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Clinical Study of Ursodeoxycholic Acid in Barrett's Esophagus Patients

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Abstract

Prior research strongly implicates gastric acid and bile acids, two major components of the gastroesophageal refluxate, in the development of Barrett's esophagus (BE) 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 BE. Twenty-nine BE patients received UDCA treatment at a daily dose of 13–15 mg/kg/day for six months. The clinical activity of UDCA was assessed by evaluating changes in gastric bile acid composition and markers of oxidative DNA damage (8-hydroxydeoxyguanosine, 8OHdG), cell proliferation (Ki67), and apoptosis (cleaved caspase 3, CC3) in BE 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. Post UDCA intervention, UDCA increased significantly to account for 93.39% of total gastric bile acids ($p<0.0001$). The expression of markers of oxidative DNA damage, cell proliferation, and apoptosis was assessed in the BE biopsies by immunohistochemistry. The selected tissue biomarkers were unchanged after 6 months of UDCA intervention. We conclude that high dose UDCA supplementation for six 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 BE epithelium.

Keywords

Ursodeoxycholic Acid; Barrett's Esophagus; Clinical Trial; Cancer Prevention; Biomarkers

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Introduction

Barrett's esophagus (BE) is a condition where normal squamous epithelium is replaced by metaplastic intestinal-like columnar epithelium containing goblet cells (intestinal metaplasia, IM). This lesion is linked to the development of esophageal adenocarcinoma, a cancer with poor prognosis, and a median survival of less than one 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 BE and its pathogenesis [3–5]. It has been shown that BE patients 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 BE biopsies ex vivo [7, 8]. Similarly, Huo et al. showed that DCA induces the production of reactive oxygen species in Barrett's cells which causes DNA damage and induces activation of the NF-κB 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 BE, 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 BE. The treatment also prevented DNA damage and NF-κB activation induced by esophageal DCA perfusion in patients with BE. However, it is unknown whether UDCA treatment will decrease the extent of DNA damage under physiological 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 8–10 mg/kg/day in patients with gallstone disease in the U.S. since 1987 and later in patients with primary biliary cirrhosis (PBC) at the dose of 13–15 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 8–10 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 13–15 mg/kg/day for a median duration of 42 months) significantly reduced the risk of colorectal dysplasia or cancer compared with placebo [14].

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We conducted a pilot clinical study to assess the clinical activity of UDCA in patients with BE. The central hypothesis to be tested in the clinical study is that supplementation with UDCA would alter bile acid composition in the refluxate and subsequently decrease oxidative DNA damage, and cell proliferation and increase apoptosis in the BE epithelium.

Materials and Methods

Study Design

The study was an open label, single-arm intervention trial conducted at the University of Arizona (UA), University of North Carolina (UNC), and Southern Arizona VA Health Care System (SAVAHCS). The study was approved by the Institutional Review Board at each institution. The study endpoints were changes in oxidative DNA damage (measured by 8-hydroxydeoxyguanosine levels), cell proliferation (measured by Ki-67 expression), and apoptosis (measured by cleaved caspase 3) in the BE epithelium and changes in gastric bile acid composition.

Study Drug

Ursodiol (300 mg) capsules were supplied by the National Cancer Institute, Division of Cancer Prevention. The initial supply was manufactured by CorePharma LLC for Rising Phamaceuticals. Following expiration of the initial supply in August 2010, the replacement supply for the remainder of the trial was manufactured by Watson Pharma Private Limited and distributed by Watson Pharma, Inc.. The study capsules were stored at room temperature and protected from environmental extremes.

Study population

We recruited healthy women and men   18 years of age with a diagnosis of BE with histologically-confirmed intestinal metaplasia anywhere in the tubular esophagus either with   2 cm of involvement or with a minimum of circumferential BE length of 1 cm. Participants were required to have normal liver and renal function. Study exclusion criteria included BE 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 QD)), history of allergic reactions attributed to UDCA, uncontrolled acute and chronic diseases, pregnant and breast feeding women, major upper GI 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 irrigation, gastric fluid was aspirated through the endoscope and collected. The circumferential and maximum extents of

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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 BE – were taken. These biopsies were processed for histopathology based on the institutional standards. One additional BE biopsy was collected close to the distal end of the BE segment and flash frozen.

Eligible subjects then initiated the six months of UDCA treatment at 13–15 mg/kg per day. Subjects returned to the clinic after three 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 six-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 post-intervention endoscopy to obtain gastric fluid and biopsies of the BE 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 (CTCAE) version 3.0.

Analysis of Bile Acid Concentrations in Gastric Fluid

Bile acid concentrations in the gastric fluid were analyzed by HPLC tandem mass spectrometry. Briefly, an aliquot of gastric fluid was mixed with the internal standards (deoxycholic acid-d4 and glycoursodeoxycholic acid-d4) and then alkalized with 1N NaOH. The mixture was extracted with hexane. The aqueous phase was collected and acidified with 5N HCl and extracted with ethyl acetate. The organic layer was dried and reconstituted with 10 mM 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 mM ammonium acetate on an Ultrasphere XL column. Mass spectrometry was run in negative ion mode using eletrospray ionization. Detection of five bile acids (UDCA, deoxycholic acid (DCA), cholic acid (CA), chenodeoxycholic acid (CDCA), and lithodeoxycholic acid (LCA)) and their respective glycine and taurine conjugates was achieved by multiple reaction monitoring.

Immunohistochemistry (IHC) for Tissue Biomarkers

IHC assays were used to assess markers of cell proliferation (Ki67), apoptosis (cleaved caspase 3, CC3), and oxidative DNA damage (8-hydroxydeoxyguanosine, 8OHdG) in BE epithelium tissue sections. The Ki67 and CC3 IHC was performed on a Discovery XT Automated Immunostainer (VMSI - Ventana Medical Systems, Tucson, Arizona) 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 DAB (diaminobenzidine) detection system was used for CC3 and a biotinylated-streptavidin-HRP and DAB system was used for Ki67. For Ki67, mouse monoclonal antibody (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

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control. The 8OHdG IHC was performed as described previously [8] with minor modifications. Briefly, the slides were baked at 65°C for 1 hr, followed by deparaffinization with xylene, isopropanol, and water. Slides were then treated with 10% H_2O_2, 4N HCl, 0.1M borax, and 5% horse serum sequentially prior to incubating with the mouse monoclonal antibody for 8OHdG (QED Bioscience, #12501 (clone 15A3), diluted 1:1000)). 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 the 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 post-intervention. The primary endpoint was the effect of UDCA intervention on 8OHdG levels in BE epithelium. Signed rank test was performed to assess pre to post-intervention 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 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.

The demographic and disease characteristics of participants who completed the intervention are summarized in Table 1. The average age was 62.5 ± 9.8 yrs. The average BMI from these participants was 28.3 ± 5.1 kg/m^2. 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

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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 six months prior to initiating the UDCA intervention. Twelve of the 29 participants who completed agent intervention were taking daily 81 mg aspirin (ASA).

For disease characteristics of participants that 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 post intervention, 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. Post intervention, 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. Due to the large variation in gastric bile acid concentrations, the individual bile acids were expressed as the percent of total bile acid concentrations 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, 10.99, 38.87, 16.94, and 0.66% of total gastric bile acids. Post intervention, UDCA and its glycine and taurine conjugates increased significantly to account for 93.39% 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), ASA use (yes vs. no), smoking status (never smokers vs. current or former smokers), alcohol intake (no current intake vs. any current intake), baseline BE length (<3 cm vs. 3cm), change in BE 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 ASA users than that in non-users [median (interquartile range): 44.99 (29.51)% (n=12) vs. 15.71 (37.41)% (n=16), respectively, $p = 0.04$]. Post intervention, the DCA and its glycine and taurine conjugates composition was similar between the ASA users and non-users [median (interquartile range): 2.87 (2.75)% vs. 5.88 (15.35)%, respectively, $p = 0.12$]. The stratified analysis showed that the pre to post-intervention change in bile acid composition was different between the ASA users and non-users [median change (interquartile range) of UDCA/conjugates: +75.65 (17.93) vs. +54.5 (57.13), $p = 0.04$; DCA/conjugates: −43.61 (44.61) vs. −8.43 (25.63), $p < 0.05$; and CA/conjugates: −15.69 (9.68) vs. −4.22 (12.12), $p = 0.02$]. 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

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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 post-intervention data on 8OHdG, Ki67, and CC3 expression were obtained from 25, 29, and 27 participants, respectively. Due to the concern of non-specific 8OHdG staining, only the percent of strongly and moderately stained nuclei was used for the statistical analysis. The median (interquartile range) baseline 8OHdG expression was 39.90 (39.14)%. The median (interquartile range) baseline Ki67 and CC3 expression, assessed as positively stained nuclei, was 35.92 (13.95)% and 1.62 (2.86)%, respectively. 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 post-intervention 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 BE. 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 BE 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 13–15 mg/kg/day for six months in patients with BE 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 any significant changes in markers of oxidative DNA damage, cell proliferation, and apoptosis in the BE 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 BE, PPI use was associated with a reduced risk of neoplastic progression [16]. High-dose PPI treatment in patients with BE 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. Bozikas et al. [19] evaluated the effect of six

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months of UDCA (600 mg BID) intervention in nine Barrett's 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 a causative factor in the pathogenesis of progression in BE. 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 BE 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 BE than to prevent the pathogenesis of BE.

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 BE patients 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 employed in this study have been correlated with the histological grade of Barrett's esophagus [21–24] and used as intermediate biomarkers to assess preventive interventions in BE patients [17, 19, 25, 26]. However, these markers have not been proven in large, well-designed 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 six 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 of 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 BE epithelium. Given recent research describing genomic alterations that develop in esophageal adenocarcinoma, future studies may consider determining the effects of UDCA on genomic alterations, as well as the effect of combining with PPI use, to determine its roles in prevention of neoplastic progression.

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Table 1

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

Variable	
Age, yr (mean ± SD)	62.5 ± 9.8
BMI, kg/m^2 (mean ± SD)	28.3 ± 5.1
Gender male/female	23/6
Race White/Multi-racial	28/1
Ethnicity Non-Hispanic/Hispanic	25/4
Smoking History Current/Former/Never	3/14/12
Alcohol Intake Heavy/Moderate/Low/Occasional/Former/Never	0/4/10/7/5/3
Length of circumferential involvement, cm, median (range)	
Baseline	4.0 (1–11)
Post-intervention	3.8 (1–12)
Length of circumferential involvement, <3 cm / 3 cm	
Baseline	13/16
Post-intervention	16/13
Change in circumferential length, decreased/no change/increased	7/18/4
Pathology grade, ND/LGD/HGD	
Baseline	20/9/0
Post-intervention	24/4/1
Change in pathology grade, improved/no change/worsened	5/22/2

Abbreviations: ND: no dysplasia; LGD: low grade dysplasia; HGD: high grade dysplasia

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Table 2

Gastric bile acid composition at baseline and post-intervention (n = 28).

	Baseline (% of total bile acid)	Post-Intervention (% of total bile acid)	P value[b]
UDCA and glycine/taurine conjugates	18.2 (26.1)[a]	93.4 (31.7)	<0.0001
CDCA and glycine/taurine conjugates	11.0 (10.2)	1.01 (3.90)	<0.0001
DCA and glycine/taurine conjugates	38.9 (44.0)	4.18 (7.82)	<0.01
CA and glycine/taurine conjugates	16.9 (18.9)	1.72 (7.21)	<0.0001
LCA and glycine/taurine conjugates	0.66 (1.30)	0.17 (0.37)	<0.001

[a] median (interquartile range)

[b] derived from signed rank test

Abbreviations: UDCA: ursodeoxycholic acid; CDCA: chenodeoxycholic acid; DCA: deoxycholic acid; CA: cholic acid; LCA: lithocholic acid

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Table 3

Tissue biomarker expression[a].

	Baseline (% positive)	Post-Intervention (% positive)	p value[d]
8OHdG (n = 25)	39.9 (39.1)[b,c]	34.9 (30.7)	0.52
Ki67 (n = 29)	35.9 (14.0)[e]	36.9 (18.3)	0.44
CC3 (n = 27)	1.62 (2.86)[e]	1.00 (2.11)	0.25

[a]longitudinally sectioned crypts opening to the lumen were selected for scoring. 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.

[b]median (interquartile range)

[c]% of strongly and moderately stained nuclei

[d]derived from signed rank test

[e]% of positively stained nuclei

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

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Table 4

Spearman correlation coefficient between changes in gastric bile acid composition of changes in tissue biomarker expression.

Bile Acid	8OHdG (N=25)	Ki67 (N=28)	CC3 (N=26)
Total UDCA	0.04; p=0.85	0.01; p=0.94	0.29; p=0.15
Total CDCA	−0.16; p=0.43	−0.20; p=0.31	0.24; p=0.24
Total DCA	−0.14; p=0.49	−0.19; p=0.34	−0.09; p=0.65
Total CA	0.24; p=0.26	−0.04 p=0.28	−0.23; p=0.26
Total LCA	−0.07; p=0.74	0.01; p=0.96	0.06; p=0.78

Abbreviations: UDCA: ursodeoxycholic acid; CDCA: chenodeoxycholic acid; DCA: deoxycholic acid; CA: cholic acid; LCA: lithocholic acid; 8OHdG: 8-hydroxydeoxyguanosine; CC3: cleaved caspase 3