



# Outcome of esophageal atresia beyond childhood

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## KEYWORDS

Esophageal atresia;  
 Esophageal  
 dysmotility;  
 Esophagitis;  
 Gastroesophageal  
 reflux;  
 Long-term outcome;  
 Metaplasia

Survivors of esophageal atresia are reaching their adulthood in large numbers for the first time enabling assessment of true long-term outcome among this group of patients. This review summarizes the current knowledge on the subject focusing on late symptoms and complications, esophageal pathology and pulmonary function. Relationships between esophageal dysmotility, gastroesophageal reflux, esophagitis and epithelial metaplastic changes including esophageal cancer are outlined. In addition to pertinent literature, institutional experience, and follow-up of patients with esophageal atresia for more than 60 years is included.

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The overall survival rate of patients with esophageal atresia (OA) has increased significantly during the last decades, and today exceeds 90% of all patients.<sup>1</sup> Today, practically all patients without concomitant severe malformations survive, and the very high mortality of very low birth weight patients and patients with severe cardiac malformation has decreased significantly. Many surviving patients, however, continue having functional problems, especially from their gastrointestinal tract and respiratory system after the initial postoperative period.<sup>2</sup> The overall impact of these problems on the long-term outcome of OA patients is not fully understood. Moreover, it is unclear what impact post-natal postoperative, usually relatively long hospitalization time, and repeated anesthetics for anastomotic dilations in many patients may have on later psychosocial well-being of the patients.

There are a limited number of reports concerning long-term outcome of patients with OA. The eventual quality of life appears to be good in most adults.<sup>3,4</sup> This assumption is based on some recent studies that have evaluated late sequelae of OA mainly by validated questionnaires. These questionnaires fail to detect subtle functional differences

and may ignore the fact that OA patients have had abnormal esophageal function from birth and may not experience functional aberrations as symptoms at all.

This review tries to summarize the outcome of OA beyond childhood. The focus will be in late esophageal and pulmonary function, late surgical complications, and complications such as persistent gastroesophageal reflux that may predispose to later malignancy. In addition to data from literature, preliminary results of institutional late follow-up of nearly 100 adult survivors following OA repair are used in this communication.

## Late clinical symptoms

Dysphagia is one of the most common symptoms that OA patients in all age groups suffer from. It is likely that dysphagia is associated with innate esophageal dysmotility that is associated with OA.<sup>5,6</sup> The role of surgical dissection and anastomosis in the development of dysphagia is unclear but may be significant. Most patients with dysphagia have no anastomotic strictures, although these have to be ruled out in patients with significant symptoms. Dysphagia is commonly associated with food impaction requiring endoscopy during childhood; the peak incidence is between 1 to 5 years.<sup>7</sup> Food impaction requiring surgical measures is

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much less common in adults despite persistence of dysphagia. The reported incidences of dysphagia are between 10% and 60%.<sup>8,9</sup> This variance is caused by definition of dysphagia. If mild symptoms, such as the need to drink fluids to facilitate swallowing of meals and occasional swallowing problems, are included, almost two-thirds of adult patients can be considered to have dysphagia.<sup>9,10</sup> In our institutional review, more than 80% of adults with OA had to use excessive liquids during eating or restrict their diet to foods that are less prone to get stuck in the esophagus.

Regurgitation and other symptoms suggesting gastroesophageal reflux (GER) are more or less as common as dysphagia. The reported incidences of reflux symptoms in preadolescent children and adults are between 27% and 75%.<sup>8,10-13</sup> However, reflux symptoms are also common in the general population. Some authors have found that the incidence of reflux symptoms in adults with repaired OA is only marginally more frequent than in the general population and the difference is not statistically different.<sup>14</sup> On the other hand, it is likely that patients with repaired OA have had reflux from birth and may not recognize milder symptoms as pathologic. Either way, it appears that subjective symptoms of reflux are often mild enough not to interfere with daily life.

Chest wall deformities occur in a significant number of patients with repaired OA.<sup>15</sup> Typical findings include scapular winging, anterior chest wall deformity, and scoliosis. All of these can be caused by surgical complication, scoliosis also by congenital vertebral anomalies. The incidence of scapular winging has been reported to be around 20%.<sup>16</sup> The incidence of scapular winging could be diminished by careful preservation of long thoracic nerve during thoracotomy. Thoracotomy and especially multiple thoracotomies are the leading cause for chest wall asymmetry in OA patients. Damage to the innervation of serratus anterior muscle may contribute to the chest wall deformity. The incidence of chest wall asymmetry has been reported to be as high as 25%.<sup>15,17,18</sup> In our adult series, the overall incidence of secondary deformities following neonatal right thoracotomy was high: over 75% of patients had shoulder height differences, one-fifth had limited motion of right upper extremity, and 14% had asymmetric thoracic wall. In addition to chest wall asymmetry, female patients may develop significant breast asymmetry that may require later plastic surgical repair.<sup>17,18</sup> Chest wall deformities are less common in patients who have undergone only one thoracotomy and no rib resection. At this time, it is still unclear whether chest wall deformities can be avoided if esophageal repair is performed by mini-invasive thoracoscopic approach.

Scoliosis may occur after thoracotomy for OA but is more common and more severe in patients with associated vertebral anomalies. The incidence of scoliosis in patients with no vertebral abnormalities has been reported to be between 14% and 47% in those with vertebral anomalies.<sup>19</sup>

In our own adult review, the overall incidence of scoliosis was around 50%. Moreover, vertebral anomalies were common, occurring most commonly in the cervical spine (over one-third of the patients had cervical vertebral anomalies). Scoliosis that is associated with thoracotomy is usually mild and does not cause symptoms. In patients with vertebral anomalies, scoliosis may become symptomatic, and some patients require spinal surgery to correct the defect and stop its progression.

## Late complications of esophageal anastomosis

Esophageal stricture is a common early sequel following repair of OA. Need for dilation of the strictured anastomosis has been reported in recent large series to occur in up to 80% of the patients.<sup>20-22</sup> Strictures are more common in patients with a long-gap atresia.<sup>2,23</sup> Anastomotic technique also plays a role; patients with one layer end-to-end anastomosis have less frequently strictures than those who have had end-to-side anastomosis or sleeve anastomosis.<sup>7</sup> Patients who have undergone staged repair have usually had long-gap atresia and, therefore, a high incidence of anastomotic strictures. Persistent strictures are usually associated with GER, and the management of GER is an essential part of treatment of recalcitrant esophageal strictures.<sup>23,24</sup> Late esophageal strictures are, on the other hand, very uncommon; esophageal dilatations are rarely required in older children and adults (Biller). Late strictures are invariably associated with severe GER.

Recurrent tracheoesophageal fistula occurs on average in 8% to 10% of OA patients. The typical age of presentation is 2 to 18 months after primary repair.<sup>2,7</sup> Recurrent fistula is more common in patients with initial end-to-side anastomosis.<sup>7</sup> Recurrent fistula is best diagnosed by tracheobronchoscopy or cineradiographic esophagography with the patient prone. Late presentation of recurrent fistula is possible. Typical symptoms of late-presenting fistula include recurrent pneumonias and pulmonary infections. Cough or choking associated with meals is less common symptoms in older patients. During the last 15 years, three adolescent and adult patients have been treated for late-presenting recurrent tracheoesophageal fistula in our institution. In two patients, the fistula was closed endoscopically by laser coagulation of the mucous lining of the fistula accompanied by fibrin glue injection; in one patient, operative closure of the fistula was required following unsuccessful attempts of endoscopic therapy.

## Esophageal motility

Various abnormalities of esophageal motor function have been repeatedly demonstrated among long-term survivors of OA.<sup>5,6,8,25</sup> Three separate studies of esophageal manometry (46 individuals total) 7 to 31 years after repair of OA

**Table 1** Incidence of gastroesophageal reflux symptoms and histologically proven esophagitis and Barrett's esophagus in long-term endoscopic follow-up studies

Reference	Age of patients (years)	GER symptoms (%)	Esophagitis (%)	Barrett (%)
Biller, et al <sup>10</sup>	22 to 31	9/12	4/12	1/12
Krug, et al <sup>11</sup>	18 to 26	13/39	9/17	2/17
Deurloo, et al <sup>12</sup>	28 to 45	15/40	19/21	1/21
Deurloo, et al <sup>4</sup>	10 to 26	23/86	30/40	0/40
Sistonen, et al <sup>31</sup>	25 to 57	17/50	10/50	1/50
Taylor, et al <sup>13</sup>	20 to 48	63/83	36/62	7/62
Combined	10 to 57	140/310 (45)	108/202 (53)	12/202 (6)

uniformly showed nearly completely uncoordinated esophageal peristaltic activity.<sup>6,8,25</sup> The contraction amplitudes of the entire esophagus were markedly lower when compared with healthy adults, and the distal esophageal contraction amplitudes remained markedly hypotonic (below 30 mm Hg) in 58% to 100% of patients.<sup>6,8,25</sup> Aperistalsis at the site of the anastomosis is also a constant finding.<sup>5,6</sup> Interestingly, despite defective motor activity of the esophageal body, the swallowing-induced relaxation of the lower esophageal sphincter (LES) appears to occur normally in majority of patients.<sup>6,8,25</sup> The nearly complete lack of propulsive esophageal contractions and decreased pressure of contractions means that, in individuals with repaired EA, the esophagus empties essentially by gravity. The above-mentioned findings convincingly explain the frequent occurrence of dysphagia after repair of OA.

Weak or missing contractions of the distal esophagus have been shown to associate with a severe impairment of esophageal acid clearing capacity and GER in children and adults with repaired OA.<sup>5,8,25</sup> How the weak esophageal contractile activity associate with development of esophagitis and epithelial metaplasia remains inadequately explored. In the setting of disorganized propulsive activity combined with weak contractile activity, ineffective esophageal acid clearance capacity is perfectly understandable following repair of OA. However, decreased distal esophageal contraction amplitude is not associated with GER in all patients, suggesting that other factors are also important in the development of GER after OA repair.<sup>6</sup> In addition to powerful coordinated esophageal peristaltic activity that clears the esophagus from refluxed gastric contents, appropriate function of the LES is essential to prevent GER. LES pressures were determined with stationary manometry in 24 OA patients at the age of 7 to 31 years.<sup>6,25</sup> Only 3 (13%) patients had hypotonic LES (<10 mm Hg). A short abdominal length of the LES was observed in 2 of 12 patients.<sup>6</sup> However, all 3 patients with a hypotonic LES also demonstrated pH-monitoring verified GER and biopsy-proven esophagitis or Barrett's esophagus.<sup>6,25</sup> Although long-term ambulatory manometric data on inappropriate LES relaxations (unrelated to swallowing) after OA repair are missing, they most likely play a significant role in the pathogenesis of GER, also among individuals with repaired OA. In patients with repaired OA, dysmotility of the upper gastrointestinal tract

is not confined to the esophagus. Delayed gastric emptying and altered gastric peristaltic activity occurred in 4 (36%) and 5 (45%) of 11 OA patients between 12 and 23 years of age, further predisposing to GER.<sup>26</sup>

In summary, based on the current knowledge, the uncoordinated esophageal peristaltic activity together with low amplitude of the distal esophageal contractions are the main long-term defects in esophageal motility following repair of OA. These motility defects result very likely from developmental neural defects affecting both proximal pouch and distal fistula.<sup>27,28</sup> Because most individuals demonstrate appropriate (stationary) LES function, permanently defective esophageal acid clearance capacity appears to be the major factor contributing to development of GER in adults with repaired OA. Further investigations and larger patient series are needed to clarify the relationships between different components of impaired esophageal motility, GER, esophagitis, and epithelial metaplasia. All the studies above included only patients amenable for primary anastomosis. Thus, defects of esophageal motility may prove to be even more severe in patients with repaired EA without fistula.

### Gastroesophageal reflux

Long-standing GER is associated with considerable morbidity, resulting in chronic esophageal inflammation and contributing to recurrent pulmonary infections and abnormalities of pulmonary function in a significant number of patients.<sup>2</sup> Moreover, GER is associated with development of columnar metaplasia that may undergo dysplastic changes and give rise to esophageal adenocarcinoma through a metaplasia–dysplasia–carcinoma sequence.<sup>29,30</sup>

As outlined in Table 1, classic GER symptoms, including heartburn, retrosternal pain, or regurgitation, are reported by 27% to 75% of older children and adults with repaired OA.<sup>10-13,31</sup> The 45% mean incidence of GER symptoms in these six studies may represent an over estimation of the true incidence at least among patients who underwent primary esophageal anastomosis. In all six studies, a group of volunteers of the initial study population was interviewed favoring selection bias toward symptomatic individuals. It is also difficult to reliably differentiate dysphagia derived symptoms from those caused by GER while a poor correlation has been described between subjective symptoms and

actual presence of GER and its complications following OA repair.<sup>32</sup> Therefore, symptoms alone are not sufficient for reliable detection of GER among patients with repaired OA.

Routine screening for GER using Ph-monitoring 3 months after esophageal reconstruction in 128 infants identified 53 patients (41%) with GER.<sup>33</sup> The incidence figures of GER as defined by Ph-monitoring and/or histological esophagitis remain at the level of 45% to 50% up to 10 years after primary repair of OA.<sup>34</sup> Several investigators have conducted esophageal Ph-monitoring to a group of long-term survivors of OA extending to early adulthood.<sup>5,8,25,35</sup> The combined mean GER rate of these studies, including a total of 84 patients, was 40% and it varied between 17% and 67%. Differences in the patient selection criteria and small number of patients studied most likely contributed to the relatively large variation of the results. Nevertheless, the rate of GER as detected by pathologic Ph-monitoring is high among infants and adults with repaired OA, suggesting that GER develops early and continues to adulthood. This is further supported by the fact that the incidence of GER symptoms in adult populations with repaired OA are at the same level with the GER rate obtained from studies using pH-monitoring in different age groups.

Surgical antireflux procedures have been commonly used to control GER unresponsive to medical treatment among patients with OA.<sup>36-38</sup> Although different types of antireflux procedures effectively control GER early after operation, their impact on long-term outcome of OA regarding GER and its complications is questionable due to high recurrence rates irrespective of the antireflux procedure used.<sup>36-38</sup>

## Esophagitis

An attempt to define the prevalence and natural history of esophagitis among patients with repaired OA is important concerning long-term outcomes of OA. Although it remains unclear whether esophagitis as itself is a preneoplastic condition, it is strongly associated with GER, which is the causal factor of columnar metaplasia in the esophagus.<sup>29</sup>

Table 1 displays rates of biopsy-proven esophagitis in long-term follow-up studies among patients with repaired EA who underwent histological examination of the esophagus.<sup>10-13,31</sup> The mean incidence of esophagitis in these 6 reports was 53%, and the majority of patients were between 20 and 40 years old. In 3 of the 6 studies, less than half of the recruited patients volunteered to histological examination of the esophagus, suggesting that proportionally more symptomatic patients were examined. Thus, the true incidence of esophagitis among adults with repaired OA may be somewhat lower. Our preliminary findings among nearly 100 adult OA patients suggest that the incidence of esophagitis is around 25%. Taken together, there is clear evidence that the incidence of esophagitis among adults with repaired esophageal atresia is markedly more common than in the general population.<sup>39</sup>

The practice in our institution has been to perform routine endoscopic follow-up on all children with OA. The first

follow-up endoscopy together with Ph-metry is performed at the of 1 year, and follow-up endoscopies are continued to puberty. Evaluation of the histological follow-up data revealed several important aspects concerning the natural history of the GER in children with repaired OA. Mild esophagitis characterized by basal membrane hyperplasia occurred in 30 of 79 (38%) children with mean endoscopic follow-up of 10 years.<sup>40</sup> In only 4 of 33 children with mild esophagitis or normal histology in their first biopsy sample did esophageal histology progress to more severe esophagitis characterized by inflammatory cell infiltrate or erosions or to metaplasia. An additional 13% of the children had moderate to severe esophagitis that developed in most by the age of 3 to 6 years. Moreover, after the age of 5 years, no new cases of histological esophagitis or pathological Ph-monitoring were detected.<sup>34</sup> Most children with pathological Ph-monitoring developed complicated GER as defined by histological esophagitis or the need for antireflux procedure after median follow-up of 5 years.<sup>41</sup> Finally, resolving of OA-associated GER or esophagitis was exceptional.<sup>34,40,41</sup> Longitudinal follow-up studies extending to adulthood are needed to confirm these findings.

As discussed above, the present data suggest that development of GER and esophagitis are an early and possibly permanent phenomena after repair of OA. Taken into account the permanent nature of the esophageal motility defects associated with OA and their crucial role in the pathogenesis of GER, this would not be unexpected. However, it should be emphasized that presence of GER is not necessarily associated with esophagitis.<sup>8</sup>

## Epithelial metaplasia and cancer

Columnar metaplasia in the esophagus is a preneoplastic lesion, which arises as a result of GER.<sup>29</sup> Columnar esophageal epithelium is a pathological condition characterized by a phenotypic change from stratified squamous to a columnar epithelium.<sup>42</sup> Adenocarcinoma of the esophagus develops in the columnar lined esophagus. It is still unclear whether the presence of intestinal metaplasia (Barrett) is needed for preneoplastic potential.<sup>29</sup> The high incidence of GER among individuals with repaired OA has raised a concern about increased risk of cancer.

Table 1 displays frequency of histologically verified Barrett's esophagus among patients with repaired OA. In these studies, Barrett's esophagus (intestinal metaplasia) was defined as columnar epithelium with goblet cells. Of the total 202 histologically examined patients, 12 (6%) had intestinal metaplasia. This figure is about 4-fold higher than the incidence of Barrett (1.6%) in normal population.<sup>43</sup> In light of increased incidence of symptomatic GER and esophagitis among adults with repaired OA, the finding of increased incidence of Barrett's esophagus is perfectly understandable. The risk of developing adenocarcinoma in patients with Barrett's esophagus has been estimated to be 0.5% per year.<sup>38</sup>

**Table 2** Reported cases of esophageal cancer after repair of esophageal atresia

Reference	Age (years)	Histology
LaQuaglia, et al <sup>44</sup>	44	Squamous cell carcinoma
Adzick, et al <sup>45</sup>	20	Adenocarcinoma
Deurloo, et al <sup>46</sup>	38	Squamous cell carcinoma
Pultrum, et al <sup>47</sup>	22	Adenocarcinoma
Alfrao, et al <sup>48</sup>	46	Adenocarcinoma
Taylor, et al <sup>13</sup>	44	Squamous cell carcinoma

In addition to the increased incidence of intestinal metaplasia, there appears to be high incidence of gastric metaplasia after OA repair. Gastric metaplasia may be present already several years after esophageal reconstruction.<sup>32</sup> During mean endoscopic follow-up of 10 years, esophageal gastric metaplasia was found in 13 of 79 (16%) children.<sup>40</sup> Gastric metaplasia is also commonly found in adults with repaired EA.<sup>31</sup> Clinical significance of gastric metaplasia remains unclear.<sup>29</sup> However, our preliminary findings suggest that, among adults with repaired EA, the most severe defects of esophageal motility are found in those with gastric or intestinal metaplasia.

To date, 6 cases of esophageal cancer have been reported.<sup>13,44-48</sup> Age of the patients and histology of cancer are shown in Table 2. All 3 patients with adenocarcinoma had history of significant GER.<sup>45,47,48</sup> We recently published a population-based, long-term follow-up for cancer among individuals with repaired EA.<sup>49</sup> With this complete follow-up of 502 patients extending to over 50 years, we found no cases of esophageal cancer; which means that the risk for esophageal cancer after repair of EA is less than 500-fold that of the normal population. Further follow-up studies in patients with EA are warranted to elucidate the risk factors for development of intestinal metaplasia and esophageal cancer as well as the need for endoscopic surveillance.

### Pulmonary function

Persistent pulmonary dysfunction after repair of OA is common in both children and adults. A significant percentage of adult patients have persisting respiratory symptoms.<sup>9</sup> Typical symptoms include wheezing, recurrent episodes of bronchitis, daily cough, and episodes of pneumonia. The symptomatic adults have also been more likely to have respiratory problems in childhood. Symptoms of GER do not appear to be associated with persisting respiratory symptoms.<sup>9</sup> This suggests that adult respiratory symptoms are secondary to permanent airway and lung damage from repeated and early childhood incidents.

Pulmonary function testing has shown variable results. Although a number of publications have shown normal pulmonary function values, low values are also common.<sup>2,9,10</sup> Recognized patterns of ventilatory abnormalities have been identified in a proportion adult patients with

repaired OA. Restrictive ventilatory defects have been found in 20% to 49% of the patients, obstructive ventilation defect in 12% to 54%, and normal lung function in 23% to 48% of patients.<sup>9,50</sup> Overall, most of the reported pulmonary function defects have been mild, and most patients have reported normal exercise tolerance with no or little limitations in normal life.

Tracheomalacia, a typical association of OA with proximal fistula, is clinically significant in less than 20% of the patients.<sup>51</sup> Tracheomalacia tends to improve with age. The typical manifestation of tracheomalacia is barking and brassy cough, which occurs nearly universally in OA patients. The typical coughing pattern may persist through adulthood.<sup>9</sup> Wheezing is another respiratory symptom that is associated with tracheomalacia. Also, occasional bouts of wheezing commonly occur in adults. The high incidence of cough and wheezing in adults suggests that some degree of tracheomalacia may persist. However, there are no reports on tracheobronchial endoscopy in adults patients with OA.

### Long-term outcome of esophageal replacement

There are a wide variety of esophageal replacement techniques that have been used to bridge long-gap defects or repair failed primary anastomosis. Typical techniques include colonic interposition, gastric transposition, gastric tube interposition, and, recently, pedicled or free jejunal interposition. All these techniques have their proponents, but prospective controlled studies regarding long-term function and outcome are completely lacking.

Long-term functional outcome following colon interposition in OA patients appear acceptable in most cases. More than half of the patients are asymptomatic as adults.<sup>52-54</sup> Typical late symptoms include symptomatic reflux to colonic graft, colonic redundancy causing swallowing problems, and food impactions. Redundancy causing dysphagia, chest pain, and pneumonia is a typical complication of colonic interposition that may develop slowly. It may require redo-surgery.<sup>55</sup> It is unclear whether there is a risk of malignant degeneration in the colonic mucosa that is exposed to gastric acid. In our institutional series of colon interpositions, we have found gastric metaplasia and chromosomal aneuploidy in some patients after a follow-up of more than 20 years.

Gastric transposition is not a new operation for esophageal replacement in OA patients but has gained increasing popularity since the 1980s.<sup>56</sup> Gastric transposition is a relatively simple operation and is associated with fewer severe complications than colonic replacement.<sup>57,58</sup> In the long term, overall function has been considered good or excellent in 90% of the patients in terms of absence of swallowing difficulties or other gastrointestinal symptoms. Most patients, however, need to eat frequently small meals.<sup>56,58</sup> The

long-term quality of life of OA patients having undergone gastric transposition appears unimpaired.<sup>59</sup>

Gastric tube interposition is an old procedure for esophageal replacement in OA patients but has never gained similar popularity as gastric pull-up and colon replacement. It has still been used by many pediatric surgeons with similar long-term functional results as in those with colonic interposition or gastric pull-up.<sup>54,60</sup> Gastric tube is an acid-secreting organ; therefore, peptic ulcerations may occur. Ulcer perforations to adjacent organs have been reported.<sup>61</sup>

Jejunal interposition either by pedicled or free grafts has been used to repair a long-gap OA by a few pediatric surgeons with significant success.<sup>62-64</sup> There appears to be significant morbidity associated with jejunal grafts, especially when free jejunal grafts are used.<sup>62,65</sup> The potential advantage of the jejunal grafts is their ability to retain peristaltic activity.

## Long-term quality of life

Until recently there have been practically no reports on the quality of life of adult patients with repaired OA. A common conception has been that quality of life of OA patients is comparable with that of healthy adults despite significant long-term sequels in esophageal and respiratory function, and frequently occurring associated malformations. Overall, the long-term quality of life of adult OA patients has been found to be good.<sup>3,4,66</sup> Both generic and disease-specific quality of life have been found to be similar as in the general population in the great majority of patients. The concomitant congenital anomalies do not appear to influence generic quality of life of OA patients.<sup>4</sup> In one study,<sup>66</sup> patients with esophageal replacement appear to do worse in terms of gastrointestinal and respiratory symptoms; another<sup>3</sup> did not show any differences between patients with primary repair and those with esophageal replacement. Despite good overall quality of life, a significant proportion of patients still experience negative consequences due to their congenital anomaly.<sup>3,4</sup> Symptoms caused by disturbed esophageal motility and respiratory tract function are the most common to impair quality of life in OA patients.

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