Clinical Study of Ursodeoxycholic Acid in Barrett’s Esophagus Patients

Bhaskar Banerjee1, Nicholas J. Shaheen2, Jessica A. Martinez3,4, Chiu-Hsieh Hsu3, Eugene Trowers1, Blake A. Gibson1, Gary Della’Zanna5, Ellen Richmond5, and H-H. Sherry Chow3

Abstract

Prior research strongly implicates gastric acid and bile acids, two major components of the gastroesophageal refluxate, in the development of Barrett’s esophagus and its pathogenesis. Ursodeoxycholic acid (UDCA), a hydrophilic bile acid, has been shown to protect esophageal cells against oxidative stress induced by cytotoxic bile acids. We conducted a pilot clinical study to evaluate the clinical activity of UDCA in patients with Barrett’s esophagus. Twenty-nine patients with Barrett’s esophagus received UDCA treatment at a daily dose of 13 to 15 mg/kg/day for 6 months. The clinical activity of UDCA was assessed by evaluating changes in gastric bile acid composition and markers of oxidative DNA damage (8-hydroxydeoxyguanosine), cell proliferation (Ki67), and apoptosis (cleaved caspase-3) in Barrett’s esophagus epithelium. The bile acid concentrations in gastric fluid were measured by liquid chromatography/mass spectrometry. At baseline, UDCA (sum of unchanged and glycine/taurine conjugates) accounted for 18.2% of total gastric bile acids. After UDCA intervention, UDCA increased significantly to account for 93.4% of total gastric bile acids (P < 0.0001). The expression of markers of oxidative DNA damage, cell proliferation, and apoptosis was assessed in the Barrett’s esophagus biopsies by IHC. The selected tissue biomarkers were unchanged after 6 months of UDCA intervention. We conclude that high-dose UDCA supplementation for 6 months resulted in favorable changes in gastric bile acid composition but did not modulate selected markers of oxidative DNA damage, cell proliferation, and apoptosis in the Barrett’s esophagus epithelium. Cancer Prev Res; 9(7); 528–33. © 2016 AACR.

See related article by Brian J. Reid, p. 512

Introduction

Barrett’s esophagus is a condition where normal squamous epithelium is replaced by metaplastic intestinal-like columnar epithelium containing goblet cells (intestinal metaplasia). This lesion is linked to the development of esophageal adenocarcinoma, a cancer with poor prognosis, and a median survival of less than 1 year (1, 2).

Animal and human studies strongly implicate gastric acid and bile acids, two major components of the gastroesophageal refluxate, in the development of Barrett’s esophagus and its pathogenesis (3–5). It has been shown that patients with Barrett’s esophagus have higher acid and bile acid exposure in their esophagus than patients with erosive esophagitis or controls (4, 5). Hydrophobic bile acids, such as deoxycholic acid (DCA), are thought to play a major role in the development of gastrointestinal malignancies (6). In humans, the incidence of cancers of the laryngopharyngeal tract, esophagus, stomach, pancreas, small intestine (near the Ampulla of Vater), and colon are all positively associated with intestinal levels of hydrophobic bile acids (6). Preclinical studies demonstrated that a combination of a cytotoxic bile acid cocktail and low pH induces oxidative stress and oxidative DNA damage in cultured esophageal cells and in Barrett’s esophagus biopsies ex vivo (7, 8). Similarly, Huo and colleagues showed that DCA induces the production of reactive oxygen species in Barrett’s cells, which causes DNA damage and induces activation of the NFκB pathway to prevent apoptosis in Barrett’s cells (9).

Ursodeoxycholic acid (UDCA), the most hydrophilic of the bile acids, was shown to protect against bile acid and low pH–induced oxidative stress and oxidative DNA damage and modulate expression of enzymes associated with protection against oxidative stress in cultured esophageal cells (10). Furthermore, in a rat model of Barrett’s esophagus, treatment with a combination of UDCA and aspirin resulted in fewer esophageal adenocarcinomas (11). Peng and colleagues (12) have recently shown that UDCA treatment (10 mg/kg) for 8 weeks increased the levels of two antioxidant enzymes (glutathione peroxidase 1 and catalase) in esophageal biopsies collected from patients with Barrett’s esophagus. The treatment also prevented DNA damage and NFκB activation induced by esophageal DCA perfusion in patients with Barrett’s esophagus. However, it is unknown whether UDCA treatment will decrease the extent of DNA damage under physiologic condition (i.e., without esophageal DCA perfusion).

UDCA is an attractive candidate for chemoprevention because of its long-term safety record. It has been used safely at the dose of 8 to 10 mg/kg/day in patients with gallstone disease in the United States (13). Studies have demonstrated that UDCA has not been associated with an increased risk of gallstone disease in patients on long-term therapy (14, 15) or with an increased risk of hepatocellular carcinoma in patients with primary or secondary bile duct obstruction (16). UDCA is metabolized in the liver by extrusion into the bile and conjugation with glycine and taurine, and then secreted into the intestine, where it is eventually reabsorbed in the colon and regurgitated into the stomach and duodenum. UDCA is associated with a reduction in the risk of colorectal adenomas and carcinomas in patients with familial adenomatous polyposis (17). Although UDCA has been associated with a decrease in the risk of colorectal neoplasms, its role in the prevention of malignancies of other organs remains to be further studied.
States since 1987 and later in patients with primary biliary cirrhosis (PBC) at the dose of 13 to 15 mg/kg/day. In the clinical trial setting, it has demonstrated potential for risk reduction for colorectal cancer with a good safety profile. UDCA treatment at a dose of 8 to 10 mg/kg/day for a mean of 32 months was associated with a statistically significant 39% reduction in recurrence of colorectal adenomas with high-grade dysplasia (13). A study of 52 patients with ulcerative colitis and primary sclerosing cholangitis showed that treatment with UDCA (at a dose of 13 to 15 mg/kg/day for a median duration of 42 months) significantly reduced the risk of colorectal dysplasia or cancer compared with placebo (14).

We conducted a pilot clinical study to assess the clinical activity of UDCA in patients with Barrett’s esophagus. The central hypothesis to be tested in the clinical study is that activity of UDCA in patients with Barrett’s esophagus. The placebo (14).

Study population

We recruited healthy women and men ≥18 years of age with a diagnosis of Barrett’s esophagus with histologically confirmed intestinal metaplasia anywhere in the tubular esophagus either with ≥2 cm of involvement or with a minimum of circumferential Barrett’s esophagus length of 1 cm. Participants were required to have normal liver and renal function. Study exclusion criteria included Barrett’s esophagus with high-grade dysplasia or carcinoma, medical conditions which would make completing endoscopies or completing the trial difficult, use of other investigational agents within 1 month, use of NSAIDs for more than 5 days a month within 1 month [except low dose aspirin (81 mg every day)], history of allergic reactions attributed to UDCA, uncontrolled acute and chronic diseases, pregnant and breast feeding women, major upper gastrointestinal surgery within 6 months, erosive esophagitis at baseline endoscopy, chemotherapy, radiotherapy, or cancer-related hormonal or immunotherapy within the last 18 months, current or planned use of anticoagulant drugs, or use of cyclosporine. Written informed consent was obtained from all participants.

Study procedure

During the initial visit, consented study subjects underwent medical and surgical history evaluation and had a blood sample collected for complete blood count (CBC) and comprehensive metabolic panel (CMP). Following the initial eligibility evaluation, subjects underwent upper endoscopy with biopsies. Prior to any mucosal irritation, gastric fluid was aspirated through the endoscope and collected. The circumferential and maximum extents of metaplasia were determined using the Prague C&M criteria (15). Systematic biopsies, one in each of four quadrants every 2 cm in the appropriate areas of the Barrett’s esophagus, were taken. These biopsies were processed for histopathology based on the institutional standards. One additional Barrett’s esophagus biopsy was collected close to the distal end of the Barrett’s esophagus segment and flash frozen.

Eligible subjects then initiated the 6 months of UDCA treatment at 13 to 15 mg/kg per day. Subjects returned to the clinic after 3 months of agent intervention to return unused pills for a pill count, receive a new supply of agents, have a blood sample collected for CBC/diff and CMP, and review the side effects with study staff. At the end of the 6-month intervention, subjects returned to the clinic to return unused pills, have a blood samples collected for CBC/diff and CMP, review the side effects with study staff, and undergo the postintervention endoscopy to obtain gastric fluid and biopsies of the Barrett’s esophagus as described for the baseline endoscopy.

Safety of UDCA intervention was assessed by reported adverse events and clinical labs. Adverse events were graded using NCI Common Terminology Criteria for Adverse Events version 3.0.

Analysis of bile acid concentrations in gastric fluid

Bile acid concentrations in the gastric fluid were analyzed by high performance liquid chromatography (HPLC) tandem mass spectrometry (MS). Briefly, an aliquot of gastric fluid was mixed with the internal standards (deoxycholic acid-d4 and glycocholic acid-d4) and then alkalized with 1 N NaOH. The mixture was extracted with hexane. The aqueous phase was collected and acidified with 5 N HCl and extracted with ethyl acetate. The organic layer was dried and reconstituted with 10 mmol/L ammonium acetate/methanol (50/50) and injected onto the LC/MS system. The chromatographic separation was achieved using a gradient system of methanol and 10 mmol/L ammonium acetate on an Ultrasphere XI column. Mass spectrometry was run in negative ion mode using electrospray ionization. Detection of five bile acids [UDCA, DCA, cholic acid (CA), chenodeoxycholic acid (CDCA), and lithodeoxycholic acid (LCA)] and their respective glycine and taurine conjugates was achieved by multiple reaction monitoring.

IHC for tissue biomarkers

Immunohistochemical assays were used to assess markers of cell proliferation (Ki67), apoptosis (CC3), and oxidative DNA damage (8OHdG) in Barrett’s esophagus epithelium tissue sections. The Ki67 and CC3 IHC was performed on a Discovery XT Automated Immunostainer (VMSI; Ventana Medical Systems)...
using VMSI-validated reagents, including deparaffinization, antigen retrieval with a borate-EDTA buffer, primary antibody staining, detection, and amplification, and hematoxylin counterstaining. A biotin-free dianinobenzidine (DAB) detection system was used for CC3 and a biotinylated-streptavidin-horseradish peroxidase and DAB system was used for Ki67. For Ki67, mouse mAb (clone: MIB-1; Dako) was diluted 1:100. Human tonsil carcinoma was used as a positive control. For CC3, anti-CC3 rabbit polyclonal antibody (Cell Signaling Technology #9661L) was diluted 1:8,000. Human tonsil carcinoma was used as a positive control. The 8OHdG IHC was performed as described previously (8) with minor modifications. Briefly, the slides were baked at 65 °C for 1 hour, followed by deparaffinization with xylene, isopropanol, and water. Slides were then treated with 10% H2O2, 4 N HCl, 0.1 mol/L borax, and 5% horse serum sequentially prior to incubating with the mouse mAb for 8OHdG [QED Bioscience, #12501 (clone 15A31), diluted 1:1,000]. Slides were then incubated with secondary biotinylated rabbit anti-mouse IgG antibody, Vectastain Elite ABC reagent, and DAB prior to counterstaining with hematoxylin. Human esophageal carcinoma and tonsil carcinoma were used as positive controls. On the IHC slides, longitudinally sectioned crypts opening to the lumen were selected for scoring. The percent of nuclei stained positive for Ki67, CC3, and 8OHdG in the selected regions was quantified by Aperio Spectrum software and confirmed by a trained pathologist. Slides with fewer than 500 total nuclei in the selected regions were excluded for the statistical analysis. The marker expression from different segments was averaged for participants with tissue sections from multiple esophageal segments.

Statistical analysis

Descriptive statistics were calculated to summarize the demographic characteristics and disease characteristics at baseline and postintervention. The primary endpoint was the effect of UDCA intervention on 8OHdG levels in Barrett’s esophagus epithelium. Signed rank test was performed to assess pre- to postintervention change in percentage of nuclei stained strongly and moderately for 8OHdG. The secondary endpoints were measurements of changes in gastric bile acid composition and Ki67 and CC3 expression. Signed rank test was performed to assess the change for each of the secondary endpoints. Spearman correlation coefficients were calculated to assess the relationship between changes in gastric bile acid composition and changes in 8OHdG, Ki67, and CC3, respectively.

Results

The study opened to accrual in April 2010 and closed to accrual in November 2013. Eighty potentially eligible participants were consented, 39 from UA, 26 from UNC, and 15 from SAVAHCS. Forty-four consented individuals did not meet all the eligibility criteria. Thirty-six met all eligibility criteria to initiate agent intervention; of these 29 completed agent intervention, 1 was taken off agent intervention due to grade 2 diarrhea, an adverse event (AE) probably related to the study agent, that did not resolve within the protocol-specified timeframe, 3 were taken off agent intervention due to AEs deemed unlikely to be related or not related to the study agent, and 3 withdrew consent. UDCA treatment was well tolerated in our study cohort. Twelve subjects experienced related grade 1 or grade 2 AEs, including diarrhea, constipation, bloating, flatulence, nausea, vomiting, burping, rash, joint pain, and stomachache.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Postintervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.0 (1–11)</td>
<td>3.8 (1–12)</td>
</tr>
<tr>
<td>Postintervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of circumferential involvement, cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3 cm/ ≥ 3 cm</td>
<td>15/6</td>
<td>16/15</td>
</tr>
<tr>
<td>Pathology grade, ND/LGD/HGD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>20/9/0</td>
<td>24/4/1</td>
</tr>
<tr>
<td>Postintervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in pathology grade, improved/no change/worsened</td>
<td>5/22/2</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Demographic and disease characteristics of participants who completed agent intervention (n = 29)

The demographic and disease characteristics of participants who completed the intervention are summarized in Table 1. The average age was 62.5 ± 9.8 years. The average BMI from these participants was 28.3 ± 5.1 kg/m². Eighty percent were male. The majority were White (97%) and 14% were Hispanic. Current smokers accounted for 10% of these participants. Fourteen percent had heavy or moderate alcohol intake. Twenty-eight of the 29 participants who completed agent intervention were treated concomitantly with proton pump inhibitor (PPI). Twenty-three of the 28 participants who used PPI had been treated with PPI for more than 6 months prior to initiating the UDCA intervention. Twelve of the 29 participants who completed agent intervention were taking daily 81 mg aspirin.

For disease characteristics of participants who completed the intervention, the median length of circumferential involvement was 4.0 cm at baseline, 13 participants with length <3 cm, and 16 participants with length ≥3 cm. The median circumferential involvement was 3.8 cm postintervention, 16 participants with length <3 cm, 13 participants with length ≥3 cm. The circumferential length decreased in 24% of participants, was unchanged in 62% of participants, and increased in 14% of participants. Biopsies from 69% of participants were not dysplastic at baseline whereas 31% of participants had at least one biopsy with low-grade dysplasia. Postintervention, biopsies from 83% participants were not dysplastic and at least one biopsy from 14% and 3% of participants had low-grade and high-grade dysplasia, respectively. The pathology grade improved in 17% of participants but worsened in 7% of participants.

There were 28 participants with gastric fluid collected at both the baseline and end of study endoscopies for bile acid analysis. Because of the large variation in gastric bile acid concentrations, the individual bile acids were expressed as the percent of total bile acid.
acidity in the gastric fluid. The sum of each individual bile acid and its respective glycine and taurine conjugates is summarized in Table 2. At baseline, UDCA, CDCA, DCA, CA, LCA, and their respective glycine and taurine conjugates accounted for 18.2%, 11.0%, 38.9%, 16.9%, and 0.66% of total gastric bile acids. Postintervention, UDCA and its glycine and taurine conjugates increased significantly to account for 93.4% of total gastric bile acids, whereas the composition of the other bile acids decreased significantly. Glycine conjugates constituted the majority of each of the five bile acid groups in the gastric fluid. We performed exploratory stratified analysis on the gastric bile acid composition by PPI use (<6 months vs. >6 months), aspirin use (yes vs. no), smoking status (never smokers vs. current or former smokers), alcohol intake (no current intake vs. any current intake), baseline Barrett’s esophagus length (<3 cm vs. ≥3 cm), change in Barrett’s esophagus length (shortened vs. no change or increased), baseline pathology grade (ND vs. LGD), and change in pathology grade (improved vs. no change or worsened). There was no difference in the baseline gastric bile acid composition in most of the stratified analysis (data not shown) except that baseline DCA and its glycine and taurine conjugates accounted for a higher fraction of total gastric bile acid in aspirin users than that in nonusers [median (interquartile range): 45.0 (29.5)% (n = 12) vs. 15.7 (37.4)% (n = 16), respectively, P = 0.04]. Postintervention, the DCA and its glycine and taurine conjugates composition was similar between the aspirin users and nonusers [median (interquartile range): 2.87 (2.75)% vs. 5.88 (15.4)% respectively, P = 0.12]. The stratified analysis showed that the pre-to postintervention change in bile acid composition was different between the aspirin users and nonusers [median change (interquartile range) of UDCA/conjugates: −75.7 (17.9) vs. +54.5 (57.1), P = 0.04; DCA/conjugates: −43.6 (44.6) vs. −8.43 (25.6), P < 0.05; and CA/conjugates: −15.7 (9.68) vs. −4.22 (12.1), P = 0.02]. LCA and its glycine and taurine conjugates accounted for a small fraction of the bile acid composition. Stratified analysis showed that those who did not currently consume alcohol had a larger fraction of LCA/conjugates than those who consumed alcohol [median (interquartile range): 0.52 (1.01)% (n = 7) vs. 0.12 (0.25)% (n = 20), respectively, P = 0.03]. Nevertheless, the stratified analysis will need to be interpreted with caution due to the small sample size and multiple comparisons.

The tissue biomarker data are summarized in Table 3. Adequate baseline and postintervention data on 8OHdG, Ki67, and CC3 expression were obtained from 25, 29, and 27 participants, respectively. Because of the concern of nonspecific 8OHdG staining, the expression of these markers did not change following 6 months of UDCA intervention. The tissue biomarker data are summarized in Table 3. Adequate baseline and postintervention data on 8OHdG, Ki67, and CC3 expression were obtained from 25, 29, and 27 participants, respectively. Because of the concern of nonspecific 8OHdG staining, the expression of these markers did not change following 6 months of UDCA intervention. We performed similar exploratory stratified analysis on the tissue biomarkers. There was no difference in the baseline and postintervention tissue biomarker expression in the stratified analysis (data not shown).

Table 4 summarizes the correlation between changes in gastric bile acid composition and changes in tissue biomarker expression. The changes in tissue biomarker expression were not correlated with the changes in gastric bile acid composition.

Discussion

Our single-arm pilot clinical study was designed to evaluate the clinical activity of UDCA in patients with Barrett’s esophagus. We evaluated the clinical activity of UDCA by assessing changes in gastric bile acid composition and markers of oxidative DNA damage, cell proliferation, and apoptosis in the Barrett’s esophagus epithelium because prior research suggested that these markers could be modulated with UDCA intervention (10, 12). The study showed that supplementation with UDCA at a daily dose of 13 to 15 mg/kg/day for 6 months in patients with Barrett’s esophagus increased proportions of cytoprotective bile acids and decreased proportions of cytotoxic bile acids in the gastric fluid. Despite the favorable change in the bile acid composition, we did not observe a change in tissue biomarker expression.

Table 3. Tissue biomarker expression

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Baseline (% positive)</th>
<th>Postintervention (% positive)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>8OHdG (n = 25)</td>
<td>39.9 (39.0)</td>
<td>34.9 (30.7)</td>
<td>0.52</td>
</tr>
<tr>
<td>Ki67 (n = 29)</td>
<td>35.9 (14.0)</td>
<td>36.9 (18.5)</td>
<td>0.44</td>
</tr>
<tr>
<td>CC3 (n = 27)</td>
<td>1.62 (2.86)</td>
<td>1.00 (2.11)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Abbreviations: 8OHdG, 8-hydroxydeoxyguanosine; CC3, cleaved caspase 3.

Our single-arm pilot clinical study was designed to evaluate the clinical activity of UDCA in patients with Barrett’s esophagus. We evaluated the clinical activity of UDCA by assessing changes in gastric bile acid composition and markers of oxidative DNA damage, cell proliferation, and apoptosis in the Barrett’s esophagus epithelium because prior research suggested that these markers could be modulated with UDCA intervention (10, 12). The study showed that supplementation with UDCA at a daily dose of 13 to 15 mg/kg/day for 6 months in patients with Barrett’s esophagus increased proportions of cytoprotective bile acids and decreased proportions of cytotoxic bile acids in the gastric fluid. Despite the favorable change in the bile acid composition, we did not observe a change in tissue biomarker expression.
not observe any significant changes in markers of oxidative DNA damage, cell proliferation, and apoptosis in the Barrett’s esophagus epithelium.

In our study, all but one participant were treated with PPI for symptom control with most treated for more than 6 months prior to initiation of the UDCA intervention. The PPI treatment may have contributed to the lack of UDCA effects on tissue markers of oxidative DNA damage, cell proliferation, and apoptosis. In a multicenter prospective cohort study of 540 patients with Barrett’s esophagus, PPI use was associated with a reduced risk of neoplastic progression (16). High-dose PPI treatment in patients with Barrett’s esophagus that results in effective esophageal acid suppression has been shown to decrease the markers of cell proliferation and inflammation and increase apoptosis (17). PPI treatment reduces the acidity and the volume of the refluxate, which may diminish the exposure of esophagus to cytotoxic bile acids (18). Therefore, modulation of bile acid composition with the UDCA intervention may not result in any further improvement in histology and the selected tissue biomarkers. Furthermore, bile acids that are cytotoxic to the mucosa in an acidic environment may lose their damaging activity at neutral pH from PPI treatment. Boxikas and colleagues (19) evaluated the effect of 6 months of UDCA (600 mg twice a day) intervention in nine Barrett’s esophagus patients treated with high dose PPI. Similarly, UDCA intervention did not lead to significant changes in histology and markers of proliferation, differentiation, and inflammation in this study with limited sample size.

An alternative explanation for the lack of change in the selected tissue biomarkers is that cytotoxic bile acid reflux may not be a causative factor in the pathogenesis of progression in Barrett’s esophagus. It was recently demonstrated in an animal model that cytotoxic bile acids and not gastric acid were pathogenic in the development of Barrett’s-like metaplasia (20); however, the progression to dysplasia may be caused by other, unknown factors. The development of Barrett’s esophagus results in a more durable epithelium that may be more resistant to insult by refluxate. Thus, UDCA treatment may be more effective to prevent the development of Barrett’s esophagus than to prevent the pathogenesis of Barrett’s esophagus.

It is important to note that the null findings in the tissue biomarkers from this single-arm pilot study will need to be interpreted with caution as the study is limited by the lack of a control arm and the small sample size. The study selected an intervention duration of 6 months to coincide with the recommended interval for surveillance endoscopy for patients with Barrett’s esophagus with low-grade dysplasia at the time of the study protocol development. Based on prior research (10, 12), it was anticipated that 6 months of UDCA intervention would be sufficient to modulate the selected tissue biomarkers. It is not known whether the selected tissue biomarkers would be modulated with a longer intervention duration.

The tissue biomarkers used in this study have been correlated with the histologic grade of Barrett’s esophagus (21–24) and used as intermediate biomarkers to assess preventive interventions in patients with Barrett’s esophagus (17, 19, 25, 26). However, these markers have not been proven in large, well-controlled study to predict the risk of development of high-grade dysplasia or adenocarcinoma. Multiple studies have shown that esophageal adenocarcinomas have extensive chromosomal instability, high levels of chromosome copy-number alterations, and frequent catastrophic chromosomal events (27–30). Li and colleagues showed that esophageal adenocarcinoma risk predicted by somatic chromosome alterations outperformed risk predicted by TP53 mutation, flow cytometric DNA content, and histopathologic diagnosis of dysplasia (31). This line of research may offer unique opportunities to identify exposures that lead to the mutation signatures in esophageal adenocarcinoma to better develop preventive strategies to target mutagens leading to the genomic alterations.

We conclude that high-dose supplementation with UDCA for 6 months in patients with Barrett’s esophagus increased proportions of cytoprotective bile acids and decreased proportions of cytotoxic bile acids in the gastric fluid. Despite the favorable change in the bile acid composition in the gastric fluid, we did not observe any significant changes in markers of oxidative DNA damage, cell proliferation, and apoptosis in the Barrett’s esophagus epithelium. Given recent research describing genomic alterations that develop in esophageal adenocarcinoma, future studies may consider determining the effects of UDCA on genomic alterations, and the effect of combining with PPI use, to determine its roles in prevention of neoplastic progression.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Authors’ Contributions**

Conception and design: N.J. Shaheen, H.-H.S. Chow


Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B. Banerjee, N.J. Shaheen, H.-H.S. Chow

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N.J. Shaheen, J.A. Martinez, C.H. Hsu, B.A. Gibson, H.-H.S. Chow

Writing, review, and/or revision of the manuscript: B. Banerjee, N.J. Shaheen, J.A. Martinez, B.A. Gibson, H.-H.S. Chow

Study supervision: B. Banerjee, G. Della’Zanna, E. Richmond, H.-H.S. Chow

Other (provided patients and examined patients): E. Trowers

Other (NCI Program Director and Medical Monitor): G. Della’Zanna

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**References**


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