INTRODUCTION

Ghrelin is an endogenous ligand of the growth hormone secretagogue receptor and a potent stimulator of growth hormone release in humans. Ghrelin is synthesized primarily by the stomach, and in substantially lower amounts by the bowel, pituitary, kidney, placenta and hypothalamus ***(Kojima et al., 2005).***

Ghrelin anticipates the initiation of meals and releases GH (growth hormone), it has been postulated that ghrelin integrates anabolic changes in the body. In catabolic situations like in cirrhosis, raised ghrelin levels may induce a combination of enhanced food intake, increased gastric emptying and food assimilation ***(Ataseven et al., 2006).***

Chronic liver disease (CLD) and cirrhosis are two of the most important health problems according to the current gastroenterology literature ***(Krimaz and Terzioglu, 2004).*** CLD are common pediatric proplems in children in developing countries ***(Debells and Lester, 1980).***

Chronic liver disease (CLD) is characterized by numerous metabolic alterations, predominantly catabolic, resulting in the clinical picture of malnutrition or even cachexia and contributing to complications such as hepatic encephalopathy ***(Tack et al., 2003).***

The mechanisms of malnutrition in chronic liver disease are not completely understood. Both poor dietary intake and increased basal energy expenditure have been reported to contribute to a negative energy balance in patients with chronic liver disease ***(Kalaitzakis et al., 2006).***

Liver cirrhosis exhibits a characteristic malnutrition status; protein energy malnutrition (PEM). Patients with liver cirrhosis often developed anorexia and exhibit body weight and muscular loss, thus resulting in PEM. Because ghrelin is one of the key hormones in regulating feeding behavior and calorie status, it is considered that ghrelin behavior may be closely associated with PEM in patients with liver cirrhosis ***(Hiroya Takahashi et al., 2006).***

In cirrhotic patients, liver failure causes both decreased protein synthesis and enhanced protein breakdown, which together with anorexia and reduced food intake can lead to severe protein energy malnutrition and limit the capacity for regeneration and functional recovery of the liver ***(Ataseven et al., 2006).***

There was a debate about the significance of studying the serum ghrelin level in patients with chronic liver disease as some reports showed some significance of studying ghrelin and some said it is of no significance ***(Tacke et al., 2003).***

Plasma ghrelin levels reflect the malnutrition state of patients with chronic liver disease, plasma ghrelin levels were significantly correlated with anthropometric parameters ***(Hiroya Takahashi et al., 2005)*.**

AIM OF THE WORK

The aim of the present study is to assess the serum levels of ghrelin in children with chronic liver diseases and to clarify their correlation with different nutritional parameters.

Chapter (1)
CHRONIC LIVER DISEASES IN PEDIATRICS

Definition:

Chronic liver diseases (CLD) in children are relatively common disorders with minimal symptoms but long-term risk of significant morbidity and mortality particularly in developing countries. They are defined by continuity of clinical 6 months ***(Suchy, 2007).***

CLD may be either active or inactive, depending on the presence of biochemical or histological evidence of hepatocellular necrosis, apoptosis and inflammation; and either compensated or decompensated, depending on the presence of clinical or laboratory features of liver failure. Chronic hepatic injury may progress to cirrhosis and predisposes to hepatocellular carcinoma (HCC) ***(Sherlock and Dooley, 2000).***

Etiology of chronic liver diseases in children:

1. Genetic disorders (Metabolic disorders):

- ***Disorders of carbohydrate metabolism e.g.***

  - Galactosemia.

  - Fructosemia.

  - Glycogen storage disease type III and IV.

- ***Disorders of lipid metabolism e.g.***

  - Gaucher disease.
  - Neimann Pick type C.
  - Wolman disease.

- ***Disorders of aminoacid metabolism e.g.***

  - Tyrosinemia and cystinosis.

- ***Disorders of mineral metabolism e.g.***

  - Wilson disease.
  - Neonatal iron storage disease.
  - Infantile copper overload.

- ***Other metabolic Disorders e.g.***

  - α-1 antitrypsin deficiency.
  - Cystic fibrosis.
  - Byler disease.
  - Zellweger syndrome.
  - Hepatic porphyria.

2. Infectious disorders e.g.

- Viral: hepatitis B, C and D and cytomegalovirus.
- Bacterial: T.B. and syphilis.
- Parasitic: schistosoma and fasciola.

3. Vascular disorders e.g.

- Veno-occlusive disease.
- Budd-chiari syndrome.
- Constrictive pericarditis.
- Heart failure.

4. Drugs and toxins e.g.

- Aflatoxins.
- Isoniazide.
- Sulphonamides.
- α-methyl dopa.
- Carbon tetrachloride.

5. Hematological disorders e.g.

- Sickle cell anemia.
- Leukemia.
- Lymphoma.
- Myeloproliferative disease.
- Histiocytosis.

6. Biliary disorders e.g.

- Biliary atresia.
- Choledocal cyst.

- Alagille syndrome.
- Choledocolithiasis.
- Sclerosing cholangitis.

7. Immunological disorders e.g.

-Autoimmune hepatitis.

- Lupus erythematosis.

- Sarcoidosis.

- Inflammatory bowel disease.

(Shepard, 2004)

Pathogenesis of chronic liver diseases:

Dysregulation of apoptosis occurs in a wide spectrum of liver diseases for example; in viral infection, neoplasia, inflammatory, toxic injury and metabolic disorders. An understanding of the cellular mechanism of apoptosis and its dysregulation during pathophysiologic disturbance will help in understanding liver diseases ***(Patel, 2000).***

Apoptosis has a highly characteristic morphologic feature. Cells undergoing apoptosis shrink and detach from adjacent cells. The cytoplasm invaginates and forms blebs which may include intact organelles. Within the nucleus, chromatin condenses around the nuclear membrane and subsequently the nucleus fragments. Eventually, the cell

disintegrates and multiple membrane bound apoptotic bodies are formed. Those bodies are rapidly phagocytosed by neighbouring cells or by Kuppfer cells in the liver ***(Krams and Martinez, 2001).***

This process differs from cell necrosis in that it is actively controlled and the integrity of the plasma membrane is maintained thus, leakage of the intracellular contents is avoided and an inflammatory response is usually not elicited. The typical morphologic changes of apoptosis are accompanied by distinct biochemical events, such as alterations in the plasma membrane and activation of proteases and endonucleases, which results in cleavage of specific proteins and DNA ***(Patel, 2000).***

Apoptotic fragments which are not phagocytosed undergo secondary necrosis, and the subsequent extracellular leakage of the intracellular contents may elicit an inflammatory response. Thus, elevation in serum aminotransferases, a common clinical marker of liver injury, can reflect increased apoptosis as well as necrosis in the liver ***(Tsujimoto et al., 2001).***

Dysregulation of Apoptosis in liver diseases:

Increased apoptosis:

- Viral hepatitis.
- Cholestatic liver diseases.

- Immune-mediated diseases.
- Drugs and toxins induced diseases.
- Metabolic disorders.
- Others (hypoxia and ischemia).

Decreased apoptosis:

Malignancy (hepatocellular carcinoma and cholangiocarcinoma).

The identification of target molecules involved in apoptosis raises the prospect of pharmacologic modulation that may result in better treatment options for patients with liver diseases. Inhibition of apoptosis is likely to be useful in treating fulminant hepatic failure or in organ preservation before transplantation. In these situations, treatment is for a limited period, and the potential hazards of nonselective long-term inhibition of apoptosis are minimized. Safe and organ-specific inhibition of apoptosis would be required for prolonged treatment of chronic liver diseases. The rapid advances in understanding of the intracellular mechanisms and the regulation of apoptosis will ultimately result in a better understanding of the role of apoptosis in the pathophysiology of liver diseases and may allow therapeutic modulation of this process ***(Patel, 2000).***

Pathological findings in chronic liver diseases:

There are multiple patterns of reactions of the liver to cell injury which may be inflammation or necrosis, which may be followed by healing process of fibrosis and regeneration nodules formation. Cirrhosis is the end result of any progressive liver disease ***(Squires, 2007).***

1- **Inflammation and/or necrosis:** Caused by viral infections, drugs or toxins, immunologic disorders and hypoxia ***(Squires, 2007).***

2- **Cholestasis:** is an alternative or concomitant response to injury, caused by extrahepatic or intrahepatic bile flow obstruction ***(Squires, 2007).***

3- **Fibrosis:** due to increased synthesis of collagen and the increase in the number of collagen producing cells (fibroblasts). This contains collagen I, III and IV, fibronectin, large glycoproteins and proteoglycans. In the normal liver; hepatocytes, fat-storing cells and endothelial cells produce the extracellular matrix. In fibrosis; hepatocytes, which normally do not synthesize type III and IV collagen, may produce them ***(Clement et al., 2007).***

4- **Cirrhosis:** defined histologically by the presence of bands of fibrous tissue that link central and portal areas and form parenchymal nodules distorting the normal hepatic

architecture. It is a potential end stage of any acute or chronic liver disease. It may be post-hepatitic, post-necrotic (after toxic injury) or may follow chronic biliary obstruction (biliary cirrhosis). Cirrhosis results in altered hepatic blood flow and so more impairement of liver cell function, in addition to the development of portal hypertension ***(Garcia et al., 2007).***

Clinical findings in chronic liver diseases:

1. **Hepatomegaly:** (enlargement of the liver) can be due to several mechanisms:

I- Increase in the number or size of the cells in the liver; due to storage (such as lipid storage diseases e.g. Gaucher and Niemann-pick, glycogen storage diseases, miscellaneous e.g. Wilson disease and α-1 antitrypsin deficiency), Inflammation e.g.(viral hepatitis) and Infilteration e.g. liver tumours; either benign or malignant, primary or metastatic.

II- Increased size of vascular space; due to, Intrahepatic obstruction to hepatic vein outflow e.g. veno-occlusive disease and Budd-chiari syndrome. And can be due to suprahepatic disorders e.g. congestive heart failure and constrictive pericarditis.

III- Increased size of biliary space e.g. congenital hepatic fibrosis.

IV- Idiopathic hepatomegaly.

2. **Jaundice:** clinically apparent jaundice in children occurs when the serum bilirubin reaches 2-3 mg/dl. Jaundice may be the earliest and the only sign of hepatic dysfunction.

3. **Pruritis:** intense generalized itching may occur in patients with cholestasis and end-stage liver diseases.

4. **Spider angiomas:** central pulsating arterioles from which small wiry venules radiate, Usually on the face and chest.

5. **Palmar erythema:** over the thenar and hypothenar eminences and tips of fingers.

6. **Xanthomas:** brown nodules on the extensor surface of the extremities due to elevation of serum cholesterol level above 500 mg/dl. Rarely, xanthelasma of eyelids develop.

7. **Hepato-renal syndrome:** functional renal failure in patients with end stage liver disease ***(Fitz, 2006).***

8. **Portal hypertension:** is the main complication of cirrhosis and manifests by visceral hemorrhage and ascites.

9. **Hepato-pulmonary syndrome:** triad of hypoxemia, intrapulmonary vascular dilatations and liver disease.

10. **Recurrent cholangitis:** ascending infection of biliary system in cholestatic liver diseases, most commonly due to gram negative enteric organisms as E. coli.

11. **Malnutrition**.

(Shepard, 2004).

Investigations of chronic liver diseases:

Diagnosis is essentially a stepwise process, involving a range of clinical, laboratory, radiological imaging, and pathological investigations for: confirming the presence and type of liver disease, determining the etiology and assessing the extent of complications ***(Younossi et al., 2005).***

I- General:

A. Hematology: Serum Bilirubin. (Total and direct), Complete blood picture, Aminotransferase level, Prothrombin time, Gamma glutamyl transferase, Alkaline phosphatase, Albumin. Cholesterol, Urea and creatinine, Ammonia and Alpha-fetoprotein.

B. Chest X-ray.

C. Hepatobiliary and renal ultrasound.

D. Upper gastrointestinal endoscopy.

E. Electrocardiogram.

F. Liver biopsy.

II- Specific (for diagnosis):

A) Biliary:

Operative cholangiogram, Endoscopic retrograde cholangiopanceatography (ERCP) and Hepatobiliary scans.

B) Hepatic:

- Viral serology [Toxoplasmosis, Rubella virus, Cytomegalovirus and Herpes (TORCH), Hepatitis B virus, Hepatitis C virus and Epstein-Barr virus (EBV)].
- Autoimmune antibodies (Antinuclear antibody (ANA), Antimitochondrial antibody (AMA), Antiactin smooth muscle antibody (ASMA), and Liver kidney microsomal antibody LKM), immunoglobulin.
- Liver copper or iron deposition.
- Urinary sugars, amino acids, organic acids, porphyrins, fatty acid degeneration products.
- Blood sugar (fasting), lactate, pyruvate, urate.
- Serum amino acids, copper, ceruloplasmin.
- Alpha l-antitrypsin, iron, ferttin, bile acids.
- Serum creatinine phsophokinase (CPK).