Nutri-Link Ltd for EDUCATION

White Paper

Researched Leadership

Bile Acids make you live longer

'a new understanding'

Contact: Nutri-Link Ltd

Address: Nutrition House Unit 24,
Milber Trading Estate
Newton Abbot, Devon
TQ12 4SG
United Kingdom

Phone: 08704 054 002
Fax: 08704 054 003
E-mail: info@nutri-linkltd.co.uk
www: nutri-linkltd.co.uk

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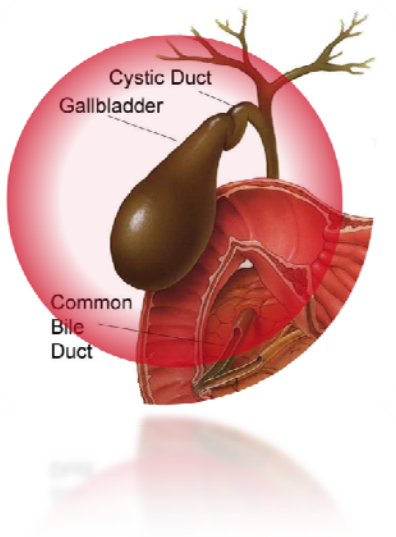
Gall Bladder Function and Bile Acids in Health and Illness

Prevent and treat diabetes, obesity, insulin resistance, atherosclerosis, mood disorders, immune disruption, leaky gut, high cholesterol, high lipids, headaches, dry skin and extend life. Is all this and more really possible by harnessing the health benefits of bile acids?

Review

In older styles of medicine, bile, a substance secreted by the liver, was believed to be partially responsible for the development of illnesses and to play an important role as a mood regulator. Greek philosophers, like Hippocrates, divided bodily fluids into four moods: black bile, yellow bile, phlegm, and sanguine (blood). Thus, too much black bile caused melancholy, too much yellow bile made people choleric, leading to bitterness and short-temperedness, too much phlegm led to slowness, and excess sanguine made people too confident and optimistic. The term biliousness was used to define someone of a peevish and ill-natured disposition. Despite this early popularity, bile, bile acids and their principle components fell into obscurity and their role was, until very recently, confined to stimulation of the absorption of dietary fat and cholesterol metabolism.[1]



New Understanding

Bile acids are increasingly being appreciated as complex metabolic integrators and signalling factors with systemic endocrine functions involved in a multitude of health problems and not just as lipid emulsifiers and simple regulators of bile-acid homeostasis.

They are understood to be significant mediators of metabolic disorders including obesity, type 2 diabetes, hypertriglyceridaemia and atherosclerosis, as well as other associated chronic diseases such as non-alcoholic steatohepatitis and various functional disorders including; dysbiosis, headaches, altered bowel habits, abdominal weight gain and skin complaints. They also have early evidence of being significant controllers of inflammation, improving stress resistance and extending healthy lifespan. The correct use of natural agents that increase the availability and or composition of the bile acid pool, such as suitable probiotics and bile acid flow promoters or replacers have tremendous therapeutic possibilities in the prevention and

Non-alcoholic steatohepatitis (NASH) is a common and often silent liver disease, which has become one of the most prevalent alcohol-independent causes of liver cirrhosis in Western countries. It has a significant inflammatory component.

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resolution of these health problems.

The use of foods and food supplements that support or promote bile acid production and synthesis represents a safe utilisation of a traditional therapy for a contemporary application.

Key Points of Clinical Relevance

- **Hepatic synthesis of bile acids is the primary pathway for cholesterol catabolism.** *The cholesterol 7α-hydroxylase enzyme (encoded by cytochrome P450 enzyme: CYP7A1) represents the rate-limiting step of the multi-enzymatic bile-acid biosynthetic pathway.*
- **Bile acids play a crucial role in dietary lipid digestion and absorption, and also act as versatile signalling molecules** *through the activation of the nuclear hormone receptor farnesoid X receptor-α (FXR-α) and the recently identified G-protein-coupled receptor TGR5.*
- **Bile-acid-mediated activation of FXR-α-signalling pathways regulate the enterohepatic recycling of bile acids, protect against their accumulation in the liver and inhibit their own biosynthesis.**
- *Through their endocrine function, bile acids also activate TGR5 signalling pathways in multiple cells*, **through which they control immune function, liver and gall-bladder physiology and glucose and energy homeostasis.**
- The development of TGR5 **agonists** could have benefits to combat many aspects of the metabolic syndrome, whereas FXR-α agonists could hold promise for reducing activation of these bile-acid-signalling pathways and is therefore a novel way to improve metabolism.

Agonist: is a term used to describe a type of molecule or drug that binds and alters the activity of a receptor. The efficacy of an agonist may be positive, causing an increase in the receptors activity or negative causing a decrease in the receptors activity.

What are bile acids?

Bile acids, cholesterol, phospholipids and bilirubin, comprise the principle constituents of bile. These are synthesised from cholesterol in the liver and then secreted from hepatocytes into the bile canaliculi (*small intercellular channels that merge to form bile ductules*) to be stored (approx 50mL) in the gall bladder. Cholesterol conversion to bile salts requires vitamin C, taurine, oxygen, nicotinamide adenine dinucleotide phosphate (NADPH), choline, and betaine or Trimethylglycine.

After ingestion of food, bile flows into the duodenum, where it contributes to the emulsification and digestion of lipid-soluble nutrients. Bile acids are then absorbed (approx 90%) by passive diffusion and active transport from the terminal ileum and transported back to the liver via the portal vein via a system known as enterohepatic circulation.[1,2]

Food increases the bile-acid levels in the intestine and liver as well as in the systemic circulation approximately three fold (from 5 µMol/h to 15 µMol/h).[3,4] Serum bile-acid levels are driven by food timing and content, providing feedback to the peripheral tissues that an energy supply is now available. Using this feedback mechanism bile acids can be employed as signalling molecules, and can through activation of G protein-coupled receptors and nuclear hormone receptors regulate not

only their own synthesis and enterohepatic recirculation, but also triglyceride, cholesterol, energy and glucose homeostasis.[5]

These **bile-acid-controlled** signalling pathways are promising targets to treat common metabolic and hepatic diseases. Bile-acid signalling and bile acid optimisation can be used to develop novel therapeutic and preventative strategies useful in the clinical management of obesity, type 2 diabetes, hyperlipidaemia and atherosclerosis. Other functional disorders that can respond to optimal bile acid production include skin problems, headaches, nausea, intractable weight gain, blood sugar irregularities, bowel sluggishness, joint and musculoskeletal problems, via the activation of immune receptors, gene expression receptors and inflammatory messengers found in the small and large intestines.

G Protein receptors: comprise a large protein family of transmembrane receptors that sense molecules outside the cell and activate inside signal transduction pathways and, ultimately, cellular responses. (TGR5)

Nuclear receptors: are a class of proteins found within the interior of cells and work in concert with other proteins to regulate the expression of specific genes controlling development, homeostasis, and metabolism of humans. (FXR-α)

Bile-acid synthesis is of course the primary pathway for cholesterol catabolism. Approximately 500mg of cholesterol is converted into bile acids each day in the adult human liver. Bile-acid biosynthesis involves modification of the ring structure of cholesterol, oxidation and shortening of the side chain, and finally conjugation of the bile acid with an amino acid.[6]

This process is highly dependent on a specific part of the phase 1 liver dominated enzymes known as CYP27A1. This enzyme's function can be increased by certain foods and nutritional supplements, [7,8] and insufficient activation of this enzyme leads to nutritional deficiencies.[9]

The most abundant bile acids in humans include the primary bile acids;

- Cholic acid (CA) (31%)
- Chenodeoxycholic acid (CDCA), (45%),

and their respective secondary bile acids;

- Deoxycholic acid (DCA) from cholic acid and
- Lithocholic acid (LCA), from Chenodeoxycholic acid and formed by deconjugation and 7a-dehydroxylation by microbial enzymes in the colon.

Before bile acids are transported out of the hepatocytes, most of them are conjugated to the amino acid glycine or taurine. Conjugation is also an important way to modulate the biological properties of bile acids improving the formation of mixed micelles and enhancing intestinal absorption of lipophilic compounds.[10]

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Cholestasis: is a condition where bile cannot flow from the liver to the duodenum, it may be reduced (sludge) or blocked – gallstone.

Biliary sludge: Composed of cholesterol crystals, calcium bilirubinate granules, and mucin glycoprotein suspended in bile.

In order to maintain a functional bile-acid pool, bile acids are extensively recycled in the body by an elaborate transport system that is active in the liver, the intestine and the kidney efficiently limiting the faecal and urinary loss of bile acids. The functional effect of limited bile acid release is mitigated by adaptive transporter functions, but will still result in adverse release of bile acids, which if chronic, may manifest as cholestasis when bile acids can be identified in the urine of affected people.[11] Jaundice, dark urine, light-coloured stools, fatty, foul smelling stools, low levels of Vit D, calcium and Vit K and generalised itchiness are characteristic symptoms of cholestasis as well as a positive Murphy's test. Biliary sludge is also a common variable in people with altered bile acid formation and excretion, and whilst it may produce transitory upper right quadrant discomfort and or eventually form gallstones, it will limit the effective release of bile acids into the duodenum and will limit its effects as a signalling factor.[12,13]

Key Signalling Molecules

What we understand now is that apart from their role in dietary lipid absorption and cholesterol homeostasis, bile acids are also versatile signalling molecules and two major bile-acid-regulated signalling mechanisms have been receiving the most attention in the scientific literature.

1. TGR5 or 'membrane bile-acid receptor' [14]
2. Nuclear hormone receptors, such as FXR-α[15]

What does TGR5 do?

The biological impact of bile-acid-dependent TGR5 activation is only partially understood and may vary according to the tissue it comes into contact with. The level of exposure to bile acids, as well as the bile-acid family present in the different tissues, is different in TGR5-expressing tissues such as the gut, the gall bladder, the muscle or brown adipose tissue (BAT).

Brown adipose tissue (BAT): Its primary function is to generate body heat and has a much higher number of mitochondria and blood vessels than white adipose tissue.

TGR5 has been defined as having four main roles:

1. An immunomodulatory role,[16]
2. Prevention of gallstones by acting as a potent antioxidant controller of nitric oxide production and protecting the liver against lipid peroxidation,[17]
3. A manipulator of metabolism[18] and mitochondrial energy homeostasis.[19]
4. Cell proliferation and apoptosis[20]

What does FXR-α do?

Apart from the role that FXR-α has in bile-acid homeostasis, increasing evidence is emerging for the importance of this receptor in lipid metabolism. Bile acids also affect triglyceride homeostasis. In fact, for a long time it has been known that there is an inverse relationship between the transhepatic bile-acid flux and hepatic very low density lipoprotein (VLDL) production in humans.[21] Bile acids containing FXR-α lead to the increased expression of key genes which enhance triglyceride and very low-density lipoprotein (VLDL) metabolism and consequently are understood to beneficially lower the levels of serum VLDL and triglycerides.[22]

Bile acids and energy homeostasis

Bile acids have been reported to reduce diet-induced obesity and prevent hyperglycaemia in rodents,[23] suggesting they have effects on energy homeostasis. The administration of bile acids to mice increases energy expenditure in BAT, preventing obesity and insulin resistance.[24] The use of oleanolic acid a naturally occurring triterpenoid, widely distributed in foods and medicinal plants such as Phytolacca Americana (American pokeweed), and garlic improves metabolic control over weight distribution via activation of TGR5.[25]

Using a bile acid promoting supplement/medication and suitable diet prevents and reverses fat accumulation and associated metabolic defects by means of a mechanism that does not depend solely on FXR-α.[26] The inclusion of a bile acid replacement can reverse the adverse effects of a high fat diet through activation of key nuclear hormone receptors and other factors that influence weight.

Bile acids and glucose metabolism

In addition to their pleiotropic effects on lipid homeostasis, bile acids also affect glucose metabolism. These effects were first seen in patients with type 2 diabetes prescribed a bile thinning drug, called cholestyramine.[27] Whilst the exact mechanisms have yet to be fully elucidated the bile acid component FXR-α is recognised to be an important player in improving insulin resistance and a recent paper revealed FXR-α activation enhanced insulin-stimulated glucose uptake as well as insulin signalling in fat cells (adipocytes).[28]

The concept that the major effect of bile acids on body weight indirectly influences their impact on whole-body glucose homeostasis has gained support recently and it seems to exert its effect in part through the reduction of oxidative stress and improving mitochondrial function. The result of this activity in humans is to increase insulin sensitivity and reduce risk for diabesity (an association of obesity and type 2 diabetes). Other studies also show insulin receptor function being improved when bile flow is increased, suggesting that bile stasis may be linked to increased risk for metabolic syndrome.[29]

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Gastrointestinal Bacteria

Bile acids are bacteriostatic in the intestine. FXR-α activation has been shown to be enteroprotective, resulting in the prevention of bacterial overgrowth and subsequent epithelial deterioration and bacterial translocation due to increased gastrointestinal permeability. Bacteriostatic agents work with the immune system to remove pathogenic microorganisms from the body.[30] The healthy production and flow of bile acids reduces risk of leaky gut and bacterial migration, as well as inhibiting pathogen overgrowth, especially for small intestinal bacterial overgrowth.

Obstruction of bile flow results in bacterial proliferation and mucosal injury in the small intestine that can lead to the translocation of bacteria across the epithelial barrier and systemic infection.[31] Increased gut permeability (IGP) can be induced due to diminished bile flow;[32] IGP has been linked to a wide range of health problems including MS[33], Psoriasis[34], IgA nephropathy[35] and RA[36] amongst others.

Bacteriostatic: Capable of inhibiting the growth or reproduction of bacteria. Different from bactericidal (capable of killing bacteria outright).

These adverse effects of biliary obstruction can be inhibited by administration of bile acids such as found in ox-bile supplements.[37] The ingestion of FXR-α agonists and or bile acids have therapeutic implications in patients that have obstructed or reduced bile flow, especially when susceptible to bacterial overgrowth. Conjugated bile acids such as those found in ox bile can regulate expression of host genes whose products promote innate defense against luminal bacteria.[38]

Anti Inflammatory properties

Another recent study has shown that, similar to its effects in the liver, FXR-α modulates lipid metabolism and promotes anti-inflammatory and antifibrotic effects in the kidney, implying the potential use of bile promoters to treat diabetic nephropathy and other fibrotic renal diseases.[39]

FXR-α antagonists and modulators

Most data is available for guggulipid, a plant extract containing the sterol guggulsterone, which is clinically prescribed in India and also sold in the West as a food supplement for lowering cholesterol levels. This putative beneficial effect was attributed to its FXR-α antagonising activities.[40,41] The use of supplemental forms of guggulsterone may either in isolation or with other food concentrates act as an FXR-α promoter.

TGR5 agonists and modulators

Triterpenoids, such as oleanolic acid, are selective natural TGR5 agonists that are devoid of activity on FXR-α.[42] Triterpenoids are ubiquitously distributed throughout the plant kingdom, and some are increasingly being used for medicinal purposes for a variety of clinical diseases in many Asian countries as antitumor, anti-inflammatory, and immunomodulatory agents.[43,44,45] Interestingly,

oleanolic acid significantly improves insulin sensitivity in mice fed a high-fat diet, which strengthens the concept that the TGR5 signalling pathway is a promising target for the treatment of metabolic diseases. Squalene is the precursor to all triterpenoids but the conversion to active triterpenoid agents within the gastrointestinal tract requires bacterial cooperation.

Gut bacteria separate the sugar glycosides from plant extracts to release the triterpenoids for absorption. Inadequate commensal bacteria may result in reduced levels of triterpenoids being synthesised from plant extracts and fruit skins such as olives as well as specific food supplements. Triterpenoids found in the ginseng families and sulforaphane found in cruciferous vegetables modulate the anti-inflammatory activity of TGR5 and reduce inflammation via the induction of phase two enzymes, providing a double beneficial strategy of dietetic intake of relevant foods to reduce disease risk linked to inflammation.[46]

Probiotics

Recently, several interesting papers have shown how the gut flora can affect systemic processes such as metabolism and inflammation.[47,48,49] The use of probiotics, that is, deliberately ingested preparations of live bacterial species that confer health benefits on the host, is therefore receiving increasing scientific attention. Many bacterial species are capable of modifying and metabolising bile acids. The principle area of bacterial initiated uptake is in the terminal section of the small intestine, heavily populated with the LAB; Plantarum, Salivarius, Rhamnosus and Bifido Bifidum.[50]

Small modulations in the species composition of the gut microbiome such as after antibiotics[51] can therefore result in major functional ecological consequences. Microbial–mammalian transgenomic metabolic interactions, whereby probiotic-induced modulation of the gut microbial functional ecosystem results in changes in bile-acid composition and enterohepatic recirculation, is therefore an attractive way to modulate systemic metabolism.

It is important when considering probiotic intervention therapy that human beings be considered as "superorganisms" due to their close symbiotic associations with the gut microbiota.[52] Superorganism metabolism must involve the integration of truly indigenous metabolic processes (coded in the host genome) with those of the microbiome. This remarkable evolution derived mutual transgenomic co-metabolism involves a great many substrates including those involved in host metabolic regulation.[53]

As practitioners faced with individual health care decisions, the superorganism concept represents an important paradigm shift in understanding human biology and should have a significant impact on the future of disease prevention and intervention therapy.[54]

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Anti-aging effects of bile

Bile acid signalling benefits extend beyond the control of metabolism; bile acids have been identified in the management of cell proliferation[55] and of inflammation.[56] Furthermore, in early stage worm studies (Caenorhabditis elegans), bile-acid-like steroid hormones called dafachronic acids, were shown to affect stress resistance and extend lifespan.[57,58]

It is therefore plausible that the various nutritional strategies to modulate bile-acid signalling pathways explained in this paper could act as anti-aging strategies through their potent hormonal activities that integrate metabolism, inflammation and cell proliferation.

Adverse aging has been linked to altered innate immune function and increased inflammation, sometimes referred to as 'inflammaging'.[59] As declining digestive capacity also increases micro and macro nutrient bioavailability problems, and immunological balance relies on an extensive array of these food stuffs, the resolution of diminished bile production makes for a safe and clinically relevant point of entry. Inflammaging is characterised by the complex set of five conditions which can be described as:

1. low-grade,
2. controlled,
3. asymptomatic,
4. chronic,
5. systemic, inflammatory state.[60]

This combination of events characterises a highly complex response to various subtle internal and environmental inflammatory stimuli which are then mediated in the main by the increased circulating levels of pro-inflammatory cytokines. Inflammaging also induces oxidative stressors called Reactive Oxygen Species (ROS) which can cause a combination of cellular damage and cytokine amplification perpetuating a vicious inflammatory cycle. This can result in a chronic systemic pro-inflammatory state where tissue injury and healing mechanisms proceed simultaneously but at the same time allowing for local and systemic damage to accumulate, often asymptomatically over many decades. This combination of events is increasingly recognised as a major component of the aging process and a risk factor for the early development of age related diseases.[61,62]

The simple mechanism for evaluation, the obvious health potential and the ease of compliance presents the patient and practitioner with a comfortable and manageable programme for modifying bile acid flow, production and immunogenic optimisation.

Conclusion

The ongoing development of natural, semi-synthetic and synthetic compounds that modulate the activity of the nuclear and/or membrane bile-acid receptors, and of other agents and probiotics that alter the availability and/or the composition of the bile-acid pool, will exploit this apparently tremendous therapeutic potential.

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Author

Michael Ash BSc (Hons). DO. ND. Dip ION mIoD began clinical practice in 1982 when he founded the Eldon Health Clinic, an Integrated Health Care Clinic during which time he treated in excess of 10,000 patients. He sold his practice in 2006, and now acts as a consultant, as well as the Managing Director of Nutri-Link Ltd. He lectures and consults internationally on the role of the immune system in health and functional illnesses. He is now spending increasing time on developing research programmes to support the clinical use of bacteria, yeast, fatty acids and other naturally occurring agents to manage varied health problems linked to loss of mucosal immune tolerance and gastrointestinal dysfunction.

- He is registered and insured with the General Osteopathic Council & The British Naturopathic Association.
- He is a registered Medico Legal Expert in Osteopathy/Naturopathy
- He is a Fellow of the Royal Society of Medicine and is an elected member of the RSM's Food and Health Council
- He is a member of the Society of Mucosal Immunology
- He is a member of the American Academy of Science
- He is a member of the New York Academy of Science
- He is a member of the Psychoneuroimmunology Research Society
- He is a member of the Institute of Functional Medicine
- He is a member of the British Society of Ecological Medicine
- He is a Fellow of the Institute of Optimum Nutrition

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