Functional Liver Detoxification Profile (FLDP)

Clinical Guide

The liver is metabolically the most complex organ in the body and serves numerous vital functions. These include energy balance regulation, blood protein synthesis and immune modulation.

Efficient liver function is necessary for the processing and excretion of endotoxic and exotoxic chemicals (hormones, drugs, chemicals etc.) which are commonly referred to as "xenobiotic" chemicals. (see figure 1).

Inefficient liver function can lead to "metabolic poisoning" which is a nondescript term referring to the build up within cells, tissues and organs of metabolites which have not been processed by the liver and excreted. These metabolites alter the pH gradient and electrolyte profile within cells and can serve as competitive enzyme inhibitors that ultimately interrupt effective bioenergetics within the cell. The symptoms of metabolic poisoning at the elevated level are reflective of poor energy dynamics and include fatigue, hypotonia and brain biochemical disturbances. Recent studies have reported a relationship between impaired detoxification capability, mitochondrial dysfunction and chronic fatigue syndrome (CFS). These reports suggest that oxidative damage due to mitochondria and the detoxification process is itself a fundamental mechanism in the development of CFS.

Well recognised examples of metabolic poisoning include the symptoms of uraemia or hepatic encephalopathy. Both of these conditions are associated with fatigue and central nervous system disturbances and are a consequence of this metabolic poisoning of specific tissues due to the build up of toxins. Assessment of liver functional capacity for detoxification has been limited due to the potential invasive nature of a test.

Cost and complexity of procedures have also limited routine clinical usage. Recently, functional liver challenge tests have evolved which can allow routine assessment of the liver's detoxification abilities.

The Role of the Liver in Detoxification and Elimination

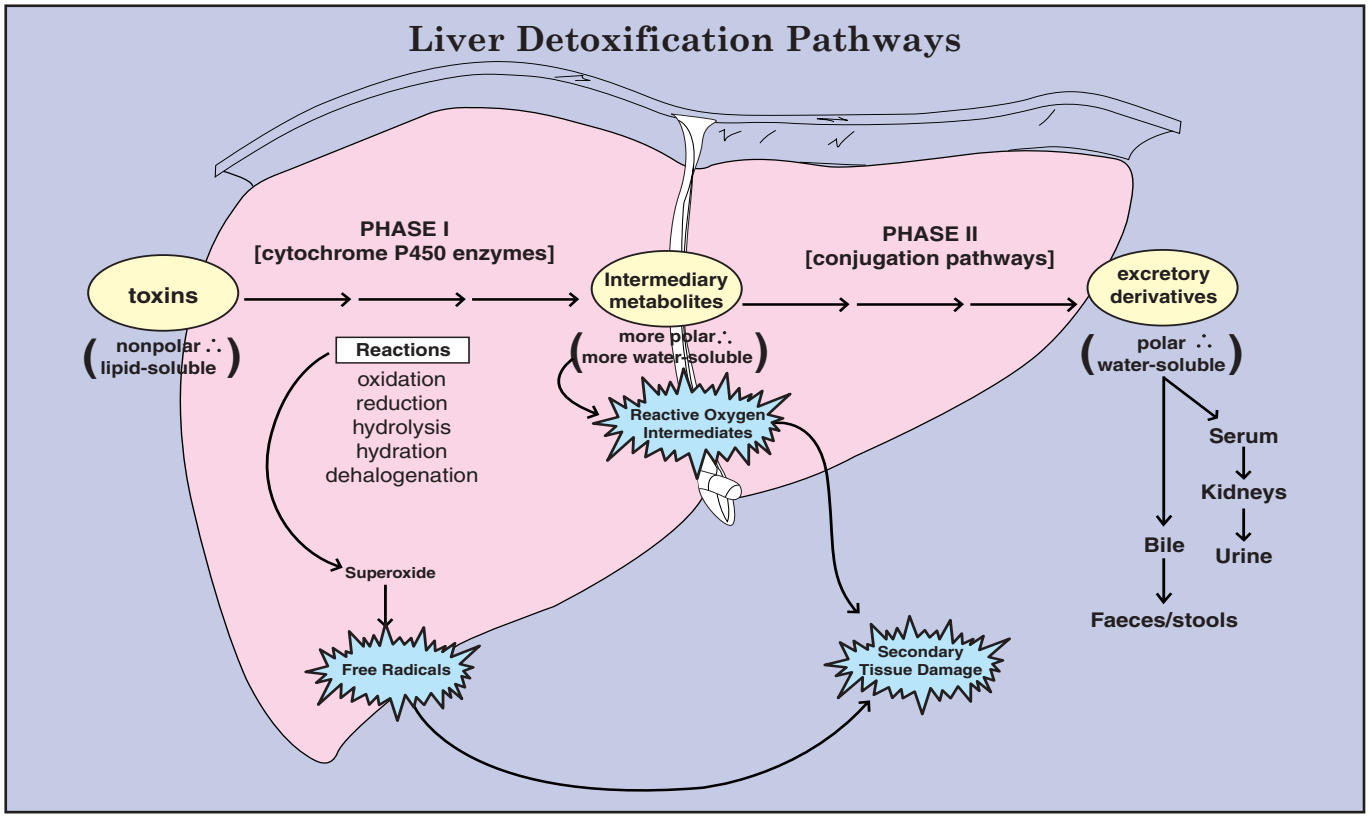
The liver possesses two mechanisms for the removal of unwanted chemicals from the body. In general these unwanted substances are lipophilic in nature and are therefore difficult to transport across cell membranes for excretion. The liver can chemically alter the compound by either an oxidation reaction (Phase I), or a conjugation reaction which adds a small molecule (Phase II).

These reactions have the effect of making the compound more polar or water soluble, thereby allowing it to be more easily excreted in the urine or bile. This biotransformation process occurs for a great number of xenobiotics such as enterotoxins (potentially toxic chemicals endogenously generated by gut bacteria), endobiotics (intermediate/end products of normal metabolism/enzymolysis etc), and exotoxins (ingested, inhaled and absorbed toxic chemicals).

Hepatic and cellular detoxification is basically the action of taking fat-soluble toxic materials and making them more polar or water-soluble in order to be excreted from the body. The process of biotransformation (i.e. detoxification) of drugs, xenobiotics (compounds entering the body from the outside environment) and endogenous substances which are produced within the body (e.g. stress hormones) are all carried out by the body's enzymatic detoxification pathways (Podolsky, et. al., 1994).

Phase I reactions are mixed function oxidase reactions, which are managed, by a large family of enzymes called the Cytochrome P450 group.

Phase II these reactions involve the addition of a small polar molecule to the chemical. This conjugation step may or may not be preceded by a Phase 1 reaction. The conjugation molecules are acted upon by specific enzymes to catalyse the reaction step. Molecules used by the liver for this purpose include glutathione, sulphate, glycine, acetate, cysteine and glucuronic acid. Adequate amounts of these



Source - Bland, J, et al., (1999). Clinical Nutrition: A Functional Approach. IFM.USA.

molecules are necessary for proper detoxification ability.

Clinical Relevance of the FLDP

Research into the detoxification processes shows that the function of the enzymes that control the Phase I and Phase II processes may vary significantly from person to person (Patel et. al., 1992). So this means an individual's functional capacity to detoxify toxic materials can present in different forms. This can relate to factors such as inherited or genetic strengths and weaknesses in a person's biochemical pathways, which can be either improved or slowed down, by many environmental or nutritional factors.

This to some extent genetic, biochemical basis for the wide-ranging detoxification capacities may explain the diverse responses individuals have when exposed to chemicals, drugs and even foods that many individuals may find they have adverse reactions to.

The Cytochrome P450 enzyme systems that carry out this detoxification process are a large family of isoenzymes also known as mixed-function-oxidase enzymes. They organize the biotransformation or conversion of fat-soluble substances, such as petrol fumes inhaled while at the service station or medication and recreational drugs, and convert them into intermediate compounds that have increased water solubility.

These enzymes provide the body with its ability to process and remove compounds that could change or even damage the function of cells. It is perhaps understandable that many types of these enzymes are concentrated in the mitochondria or energy-producing component of our body's cells.

With mitochondria present in muscle cells, nerve cells and brain tissue as well as cells in all the body's organs, it could be expected that a build up of any compounds capable of affecting tissue function by either slowing or speeding up mitochondrial performance could exert a profound effect on an individual's health.

Why Liver Testing Best Reflects Detoxification Ability

The most effective form of evaluating the body's ability to detoxify both exogenous (from the external environment) and endogenous (produced within the body) compounds are to test liver function using up to date and appropriate pathology testing.

The mixed-function oxidase activity found in the liver allows lipid-soluble compounds to be transformed into a water-soluble compound, which then allows for it to be removed via the pathway created by water entering and then leaving the body.

Liver Function Evaluation

The standard general pathology liver function test (LFT) is limited to its evaluation of liver enzymes and does not provide any information on liver detoxification. To establish or truly evaluate liver function the LFT is medically of little use.

This was clearly highlighted by Professor Eddlestone years ago in the Oxford Textbook of Medicine (Eddleston, 1984, Sect. 12 p. 196) when he pointed out while the standard tests "routinely used as indices of liver damage are usually referred to as liver function tests, most are not true tests of function but rather reflect hepatocellular damage or cholestasis".

To test this function in detail is important, as without proper enzyme function the liver will be less able to excrete substances such as hormones, drugs and other chemicals, which may significantly affect an individual's health status. Impaired Phase II pathways may influence or impair the metabolism of hundreds of different xenobiotics or drugs and substances of dietary or endogenous origin.

Example of LFT and FLDP Findings

47 year old male presented with:

- Exhaustion over 2 months
- Systemic lymphatic swelling
- Ultrasound showed liver, kidneys & spleen normal
- LFT also showed no abnormal readings
- FLDP showed significantly abnormal Phase 1

Typical symptoms associated with suboptimal liver detoxificaiton

- Chronically recurring infections
- Muscle weakness or pain
- Headaches or migraine
- Chronic tiredness
- Digestive discomfort, loss of appetite
- Nausea
- Abdominal bloating
- Intolerance to fatty foods
- Multiple chemical sensitivities
- Hormonal imbalances

General Information

Test Principle

Low doses of Caffeine, Aspirin and Paracetamol are taken orally. Saliva and urine samples are collected at timed intervals and returned to the laboratory for analysis.

Patients

Once the patient has a request form from their practitioner they contact ARL on 1300 55 44 80 to order a specific collection kit. The kit will be sent directly to the patient via courier.

Collection kits

The functional pathology tests available are non-invasive and designed for the patient to collect specimens in the privacy of their home. This also allows for multiple specimen collection over a period of days if necessary. These kits can be dispatched anywhere within Australasia.

The collection kit contains easy-to-follow instructions and a pre-paid airfreight satchel for its return to the laboratory.

Results

Patient results can be mailed, faxed or electronically downloaded to practitioners.

Practitioner support

ARL has Regional Mangers in NSW, QLD and Victoria who are always available for technical advice, education, clinical discussion, result interpretation and on-going practitioner support.

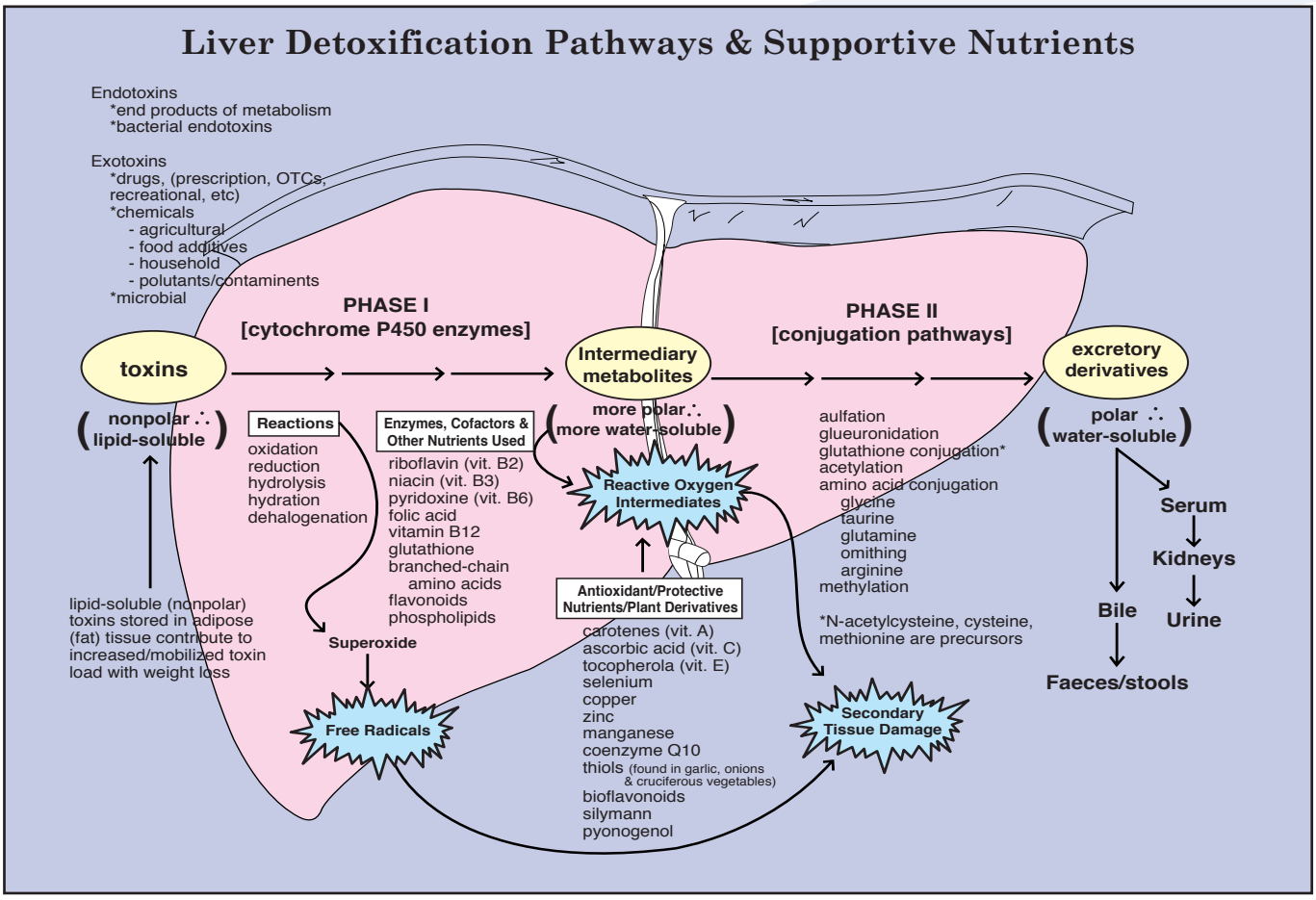
More information

From within Australia call 1300 55 44 80 to find out more information. If calling from overseas call 61 3 9529 2922.

Web and email

ARL continually updates its web information pages, which can be accessed at www.arlaus.com.au

All email enquiries to info@arlaus.com.au



PHASE I REGULATION

B2, B3, B6, B12 and folate. Glutathione (glycine, glutamine and cysteine) or NAC. Branched chain amino acids (leucine, isoleucine and valine).
Selenium.
Vitamins C, E, CoEnzyme Q10.
Bioflavonoids (quercetin, green tea catechin, silymarin, Ginkgo).
Naringenin (glycoside found in grapefruit juice) will slow Phase 1 down in the gut.

INTERMEDIATE

Vitamins A, C & E, CoEnzyme Q10 Zinc, Selenium, Magnesium, Manganese.

* Up-regulation of Phase 1 will cause an increase in free radical production and activity.
Antioxidents will help prevent cellular damage caused by free radicals.

PHASE II REGULATION

GLUTATHIONATION - N-acetyl cystein (precursor to GSH synthesis and enhances glutathion-S-transferase activity); also supports sulphation conjugation (sulphur donor), Glutamine and Glycine.
Selenium. B6, B12, Folate.
Carnosol and camosic acid (Rosemary), Curcumin (may inhibit Phase I - use only when Phase I is normal).
Indole-3-Carbinol.

SULPHATION - Sulphur containing amino acids (cysteine, cystine, methionine and taurine), Vitamin A, Adequate protein, Garlic and onions, Sodium sulphate.

GLUCURONIDATION - Calcium d-glucerate, Magnesium, Essential fatty acids.

GLYCINATION - Glycine, glutamine, gluceronic acid, ornithine and arginine.

Glycine, glutamine, arginine, ornithine and taurine are used in amino acid conjugation.

The biotransformatin of homocysteine to methionine is supported by methyl donors (methionine conjugation), such as betaine, folic acid and adenoslcobalamin.

Sample report:

FUNCTIONAL LIVER DETOXIFICATION PROFILE (FLDP)

	Within Ref. Range	Outside Ref. Range	Ref. Range
Phase I			
Caffeine Clearance		4.2 H	0.5 - 1.6 ml/min/Kg
Phase II	% Recover	% Recover	
Glutathionation		0.9% (L)	5.6 - 11.4
Sulphation		4% (L)	16 - 36
Glucuronidation		10% (L)	27 - 56
Glycination		11% (L)	30 - 53
Ratios			
Sulphate: Creatinine	1.4		1.0 - 3.0
Phase I: Glycination		39.4 (H)	1.3 - 3.5
Phase I: Glucuronide		43.8 (H)	1.9 - 4.2
Sulphate: Glucuronide	0.5		0.3 - 0.7
Phase I: Sulphation		96.2 (H)	3.5 - 13.0

RESULTS LEGEND

NA = Not Able to Assay N/ = Not Applicable NG = Not Given
ND = Not Detected (L) = Low Result (H) = High

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