire and closely monitor their completion or seek out a different reflux symptom assessment tool

altogether, which is validated in the main EU5 languages and which also has information on the Minimally Important Difference (MID) of results.

In the present study, for both the RDQ and QOLRAD scores, the clinical significance of the observed changes in the osteopathic group is unclear. Improvements of 5.1 points on the regurgitation scale, 4.2 points on the dyspepsia scale and 4.6 points on the heartburn scale of the RDQ instrument are reported to be associated with minimal important changes in symptoms (Nocon et al., 2005). According to these thresholds, the results of our study would not be considered clinically relevant. However, the study population with which the MID of the German reflux population was established, was entirely different to the population in our study. Nocon et al. included patients who were recruited directly from endoscopy units, and tested a pharmacological treatment, which may have raised different expectations and/or experiences with regards to the magnitude of a clinically relevant effect compared to osteopathic treatment, which may be facilitated by the potential effects and/or side effects of the treatment received.

The health-related quality of life in patients with reflux disease has been shown to be significantly impaired compared to the general population, for example patients may suffer from reduced sleep, generalized pains, anxiety and an impaired sex life (Wiklund 2004a,b).

The QoL results in our study indicate a statistically significant improvement in the total score of more than 0.5 in the osteopathic group, which was sustainable through week 20, but no change in the control group. A change of 0.5 represents a clinically significant difference in the QOLRAD (Wiklund 2000).

Our study results could be interpreted as clinically significant, however, our patient population likely was a different one than in the original study and the same notions with regards to the intervention under study applies, as previously mentioned.

Recent studies on manual therapy approaches in patients with GERD have found a significant improvement in symptoms compared to sham controls; however, the clinical significance of these findings has not been discussed by the authors and is, therefore, unclear (Martínez-Hurtado et al., 2019; Eguaras et al., 2019).

Future studies should introduce a measure of the global rating of change (GRC) in the patient population under investigation, for example the Overall Treatment Evaluation (OTE) questionnaire administered by Shaw et al., (2008). Although with these GRC scales patients will consider changes in their symptoms, disability, and quality of life when assessing their global improvement or deterioration, they nevertheless provide a flexible, quick and simple method of patient self-assessment of clinical progress (Kamper et al., 2009).

The study design was of pragmatic nature, taking all elements of a real-life situation – including non-specific treatment effects and individualized treatment approaches – into account, and therefore represents significant external validity in terms of generalizability to the 'real-world' population. Due to the 'waiting list design' of this trial, patients in the control group only received two osteopathic treatments once the study was finished. However, since they were allowed their usual medication to be taken when needed, those patients were not deprived of the currently recommended standard of care. The waiting list design was considered appropriate, because GERD symptoms were expected not to change relevantly without intervention, and indeed remained stable over this period in the control group.

With regard to medication use, it appeared that drug consumption has decreased in the osteopathic treatment group compared with the control group, however, due to the small numbers of patients in each group taking medication initially and a higher number of drugs taken in the osteopathic group at baseline, it is unclear whether these differences could be due to chance. Future studies should specify more stringent on medication use as an inclusion criterium in order to achieve balanced drug use at baseline.

The treatments were performed by three different osteopaths with similar levels and years of training and practical experience. Additionally, the study conditions were kept identical as much as possible and the random allocation of the patients to the intervention groups and practitioners was adequately concealed. Hence, the risk of bias that increases with only one practitioner delivering the treatment has been limited within the constraints of this study.

For the assessment of osteopathic dysfunctions, it is widely recognized that the reliability of palpatory findings is insufficient (Seffinger et al., 2004, Cooperstein et al. 2016), however, these findings were reported for internal use only and serve as hints for future studies on where these osteopathic dysfunctions might be present, but they are not to be seen as a major outcome of this study.

The limitations of this study derive from the chosen 'waiting list' design. Patients in the control group are aware that they do not receive the intervention, which may increase the risk of bias due to potential under-reporting, and like-wise possible over-reporting of those patients who do receive the intervention. Potential placebo-effects, such as deriving from establishing patient-practitioner relationships, having certain treatment expectations, a particular treatment environment, and having a specific perception of treatment credibility, were not controlled for due to a lack of patient blinding, however, effects seen with this trial design can give valid information of the extent of change associated with the decision to see an osteopath.

The osteopathic treatment, including the hands-on techniques plus potential advice given, were individualized, according to patients' needs, hence, this variability may limit the reproducibility of the study results. Future clinical studies should start to address those shortcomings by introducing adequate sham controls and assess patient blinding, and report on treatment approaches used.

Our study results report on a change in mean symptom or QoL scores. According to a consensus document on clinical trial design in adult reflux disease, a treatment responder should be predefined in the study protocol, with the amount of improvement in a specific symptom specified that is clinically meaningful (Dent et al., 2008). The definition of a responder should incorporate the primary outcome measure which may be the proportion of patients who achieved the improvement necessary to be a responder (Dent et al., 2008). Additional strong consensus was reached that absence or almost complete relief of symptoms is the best measure of treatment efficacy, which is in line with the research literature (Dent et al., 2008; Junghard et al., 2003; Fraser et al., 2005).

5. Conclusions

Results of this study show that a series of osteopathic treatments may be of longer-term benefit to patients with GERD. Considering low response rates and occurrence of adverse events on PPI therapy, an osteopathic intervention may be a safe and effective complementary healthcare option in addition to standard medication therapy for patients according to their preferences and needs. Future studies should seek to reproduce these results with longer follow-up times and predefine treatment responders as the primary outcome and/or confirm patient-reported changes in symptoms and quality of life with a global rating of change to establish the minimally important difference of the outcomes used.

Clinical relevance

- Conventional therapy with PPI is often accompanied with low response rates and occurrence of adverse events
- Osteopathic treatment of patients with GERD may be of longer-term benefit to these patients
- An osteopathic intervention may be a safe and effective intervention option in addition to standard drug therapy

Trial registration

German Clinical Trials Register: DRKS00006824. Date of registration: September 30, 2014.
(https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00006824)

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CRediT authorship contribution statement

Andreas Lynen: Conceptualization, Methodology, Investigation. **Meike Schömitz:** Conceptualization, Methodology, Investigation. **Maik Vahle:** Conceptualization, Methodology, Investigation. **Anne Jäkel:** Writing – original draft. **Michaela Rütz:** Statistics. **Florian Schwerla:** Methodology, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no competing interests.

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