Introduction

Gonadal function is significantly affected in many chronic systemic diseases. Hepatic cirrhosis is associated with hypogonadism and signs of feminization. Testicular atrophy, low testosterone levels, decreased libido, infertility, reduced secondary sex hair and gynecomastia are found in men with cirrhosis. Fifty percent of patients with cirrhosis present reduced spermatogenesis and peritubular fibrosis ***(Karagiannis & Harsoulis, 2005).*** Sexual Dysfunction (SD) is highly prevalent among men with chronic liver disease, and negatively impacts Health-Related Quality of Life (HRQOL) in those patients ***(Danoff et al., 2006).***

In cirrhotic patients, the estrogen/androgen ratio is usually increased. The levels of testosterone and dihydroepiandrosterone are reduced, while the estradiol levels are normal or slightly elevated. These alterations are dependent on the severity of the liver disease and are more pronounced in patients with higher Child–Pugh score ***(Terasaki et al., 1988).***

Several other factors may contribute to these hormonal changes in cirrhosis, including hepatic overproduction of sex hormone binding globulin (SHBG), changed SHBG isoforms

with different steroid-binding affinities, elevated prolactin levels, direct suppression of Leydig cell function by estrogens, increased estrogen receptors in the liver and cyclic variation in the severity of the liver illness producing the hormonal changes of gynecomastia. It must be kept in mind that the gynecomastia and impotence of cirrhotics are augmented by the chronic use of spironolactone, a receptor antagonist of aldosterone and testosterone, which reduces the testosterone levels and slightly increases the levels of estradiol ***(Karagiannis & Harsoulis, 2005).***

Aim of Work

The aim of this work is to assess changes of levels of sex hormones in decompensated chronic liver disease patients and its reflection on clinical findings.

Chapter (I)

Liver Functions

Introduction:

The liver is the largest organ of the body weighting three to five pounds in adults. It uses 12-20% of the total energy of the body. The liver routinely performs many known functions to regulate cellular metabolism. It is the chemical wizard of the body, transforming toxins into harmless chemicals for excretion, and also transforms digestively absorbed nutrients into the proper biochemical forms that can be used by cells. Yet the liver is probably the organ most assaulted by toxins, pollution, stress, junk foods, drugs, etc ***(Diehl, 1993).***

(A) Liver Functions:

(I) Metabolic Functions:

(A) Carbohydrate Metabolism:

1. The liver serves as the main glucose buffer, preventing high or low extremes of blood sugar: It is the key regulator of blood sugar between meals, due to its manufacture, storage and release of glycogen. Glycogen is the starch form of glucose in which the body can store. When the blood sugar is low, a healthy liver converts stored glycogen into glucose, releasing it

into the bloodstream to raise blood sugar levels. When blood sugar is to high, the healthy liver will remove much of it, converting the excess into stored glycogen or fat ***(Campbell, 2006).***

2. The liver can make glucose from dietary or body-derived amino acids: This process is called gluconeogenesis; it ensures adequate brain and muscle carbohydrate fuel supplies even when the diet provides little or no carbohydrates. The liver produces as much as 20-25% of the blood sugar athlete's muscles might burn during intense training by converting the amino acid alanine (released from muscle tissue) into glucose ***(Tso and McGill, 2008).***

3. The liver converts lactic acid from a toxic waste to an important storage fuel: Lactic acid is produced when glucose is metabolized through the glycolytic energy production cycle, and may irritate nerves and muscles if it accumulates to excessive levels. However, a healthy liver extracts lactic acid dumped into the bloodstream by hard-working muscles and converts it into the important reserve fuel glycogen ***(Tso and McGill, 2008).***

(B) Protein Metabolism:

The liver is the chief regulator of protein metabolism: It converts different amino acids into each other as needed. The

liver also synthesizes creatine from the amino acids glycerin, arginine, and methionine ***(Mitra and Metacalf, 2009).***

(C) Lipid Metabolism:

The liver produces cholesterol and packages it into different forms for blood transport: HDL, LDL and VLDL. Essential fatty acids, such as linoleic acid, must also be properly packaged by the liver into appropriate lipoprotein forms (VLDL) to allow transport through the blood for using them ***(Tso and Mc Gill, 2008).***

(D) Hormonal Metabolism:

1. The liver converts the thyroid hormone thyroxin (T4) into its more active form tri-iodothyronine (T3): Thyroid hormones act as the body's thermostat, regulating the rate at which virtually all biochemical reactions occur in the body. Inadequate conversion of T4 to T3 by the liver may lead energy-depleting hypothyroidism, leading to chronic fatigue, weight gain and poor memory ***(Daher et al., 2009).***

2. The liver creates Glucose Tolerance Factor (GTF) from chromium, niacin and possibly glutathione: GTF is needed for the hormone insulin to properly regulate blood-sugar levels. Due to its critical role in facilitating amino acid entry into muscle cells, GTF is also a necessary co-factor for Growth

Hormone to be effective in promoting muscle growth in response to athletic training programs ***(Mertz, 2009).***

3. The liver is the main organ for breaking down hormones after they have served their messenger function to their target cells: For example, if the liver does not break down insulin quickly enough, hypoglycemia results as the still circulating insulin continues to lower blood sugar. If the liver does not metabolize estrogen properly, Pre-Menstrual Syndrome **(PMS)** will result. Failure to dispose of adrenaline (the "fight" or" flight" hormone) after it has outlived its usefulness may lead to chronic irritability and temper explosions ***(Tso and McGill, 2008).***

(II) Synthetic Functions:

1. The liver manufactures bile salts: These are used to emulsify fat for absorption. The liver also removes some fat-soluble toxins from the body by first dissolving them in bile salts, then dumping the bile and toxin mixture into the intestine for eventual fecal excretion ***(Hofman, 1999).***

2. The liver manufactures carnitine from lysine and other nutrients: Carnitine is the only known bionutrient which can transport fats into the mitochondria, where the fats may be "burned" to generate ATP bio-energy. It is also necessary to get

branched chain amino acids (BCAA) into the mitochondria. BCAA supplied either from breaking down existing muscle tissues or supplements, are known to provide a major protein for muscle cell fuel needs during prolonged, intense athletic training ***(Rassoul et al., 2005).***

3. The liver synthesizes plasma proteins, including those necessary for blood clotting: Most of the 12 clotting factors are plasma proteins produced by the liver. If the liver is damaged or diseased, it can take longer for the body to form clots. Other plasma proteins produced by the liver include albumin which binds many water-insoluble substances and contributes to osmotic pressure, fibrinogen which is the key of the clotting process, and certain globulins which transport substances such as cholesterol and iron ***(Tripodi et al., 2009).***

(III) Detoxification Functions:

1. The liver is the main poison-detoxifying organ in the body: It breaks down everything toxic to the body, from metabolic wastes, to insecticide residues, drugs, alcohol industrial and food processing chemicals, etc. Failure of this function will usually cause death in twelve to twenty-four hours. The liver uses a relatively small number of enzyme-systems - called "Mixed Function Oxidases" - to detoxify the

10.000 or more chemicals polluting food, air, and water ***(Mitra and Metacalf, 2009).***

2. The liver must dispose of ammonia, an extremely toxic by-product of protein metabolism: The amino acids arginine and orthinine are used by the liver to control ammonia levels. Ammonia can cause brain irritation and even death, at surprisingly low levels ***(Campbell, 2006).***

(IV) Bioactivation Functions:

The liver activates vitamins and minerals into their biologically active coenzyme forms: B1 must be activated into thiamin pyrophosphate, B2 into flavine adenine dinucleotide, B3 into nicotinadenine dinucleotide, etc. The plant vitamin A precursor beta-carotene must be turned into real vitamin A. Other nutrients, such as iron and copper, must be changed by the liver into their appropriate bloodstream transport or storage forms, such as ferritin or ceruloplasmin. Virtually every nutrient, whether it is vitamin or mineral, must be biotransformed into its proper biochemical form in which the nutrient may be stored, transported or used in cellular metabolism. If the liver does not properly activate nutrients into their bioactive forms, then even the most well-absorbed,

high potency, broad spectrum supplement will be useless ***(Tso and McGill, 2008).***

(V) Storage Functions:

The liver stores various nutrients, especially A, D, B12 and iron, for release when needed ***(Tso and McGill, 2008).***

(VI) Immunological Functions: -

The liver produces immune factors and removes bacteria helping the body to fight infection: The phagocytes in the liver produce acute-phase proteins in response to microbes. These proteins are associated with the inflammation process, tissue repair, and immune cell activities ***(Knolle and Gerken, 2002).***

(VII) Excretory Functions:

The liver Removes and excretes body wastes and hormones as well as drugs and foreign body substances: These substances have entered the blood either through production by metabolism within the body or from the outside; in the form of drugs or other foreign compounds. Enzymes in the liver alter some toxins so they can be more easily excreted in urine ***(Richen andPaumgartner, 1980).***

Table (1): The liver functions

Metabolism	Glucose
	Proteins
	Fat and Cholesterol
	Hormones
	Vitamins, in particular fat-soluble ones (A, D, E, K)
Synthesis	Proteins including the clotting factors
	Bile acids
	Heparin (anti-coagulant)
	Somatomedins (hormones that promote growth in bone, soft tissues)
	Estrogen
	Angiotensinogen
	Cholesterol
	Acute phase proteins
Storage	Vitamins
	Glycogen
	Cholesterol
	Iron, Copper
	Fats
Excretion	Cholesterol, Bile Acids, Phospholipids
	Bilirubin
	Drugs
	Poisons including heavy metals
	Hormones
Detoxification	Poisons
	Nutrients including amino acids, sugars, and fats
	Bilirubin, Bile Acids
	IgA
	Drugs
	Dead or damaged cells in circulatory system
Immune	Excretes IgA into digestive tract
	Kupffer cells (macrophages) filter out antigens

(Sherwood, 2008)

(B) Who are at Risk for Liver Dysfunction? *(Tajimai et al., 1998):*

1. ***People routinely consuming large amounts of overheated, hydrogenated, "junk food" fats*:** For example, French fries, fried chicken, doughnuts, chips, etc. These heated "junk foods" are a major source of liver-toxic lipid peroxides (rancid fats) and trans-fatty acids (abnormal structure fats). Lipid peroxides are powerfully immuno-suppressive, and damage liver cell membranes. Trans-fatty acids suppress production of prostaglandin E1 (PGE1), a major liver-protecting anti-inflammatory prostaglandin.

2. *Coffee drinkers*. Carcinogenic hydrocarbons are produced during roasting. It is also may be sprayed by some pesticides.

3. *Regular alcohol users*. The liver converts alcohol into toxic acetaldehyde during its alcohol detoxification process. Acetaldehyde inhibits PGE1 production, is a powerful free radical inducer, and is largely responsible for the liver, brain, heart, kidney, skin and blood vessels lining damage associated with chronic alcoholism.

4. ***Smokers*.** While many people are aware of smoking's negative effect on the lungs, less consideration is usually given to its effects on the liver. Tobacco and marijuana smoke are rich airborne stews of toxic benzpyrene, polycyclic aromatic hydrocarbons, cyanide, acetaldehyde, tars, acrolein, etc. Since

these get into the bloodstream through the lungs, the liver must detoxify them. And all the constituents of smoke are known to be at least mildly liver-damaging.

5. ***People regularly driving on crowded, exhaust-filled roads and highways.*** Auto and diesel exhaust contain dozens of liver damaging poisons including lead, sulfur, nitrogen oxides, acetaldehyde, cadmium, and peroxyacetylnitrite.

6. ***Women using birth-control pills.*** In some cases, even as little as two or three weeks of use have been documented to affect the liver. The livers of women on vitamin B/protein deficient diets may have difficulty metabolizing estrogen into non-toxic estriol, leaving it instead in the form of liver toxic estradiol.

7. ***Candida Patients.*** Candida yeast ferments dietary sugars into liver-toxic acetaldehyde in the process of turning sugar into energy. Candida also seems to increase gut and urinary levels of ammonia, another liver toxin.

8. ***Arthritis, rheumatism and other chronic pain sufferers who frequently use analgesics.***

9. ***Farm workers and pest control workers who are routinely exposed to higher than normal levels of pesticides.*** Pesticides such as DDT, Aldrin, chlordane, lindane, 2,4,5 T-dioxin, and toxaphene can cause chronic liver damage, even at body levels

measured in parts per billion, and tend to accumulate in body fat over time.

10. ***Industrial and service workers routinely exposed to heavy metals*** (lead, cadmium, and mercury), radioactive chemicals, hydrocarbon solvents such as sulfuric acid and mixes like paint sprays.

11. ***Gas station workers and auto mechanics*****.** Gasoline, diesel fuel, motor oil and degreasing agents are all liver toxic and may be absorbed through the skin or by inhaling them.

12. ***Athletes using anabolic-synthetic variations of male hormone testosterone*****.** Serious liver damage is a medically recognized major side effect of chronic steroid abuse**.**

Chapter (II)

SEX HORMONE BINDING GLOBULIN (SHBG)

Introduction:

Sex hormone binding globulin (SHBG): is a multifunctional protein that acts in humans to regulate the response to steroids at several sites. It was originally described. as a hepatically secreted protein that is the major binding protein for sex steroids in plasma, thereby regulating the availability. of free steroids to hormone-responsive tissues. SHBG also functions as part of a novel steroid-signaling system that is independent of the classical intracellular steroid receptors. Unlike the intracellular steroid receptors that are ligand-activated transcription factors, SHBG mediates androgen and estrogen signaling at the cell membrane of cyclic AMP (c.AMP) ***(Khan et al., 2002).***

Biologic availability of androgens is related to the concentration of SHBG. Only free androgens and those non-specifically bound to circulating albumin are able to enter tissues and produce biologic effects. SHBG has the greatest affinity for dihydrotestosterone (DHT), then for testosterone,