Potential Therapeutic Benefit of Ursodeoxycholic acid (UDCA) in the Management of Non Hepato-Biliary Upper Gastrointestinal Disorders: A Systemic Review.

Yasir M Khayyat[1], FACG, FRCPC, FACP, Mohammed Y Khayyat[2]

1.Department of Medicine, Faculty of Medicine, Makkah, Saudi Arabia
2. College of Medicine, King Abdul Aziz University, Jeddah, Saudi Arabia.

Introduction

- **Ursodeoxycholic acid (UDCA) is a secondary bile acid with physiologic and different therapeutic effects on the hepatobiliary tree.**
- **Little is known of its local effects as a therapy of upper gastrointestinal tract disorders (UGID) and its chemoprevention.**
- **Several unmet needs in the management of UGID including poor response to management of acid related disorders.**
- **Our aim to search for UDCA therapeutic effect and review its role on the management effect of diseases of the esophagus, stomach and Duodenum if exist and describe its therapeutic potential.**

Methods

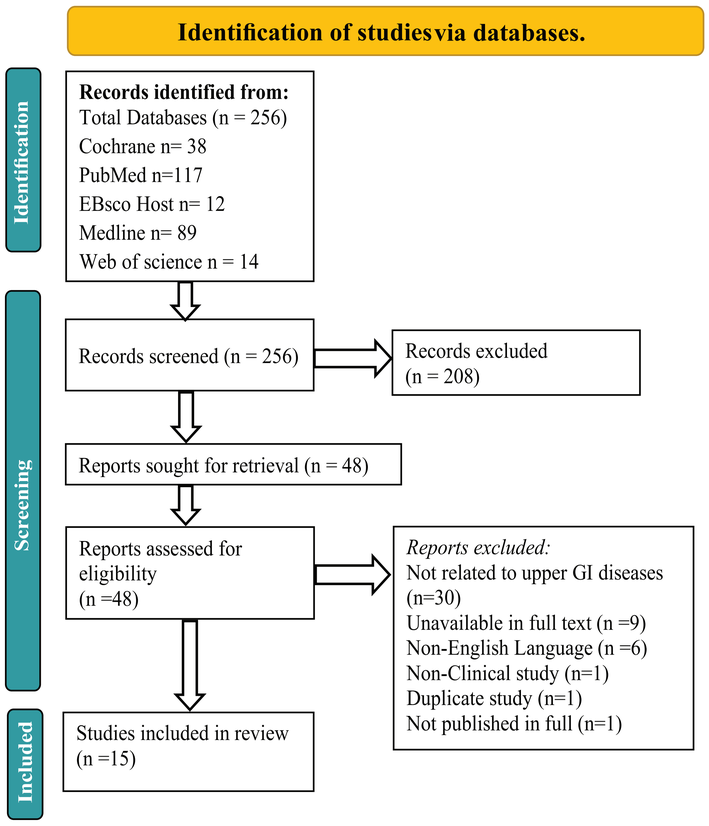
- A Systemic review performed for search terms at basic science and clinical literature within the major search engines which are PubMed, Medline, EMBASE, Google scholar and web of science performed for human and experimental human cell lines or cultures.
- Review of the major gastroenterological societies guidelines was undertaken as well to search for their own recommendations of UDCA use in UGI diseases.
- Exclusion criteria are Pediatric age, non-English literature, animal or veterinary literature and literature that discussed hepatic or biliary UGI diseases.
- Metanalysis is planned based on the availability of the results.
- The review is registered at PROSPERO, International Prospective Register of Systemic review, University of York, York UK, Year of Registration 2021.Registration: PROSPERO CRD42021267689.

Results

- **Search results shown on Figure 1.**

Esophageal disorders: studies on the effect of secondary bile acids on Barret's esophagus and its dysplastic changes. No studies nor clinical guidelines found to demonstrate the effect of UDCA on the spectrum of GERD management, esophageal motility disorders and eosinophilic esophagitis found.

Figure 1: Search Protocol of the role of UDCA in the Management of Non hepatobiliary Upper Gastrointestinal Disorders.



I. Esophageal Disorders:

Barret's esophagus (BE): Hydrophobic bile acid Deoxycholic acid (DCA) exerts deleterious effect on DNA damage of Barret's cells and activation of NF-κβ subunit p65 and its transcriptional activity.

Positive Results:
- (8 weeks) omeprazole 20 mg po twice daily and UDCA with a dose of 10mg/kg showed: it prevents DNA damage and significantly increase mRNA and protein expression of the antioxidants studied which are Glutathione peroxidase 1 (GPX1) and catalase.[1]
- It has inhibitory effect on: DCA induced NF-κβ and its translocation, DCA induced Activator Protein-1 (AP-1) activation and induce upstream signaling proteins in esophageal cells.[2]

Negative Results:
- Upon a follow up of 9 years treatment period of high dose of PPI and UDCA at a dose of 600 mg twice daily for six months in whom several outcomes evaluated (clinical, biochemical and histological outcomes) found to be not altered.[3]
- Cohort of 29 patients who were pretreated with PPI for 6 months that UDCA at a dose of 13-15 mg/kg/day showed no improvement in BE pathology grade, oxidative DNA damage as demonstrated by 8-Hydroxydeoxyguanosine (8-OHdG), Cellular proliferation using Ki67 index nor cellular apoptosis as shown by Cleaved Caspase 3 (CC3).[4]
- Aspirin in addition to the intervention drugs were noted to alter the concentrations of DCA and its glycine and Taurine conjugates within the bile acid composition, however that did not alter the study outcomes.[4]

II. Gastric disorders:

Gastritis: The gastric lumen is constantly exposed to acidic medium of the HCL released from parietal cells and reflux of duodenal contents containing mixture of pancreatic and biliary juices.

Positive results:
- Cohort of 12 patients who undergone bill Roth 2 gastrectomy, UDCA at a dose of 1000 mg/day for 4 weeks while off treatment with other acid inhibitory medications (PPI, antacid) and cholestyramine, significant reduction of cholic acid (CA), DCA and Litholic acid (LA) with significant improvement in symptoms score. However, no histological changes noted with UDCA treatment.[5]

Helicobacter Pylori infection:
Negative Results:
- Among documented uneradicated helicobacter pylori infection (n=40 patients), UDCA treatment alone at a daily dose of 300 mg for 28 days yield no significant outcome in reduction of helicobacter pylori density, mononuclear cellular infiltration nor polymorphonuclear infiltration.[6]

Functional dyspepsia:
Positive Results:
- In 24 patients with Functional dyspepsia according to ROME 3 criteria and associated small intestinal bacterial overgrowth (SIBO) at a dose of 300 mg daily for two months. A statistically significant decrease in functional dyspepsia index is noted as well as decrease in methane and hydrogen producing SIBO patients using breath tests as compared to placebo.[7]
- Symptom response of dyspepsia in 26 patients using UDCA at a dose of 300 mg/d or placebo demonstrate better symptom improvement (55%) in UDCA versus Placebo (21%).[8]

III. Duodenal disorders:

Familial Adenomatous polyposis:
Positive Results:
- Post proctocolectomy FAP patients with duodenal adenomas who were treated with UDCA at a dose of 10 mg/kg/day compared to placebo for 24 months. Follow up endoscopically for regression of the duodenal polyps using spigelman severity score showed, 9 patients who were treated with UDCA versus 7 patients treated with placebo demonstrated no superiority benefit of UDCA.[9]
- Pilot study evaluated cellular proliferation of a small cohort of FAP comprising five patients using high dose of UDCA of 25mg/kg, showed by staining less duodenal mucosal cyclooxygenase-2 (COX-2) expression. UDCA cytotoxicity of bile acids had been significantly attenuated post intervention.[10]
- Celecoxib is a cyclooxygenase-2 inhibitor with antioxidant properties evaluated in conjunction with UDCA to evaluate duodenal FAP.
- A 37 patients with documented FAP using endoscopy or APC gene documentation, UDCA at doses ranged between 1000 to 2000 mg daily in combination with celecoxib at a dose of 800 mg daily compared to celecoxib 800 mg daily and a placebo showed that Celecoxib and placebo exerted reduction of duodenal polyp density, reduction of cellular proliferation (using Ki67), reduction of apoptosis (using cleaved cytokeratin 18) and reduction in COX-2 expression as a tumorigenic marker compared to Celecoxib and UDCA ,thereby high dose of UDCA counteracts Celecoxib effect.[11]

Negative Result:
- Significant lower mRNA measured at GSTA1 (a detoxification enzyme) and Caspase-3 (apoptotic marker) found at the normal mucosa of FAP and hence lower capacity to detoxify carcinogens and toxins. These genetic markers were not influenced by UDCA at a dose of 20-30 mg/kg and Celecoxib 800 mg daily compared to Celecoxib and placebo.[12]

Dosage and Side effects:

They were reported either as a weight based or fixed doses,
- Weight based dosing ranged between
- 10 mg/kg/day for chemoprevention of Barret's esophagus indication.
- up to 20-30 mg/kg/day for prevention of dysplastic changes in FAP.
- Fixed doses ranged between
- oral doses of 300 mg daily for indication of treatment of Functional dyspepsia.
- SIBO and non-organic dyspepsia up to 1000 mg for the indication of treatment of Bile reflux gastritis.
- No Intravenous UDCA reported in the studies for use as an indication of UGI disorders.

- **Side Effects:**

There are predominantly Gastrointestinal side effects (20 events, 50 %) among the total side effects profile, Table 1.

Table 1: Side effects of UDCA use.

Type	Events (n) Frequency
Gastrointestinal	• Abdominal Pain (1) **2.5 %** • Anal and Perianal Pain (4) **10%** • Heartburn (1) **2.5 %** • Constipation (3) **7.5 %** • Diarrhea (2) **5 %** • Bloating (1) **2.5 %** • Flatulence (1) **2.5 %** • Nausea (1) **2.5 %** • Vomiting (1) **2.5 %** • Dyspepsia (3) **7.5 %** • Terminal ileum Ulceration (1) **2.5 %** • Elevated AST and GGT (1) **2.5 %**
Neurologic	• Dizziness (1) **2.5 %** • Mood alteration (1) **2.5 %** • Neuropathy, Carpal tunnel syndrome (1) **2.5 %**
Renal	• Lower urinary tract symptom, Prostatism (1) **2.5 %**
Skin	• Hair loss (1) **2.5 %** • Skin Rash (2) **5%**
Hematology	• Anemia (1) **2.5 %** • Leukopenia (1) **2.5 %**
Auditory	• Otitis (1) **2.5 %**
Infection	• Dental Infection (1) **2.5 %** • Skin Infection (1) **2.5 %** • Gastroenteritis (1) **2.5 %**
Lymphatics	• Lower Limbs edema (2) **5%**
Metabolic	• Hypokalemia (1) **2.5 %**
Constitutional	• Fatigue (2) **5 %** • Insomnia (1) **2.5 %**
Malignancy	• Basal cell carcinoma, nose (1) **2.5 %**
Total Events (n) %	40

Conclusion

- UDCA has limited therapeutic role in few uncontrolled small studies for functional dyspepsia.
- Its chemopreventive role is promising for Familial adenomatous polyposis and Barret's esophagus, await further studies to support these roles.

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