Idiopathic esophagopathies resembling gastroesophageal reflux disease in dogs

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Key words
Esophagus, endoscopy, radiology, supra-esophageal complication, canine

Summary

Objective: Pathologic gastroesophageal reflux (GER) has been demonstrated experimentally in dogs, and it is suspected to occur naturally in dogs, yet its clinical significance is unknown. The aim of the study was to demonstrate clinical indicators of pathologic GER in dogs with idiopathic esophagopathies. Materials and methods: Dogs with clinical signs suggestive for esophageal disease (regurgitation, ptyalism, or dysphagia) and where extraesophageal and specific esophageal diseases had been ruled out, were retrospectively diagnosed with idiopathic esophagopathies. History, physical examination findings, clinicopathologic, radiographic, and endoscopic data, and treatment results were obtained from medical records, reviewed and evaluated. Results: Out of 67 dogs with anamnestic esophageal signs, 12 (17.4%) dogs were identified as having idiopathic esophagopathies and were included in the study. Median age was 3.0 years (range 1.0–11.0), and median bodyweight was 28.2 kg (range 8.2–44.0). The most frequent anamnestic esophageal signs were ptyalism (10/12 dogs), regurgitation (8/12 dogs), signs of discomfort, pain (8/12 dogs), and cough (5/12 dogs). The most common radiographic abnormality was segmental esophageal dilation (8/12 dogs). Esophagoscopy revealed single mucosal surface defects at the gastroesophageal junction in 3/12 dogs. In dogs with altered esophageal motility, cytological and microbiological examinations of bronchial aspirates showed goblet cell hyperplasia (8/8 dogs), neutrophil infiltration (5/8 dogs) and cultivable bacteria (4/8 dogs), respectively. All dogs were treated with omeprazole (median 0.7 mg/kg once per day, range 0.5–1.2). Reported median treatment duration until remission of the main clinical signs was 20.0 days (range 8.0–54.0 days). This endpoint was reached in 11/12 dogs. Conclusion and clinical relevance: Results suggest that in some dogs with esophageal clinical signs, and where no primary disease could be identified, clinical indicators of pathologic GER such as pain, mucosal lesions and motility disturbances of the esophagus, respiratory complications, and response to therapy can be observed.

Schlüsselwörter
Speiseröhre, Endoskopie, Radiologie, supraösophageale Komplikation, kanin

Zusammenfassung

Gegenstand und Ziel: Ein Vorkommen des in experimentellen Untersuchungen demonstrierten pathologischen gastroösophagealen Refluxes (PGR) wird bei natürlich erkrankten Hunden vermutet, aber die klinische Bedeutung ist unbekannt. Ziel der Studie war der Nachweis klinischer Indikatoren für PGR bei Hunden mit idiopathischen Ösophagopathien. Material und Methoden: Aufnahme in diese retrospektive Studie fanden Hunde mit ösophagealen Symptomen (Regurgitieren, Ptyalismus oder Dysphagie), bei denen extraösophageale und spezifische ösophageale Krankheiten ausgeschlossen worden waren. Diese Fälle galten als idiopathische Ösophagopathien. Ergebnisse der Anamnese, der körperlichen, labordiagnostischen, radiologischen und endoskopischen Untersuchungen sowie der Behandlungen wurden den Krankenakten entnommen und bewertet. Ergebnisse: Bei 12 von 67 (17,4%) Hunden mit ösophagealen Symptomen konnte eine idiopathische Ösophagopathie identifiziert und die Tiere in die Studie eingeschlossen werden. Das mediane Alter betrug 3,0 Jahre (Bereich 1,0–11,0), das mediane Körpergewicht 28,2 kg (Bereich 8,2–44,0). Die laut Anamnese häufigsten Symptome waren Ptyalismus (10/12 Hunde) und Regurgitieren (8/12 Hunde), ferner Unwohlsein oder Schmerzen (8/12 Hunde) und Husten (5/12 Hunde). Als häufigstes Röntgenbefund lag eine segmentale ösophageale Dilatation vor (8/12 Hunde). Ösophagoskopisch ließen sich einzelne Mukosadefekte am gastroösophagealen Übergang (3/12 Hunde) darstellen. Bei Hunden mit gestörter Ösophagusmotilität zeigten zytologische und mikrobiologische Untersuchungen von Bronchialspülproben Becherzellhyperlplasie (8/8 Hunde), neutrophile Infiltrationen (5/8 Hunde) und kultivierbare Bakterien (4/8 Hunde). Alle Hunde erhielten zur Behandlung Omeprazol (median 0,7 mg/kg einmal täglich, Bereich 0,5–1,3). Die Hauptsymptome gingen unter Therapie in median 20,0 Tagen (Bereich 8,0–54,0) zurück. Diesen Endpunkt erreichten 11/12 Hunden. Schlussfolgerung und klinische Relevanz: Den Ergebnissen zufolge finden sich bei Hunden mit idiopathischen Ösophagopathien ohne nachweisbare Primärkrankheiten klinische Indikatoren für PGR wie Schmerzen, ösophageale Schleimhautläsionen und Motilitätsstörungen sowie respiratorische Komplikationen, die bei adäquater Therapie sistieren.
Introduction

Gastroesophageal reflux (GER) develops when, in absence of vomiting, gastric contents move through the lower esophageal sphincter into the esophagus. GER occurs in dogs as a normal postprandial event when the lower esophageal sphincter (LES) relaxes transiently (38). In dogs, the LES or cardiac sphincter muscle is composed of an outer layer of longitudinal striated and an inner layer of circular smooth musculature, which thickens at the gastroesophageal junction (16). Functionally, the LES is located at the level of the diaphragm as a 1 cm long area with increased pressure inside the esophageal lumen between oesophagus and stomach. The LES works in conjunction with the diaphragm to create a physical barrier against the entry of gastric contents into the esophagus and maintains the unidirectional flow of ingesta (3, 54). The transient relaxation of the LES is mediated vagally and by local reflexes, and is associated with swallowing and triggered by gastric distension (14).

The presence of GER does not necessarily cause clinical signs, because several factors protect the esophageal mucosa from injury. In dogs, normal LES function is thought to be the main mechanism for preventing reflux (3). Other protective mechanisms include the physiologic esophageal peristalsis clearing the esophagus from refluxed material, the buffering of gastric acid by bicarbonate secreted into the saliva, and the natural resistance of the esophageal mucosa to injury due to its stratified squamous epithelium, its submucosal glands, and its vascularity (30, 48, 50).

GER may lead to complications when the protective mechanisms are altered. Experimentally, LES function in dogs can be impaired by surgically created hiatal hernias, gastric distension, vagally acting anaesthetic agents, and intraabdominal surgical procedures (18, 19, 29, 40, 47). If LES function, esophageal clearance mechanisms, or mucosal resistance are altered experimentally in dogs, refluxed gastric or duodenal contents such as acid, pepsin, bile acids, and trypsin can contribute to esophageal damage (12, 13, 48, 50). GER becomes pathologic, when clinical complications such as regurgitation, painful esophagitis, formation of benign strictures after scarring, or intestinal metaplasia (Barrett’s esophagus) occur (7).

In dogs, the association between GER and esophageal complications is clinically still not proven, because specific diagnostic tools such as esophageal pH monitoring, esophageal manometry, and esophageal impedance measurement are typically not used in clinical settings (17, 42). In naturally diseased dogs esophageal complications presumed to be caused by pathologic GER are most commonly reported secondary to previous anaesthesia and surgical interventions (1, 25, 27, 33, 39, 57), or secondary to structural anomalies such as hiatal hernias, megaesophagus, and neoplasia (8, 11, 20, 32, 34). Furthermore, cases of suspected pathologic GER have been reported in dogs and cats with esophagitis, benign strictures due to scar formation, perforating ulcers, or intestinal metaplasia (1, 6, 23, 24, 27, 33, 43). In contrast, pathologic GER is one of the most commonly diagnosed gastrointestinal disorders in humans (55). The true incidence of pathologic GER in dogs is unknown but probably more common than clinically recognized, possibly due to the difficulties in detecting specific causes (25). Thus, the aim of this retrospective study was to test the hypothesis that in dogs with idiopathic esophagopathies, clinical indicators of pathologic GER as known from humans and experimental studies can be demonstrated.

Material and methods

Case selection

Medical records of dogs that had undergone upper gastrointestinal endoscopy between February 2006 and January 2010 were reviewed. Sixty-seven dogs were considered for this study, because they had shown esophageal signs indicating esophageal disease in their anamnestic (regurgitation, ptyalism, or dysphagia). None of the dogs had shown clinical or endoscopic evidence of oral or pharyngeal diseases.

Next, 55 dogs were excluded from the study because the clinician’s primary diagnosis was a specific esophageal disease such as megaesophagus (n = 10), a specific gastric disease such as benign gastric outflow obstruction (n = 3), and gastric carcinoma (n = 2), a specific intestinal disease such as parasitic infections (n = 7), salmonellosis (n = 2), histologically confirmed gastritis or gastro-duodenitis including inflammatory bowel disease (n = 24), chronic colitis (n = 1), or an extraintestinal disease such as pancreatitis (n = 2), hepatitis (n = 2), and hypothyroidism (n = 2). These dogs were excluded because reported anamnestic esophageal signs could have been caused secondary to non-esophageal diseases.

Finally, 12 dogs were included into the study because of the presence of anamnestic esophageal signs without evidence for specific primary esophageal diseases, such as foreign body, esophageal neoplasia, esophagitis due to infection, ingestion of caustic agents or recent application of doxycycline or clindamycin pills, potassium containing drugs, pancreatic enzyme powders, chemotherapeutics, recent anaesthesia, recent trauma, or excessive vomiting. Since specific esophageal and extraesophageal diseases had been ruled out, these dogs were presumed to have idiopathic esophagopathies.

Review of medical records

The information summarized from each dog’s medical record included signalment, clinical signs, and physical examination findings, results of faecal, serum biochemical, and haematological analysis, results of survey radiography, contrast radiography, and further diagnostic imaging, results of esophagoscopy, results of cytological and microbiological examinations of specimens collected using bronchial wash procedures, and treatment results and outcome.
Clinical, clinicopathologic, radiologic, and endoscopic procedures

Signalment, historical, and clinical examinations was performed by two clinicians (MM, AH), using a standard examination protocol. Haematological (PCV, WBC, and platelet count) and biochemical data (bilirubin, creatinine, urea nitrogen, glucose, total protein, albumin, globulin, cholesterol, triglycerides, sodium, potassium, calcium, serum enzyme activities of alkaline phosphatase, AST, amylase, and lipase) were collected from all enrolled dogs. Individual blood analyses had been processed in four different laboratories and the reference ranges varied between those laboratories. Therefore, individual data were compared to reference ranges as reported by the respective laboratory. Faecal specimens sampled during a period of 3 days were submitted for parasitological examinations (direct faecal smears, flotation, sedimentation, and faecal antigen testing).

Chest survey radiographs were performed in all dogs in right lateral recumbency. Furthermore, static esophageal contrast studies (TelebrixN300® 1-2 ml/kg per bolus, right lateral recumbency, Bucky table and automatic exposure) were performed in all dogs. Abdominal sonography was reported from 7 dogs. All examinations were performed in dorsal recumbency using a General Electric Logiq 500 with linear transducers (7 Mhz and 9 Mhz, respectively). Esophagoscopy was performed in all dogs under general anaesthesia in left lateral recumbency using a paediatric fiberscope (Olympus GIF PQ 20). Endoscopic data were recorded by using a standardized report form (www.vetgastro.de).

Cytological und microbiological examinations of bronchial wash specimens were reported from 8 dogs. All cytological specimens were submitted to the Institute for Veterinary Pathology, Vet-Suisse-Fakulty, University of Zurich. Microbiological specimens were submitted for culture and identification of bacteria to the Institute of Microbiology and Epizootics, Freie Universität Berlin.

All dogs were treated and the outcome was recorded by one clinician (MM) at clinical follow-up examinations after a minimum of 60 days. Results were obtained from the medical records. Remission was defined as a reduction of the pre-treatment severity of the main clinical signs by ≥ 50% as reported by the owners.

Statistical analysis

Gaussian distribution for quantitative data was tested by Kolmogorov-Smirnov-test. Normally distributed data was reported as mean and standard deviation. Data not following a Gaussian distribution were expressed as median and range. Categorical data were analyzed by use of a Fisher’s exact test or a chi² test, as appropriate. Significance was set at p < 0.05 for all statistical analyses. Statistical analysis was performed by use of standard computer packages (WinSTAT® for Excel®, R. Fitch Software, Bad Krozingen, Germany).

Results

The final study population comprised 12 dogs with idiopathic esophagopathies (7 pure breed dogs and 5 mixed breed dogs, Table 1). The median duration of clinical signs was 5.0 months (range 1.25–38.0 months). Ptyalism, regurgitation, and discomfort/pain were the most frequently detected clinical signs that were reported from 10, 8, and 8 dogs respectively. Vomitus and retching were reported from 6 dogs. Excessive grass eating, cough, anorexia, and dysphagia were less frequently detected clinical signs, being reported from 5, 5, 4, and 3 dogs respectively (Table 2).

<table>
<thead>
<tr>
<th>Results</th>
<th>Dogs (n)</th>
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<tbody>
<tr>
<td>Historical findings</td>
<td></td>
</tr>
<tr>
<td>Ptyalism</td>
<td>10</td>
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<tr>
<td>Regurgitation</td>
<td>8</td>
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<tr>
<td>Discomfort/pain</td>
<td>8</td>
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<tr>
<td>Vomitus</td>
<td>6</td>
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<tr>
<td>Retching</td>
<td>6</td>
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<tr>
<td>Excessive grass eating</td>
<td>5</td>
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<td>Cough</td>
<td>5</td>
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<td>Anorexia</td>
<td>4</td>
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<td>Dysphagia</td>
<td>3</td>
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<tr>
<td>Clinical findings</td>
<td></td>
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<tr>
<td>Abnormal abdominal palpation</td>
<td>5</td>
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<tr>
<td>Decreased body condition</td>
<td>4</td>
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<tr>
<td>Abnormal lung sound</td>
<td>4</td>
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<tr>
<td>Systolic heart murmur</td>
<td>2</td>
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</table>

Table 1

Signalement of 12 dogs with idiopathic esophagopathies.

<table>
<thead>
<tr>
<th>Breeds</th>
<th>Age (years; median, range)</th>
<th>Sex</th>
<th>Bodyweight (kg; median, range)</th>
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</thead>
<tbody>
<tr>
<td>American Staffordshire terrier, Australian Shepherd, Great Dane, Entlebucher Mountain Dog, French bulldog, Golden Retriever, Rottweiler, mixed breeds</td>
<td>3.0 (1.0 –11.0)</td>
<td>male: 5 dogs, 2 neutered female: 7 dogs, 4 neutered</td>
<td>28.2 (8.2–44.0)</td>
</tr>
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Table 2

Historical and clinical findings in 12 dogs with idiopathic esophagopathies.
fort/pain, were the most commonly historical signs (Table 2). Signs of ptyalism were recorded as excessive lip licking, smacking and "empty" swallowing, repeated swallowing motions or obvious hypersalivation (Fig. 1). If signs of vomiting were reported by the owners, it was differentiated either into a combination of regurgitation and vomiting (n = 5), regurgitation (n = 3), and true vomiting (n = 1). The other 3 dogs showed neither vomiting nor regurgitation. Other described abnormalities were vomiting of bile, expelling of undigested food (in one case in tubular form), retching, and production of white foamy or mucoid liquids. Reported esophageal signs of dogs with idiopathic esophagopathies were compared to dogs with specific esophageal diseases, and dogs with extra-esophageal diseases, respectively. Ptyalism was significantly more frequently reported (\(\chi^2 = 17.1; p = 0.0002\)) in dogs with idiopathic esophagopathies than in dogs of the two other groups. No significant differences were found for the frequency of regurgitation and dysphagia, respectively.

Discomfort/pain as given in Table 2 summarizes a variety of owner observations: sudden restlessness, sometimes in association with ptyalism, gagging, vomiting or regurgitation, panting, signs of a painful abdomen, disturbing the owner at night by gnashing the teeth, or showing the intention to go outside. Signs of discomfort or pain during the night or in the early morning were reported in 5/8 dogs. The most common finding of physical examination (Table 2) was mild pain during the abdominal palpation in 5/12 dogs, such as mild reactions due to deep palpation of the epigastria (starting to lick the lips and smacking, suddenly increased tension of the abdominal wall, and escape movements).

Results of haematology and biochemistry were mostly normal in all dogs, except mild anaemia in 3 dogs (PCV 42%, 44%, and 44%, respectively; reference range 47–55%), mild leukocytosis in one dog (leukocytes 14.900/µl; reference range 6.000–12.000/µl), mildly decreased total protein concentration in one dog (5.1 g/dl; reference range 5.5 g/dl–7.5 g/dl), and mildly increased AST activity in one dog (150 IU/L; reference range < 80 IU/L), respectively.

The most frequent abdominal ultrasound findings were unspecific (5/7 dogs), with mild enlargement of the abdominal lymph nodes, and moderate wall thickening of the duodenum (1/7 dogs, respectively). In chest survey radiography, findings for the esophagus were unremarkable (8/12 dogs), or showed small amounts of intra-esophageal gas in the cervical part of the esophagus (4/12 dogs). Findings of contrast radiography revealed segmental esophageal dilation (8/12 dogs) (Fig. 2), gastroesophageal reflux (2/12 dogs) (Fig. 3), and unpecific signs (3/12 dogs). A common observation at esophagoscopy was mucosal erythema (5/12 dogs) in the area of the lower esophageal sphincter. Furthermore, single mucosal defects with red or whitish surface at the gastroesophageal junction occurred in 3/12 dogs. Further findings were abnormal intraesophageal contents (5/12 dogs) consisting of more than normal amounts of saliva and presence of bile fluid.

Bronchial wash procedures were analysed in dogs with radiologic evidence of esophageal motility disorders. Dogs with bronchial aspirates (Table 3) positive for isolates of Streptococcus canis and Staphylococcus spp. showed evidence of bronchial irritation such as goblet cell hyperplasia. One dog with an isolate of Escherichia coli and Bordetella bronchiseptica, and one dog with an isolate of Staphylococcus spp. each showed evidence for bronchial neutrophilic inflammation upon cytological examinations. All 5 dogs with cough and 8/8 dogs with pathologic findings from the esophageal contrast studies had abnormal bronchial aspirates.

Treatment results were available for all dogs included in the study. The standard treatment regimens in all dogs were oral proton pump inhibitors (omeprazole, median dosage 0.7 mg/kg once per day; range 0.5–1.2), accompanied by medications aimed towards improving gastric motility and lower esophageal sphincter pressure such as ranitidine (median dosage 5.3 mg/kg divided in two applications per day; range 3.0–9.0) and metoclopramide (median dosage 0.2 mg/kg divided in three per day;
Discussion

The aim of this retrospective study was to demonstrate clinical indicators of pathological gastroesophageal reflux in dogs with unspecific esophagopathies. The presence of physiologic and pathologic GER has been demonstrated in humans and dogs by specific diagnostic procedures such as esophageal pH measurements (10, 13). In contrast to humans, because of practical limitations, such diagnostic procedures remain of experimental nature in dogs (17, 37). Therefore, the recognition of pathologic GER in clinical practice still remains a diagnosis of exclusion. In the present study, 12 out of 67 dogs with idiopathic esophagopathies were enrolled after exclusion of other specific causes of disease (36). Ptyalism showed some statistical association with idiopathic esophagopathies. However, because this was a retrospective study, it is possible that some esophageal signs were not reported in the clinical history, limiting the meaningfulness of this observation.

Predominantly young dogs and large breeds were affected. Reversible esophageal dysmotility has been described in younger terrier breeds, and younger animals are thought to be at higher risk for GER because of developmental immaturity of the esophagus and the gastroesophageal sphincter (5).

Reported historical and clinical results suggest that signs of pain in dogs may be present during the day, during the night or in the early morning, and this would be consistent with findings in humans (45). Dogs with presenting signs of discomfort or visceral pain may suffer from chest pain, and associated esophageal symptoms. Painful complications such as esophagitis, erosions, or stricture formations should be considered in these animals.

The radiologic and endoscopic results of the study suggest that esophageal signs may be associated with esophageal complications such as esophageal motility disturbances and esophageal mucosal injury. Such esophageal complications have been reported previously in cats with suspected reflux-esophagitis (24, 26) and in dogs with suspected reflux induced benign stricture formation (57). In humans, several endoscopic grading systems such as the Los Angeles classification system, or the Prague classification system have been established to standardize the diagnosis of GERD.
and Barrett's esophagus (4, 46), respectively. Mucosal “breaks” (defined as sharply contrasted defects, such as an erosion or an ulcer) < 5 mm size as reported in 3 dogs in our study would in humans approximate a grade A reflux esophagitis according to the Los Angeles classification. Lesions without obvious mucosal breaks such as erythema, as reported in 5 study dogs, are mostly classified as normal endoscopic findings in human medicine (53). Minimal changes such as small erosions, an atypical gastroesophageal junction, changes in vascular architecture, and others have been demonstrated in humans using magnifying endoscopy (31). In the present study, these minimal changes remained undetectable because a fiberscope was used.

In dogs and cats, esophagitis and intestinal metaplasia are histological defined diseases (21–24). Nevertheless, similar as in the present study, biopsies from the esophagus are rarely obtained during routine gastroscopy in veterinary practice settings. Therefore, some clinicians diagnose esophagitis based on endoscopy findings alone (22, 25). In human medicine however, histological examination of esophageal biopsy specimens represents an important diagnostic tool (2, 15).

The cytological and microbiological results from bronchial washings suggest that esophageal signs and esophageal motility disturbances may be associated with supra-esophageal complications such as respiratory signs and bronchial irritation or aspiration. Interpretation of these microbiological results seems difficult, because the tracheobronchial tree does not represent a sterile site in normal dogs, and cytological results such as goblet hyperplasia may be an unspecific finding as well. Nevertheless, respiratory complications have been reported in dogs with esophageal motility disorders and suspected GER (56) and in humans with pathologic GER (41). Dogs with chronic upper and lower respiratory signs should be closely examined for the presence of anamnestic esophageal signs, esophageal motility disturbances, and esophagitis.

To our knowledge this is the first case series study in naturally diseased dogs that attempts to demonstrate a clinical association between pain, esophageal signs, esophageal mucosal lesions, esophageal motility disturbances, and respiratory alterations. We observed in these systematically investigated dogs some analogy to gastroesophageal reflux disease (GERD) as defined in humans (7, 51): clinical signs resembling heartburn or chest pain, the presence of regurgitation, and the presence of esophageal or supra-esophageal complications. Furthermore, treatment with proton pump inhibitors, an accepted diagnostic approach in humans with suspected GERD (9), was most probably effective in the dogs in the present study. However, impact of other medications on treatment results cannot be excluded, particularly in regards to the low doses of omeprazole reported in some cases (49). Nevertheless, in the future the existence of GERD in dogs could be confirmed using specific diagnostic tools such as minimal invasive wireless esophageal pH measuring instruments (28), as recently experimentally tested in dogs (44). Furthermore, endoscopic biopsy and histopathology from the canine gastroesophageal junction may become helpful to demonstrate esophageal complications of GER (2, 23, 24, 26, 35).

Conflict of interest
The authors confirm that they do not have any conflict of interest.

References


