IMPACT OF LIVER TRANSPLANTATION ON NUTRITIONAL STATUS OF CHRONIC LIVER DISEASE EGYPTIAN PATIENTS

Thesis

Submitted for Partial Fulfillment of Master Degree
in Tropical Medicine

Submitted by

Dina Magdy Ahmed
M.B., B.Ch,

Under Supervision of

Prof. Dr. Waheed Abd El-monsef Mahmoud

Professor of Tropical Medicine
Ain Shams University

Prof. Dr. Ibrahim Mostafa Ibrahim

Professor of Tropical Medicine
Theodor Bilharz research Institute

Dr.Doaa Zakaria Zaky

Lecturer of Tropical Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University
2014

دراسة متقدمة عن مدى تأثير عملية زراعة الكبد من الاحياء فى المرضى المصريين الذين يعانون من امراض الكبد المزمنة على الوضع الغذائى

رسالة

توطئة للحصول على درجة الماجستير
فى طب المناطق الحارة و صحتها

مقدمة من

دينـــا مجـــدى أحمـــــد
بكالوريوس طب والجراحة
جامعة عين شمس

تحت إشراف

أ.د./ وحيد عبد المنصف محمود
أستاذ، طب المناطق الحارة
جامعة عين شمس

أ.د./ ابراهيم مصطفى ابراهيم
أستاذ، الجهاز الهضمى والكبد
معهد تيودور بلهارس للابحاث

د./دعـــاء زكريـا زكـــى
مدرس، طب المناطق الحارة
جامعة عين شمس

كليـــة الطـــب
جامعة عين شمس
2014

INTRODUCTION

Liver transplantation is a lifesaving procedure for patients who have chronic end-stage liver disease and acute liver failure***(Yu et al., 2003).***

The most common indications for liver transplantation in the United States are hepatitis C virus (30%)(***Middleton et al., 2006).***

There are 3 types of liver transplantation that are practiced in the world. They are cadaveric, live donor and split-liver/ reduced size transplant &there are options of liver transplant called Auxiliary liver transplantation, domino liver transplantation, hepatocyte liver transplantation and xenotransplantation which exists in occasional patients***(Sherlock 2012)***. In Egypt, the use of cadaveric donors is still prohibited, forcing some capable patients to seek this service abroad. Thus, to date, LDLT is the only possible option for end stage liver disease patients in Egypt***(EL-Meteini et al., 2003).***

Organs from living donors offer many potential advantages over organs from deceased donors. The most important advantages of living donation are that it optimizes the timing of transplantation and frees patients from the waiting list. Secondly preservation time is minimal, so there is significantly less ischemic damage to the liver. Therefore, the quality of the donated liver is much better. Most importantly, LDLT increases the global

pool of transplantable organs, allowing more people to get transplantation as a life-saving therapy***(Nadalin et al., 2007)*.**

The nutritional status of patients with hepatic failure undergoing liver transplant evaluation continues to deteriorate, therefore, once malnutrition is diagnosed, efforts should be made to correct any vitamin and mineral deficiencies present and prevent further complications ***(Hasse, 1990).*** The main purpose of nutritional support before liver transplantation is to prevent further nutrient and muscle depletion.Improvement in nutritional status influences liver metabolism and immune status and may decrease the risk of infection ***(Campos et al., 2002).***

Nutrition assessment and therapy in end-stage liver disease has become increasingly important with the advent of living donor liver transplantation. Reduced lean body mass, increased risk of sepsis, and altered metabolism of carbohydrates, protein, and fat are characteristic of patients with liver dysfunction***(Akerman PA et al., 1993).***

For assessing nutritional status in patients with ESLD on the transplant waiting list, there is One useful, easily applicable, and validated approach is subjective global assessment (SGA). This method integrates a detailed medical and dietary history, body weight and height, coexisting medical conditions, and physical activity to rate patients either “well-nourished”, “moderately malnourished”, or “severely malnourished”. SGA is

highly specific (96%) for the detection of malnutrition in liver transplant candidates***(Hasse et al.,1993).*** Easily applicable techniques include anthropometric measurements such as body mass index (BMI), Mid arm circumference (ranging 23-25.5cm in male & 21-23 cm in female), triceps skin fold thickness (ranging 7.5-12.5mm in male & 10.5- 16.5mm in female|)and mid-arm muscle circumference (MAMC) Values of MAMC below the fifth percentile of a reference population are considered as severely altered and those below the 10th percentile as moderately altered.. MAC & TSF measurements are easy to make. The first reflects muscle mass and the second body fat (MAMC) is derived from mid-arm circumference (MAC) and triceps skin fold thickness (TST). Unfortunately, most of the easily applicable methods are confounded by significant fluid retention in cirrhosis with ascites and peripheral oedema.

So; Nutritionalassessment recommended by the European Society of Parenteral and Enteral nutrition to be adequate in identifying those patients at a risk of malnutrition as following:

- **Anthropometric measurements which include** (body weight, upper arm anthropometry: BMI, TSF, MAC, MAMC).

- **Laboratory assessment which include (lymphocytic count)** which is accurate assessment for immunity status. Account < 1, 000/mL showed immunity incompetence.

- **Functional methods, which include Measurement of handgrip strength (hand dynamometry):**

Measurement of handgrip strength has the advantage of being Simple, quick to perform, inexpensive, and noninvasive. In patients with end stage liver disease, handgrip strength is a sensitive marker of body cell mass depletion, because muscle function indices have been shown to improve with refeeding ***(Stephenson et al., 2001).***

- **Nutritional screening tool which include (the subjective global assessment and the royal free hospital subjective assessment)** ***(Morgan M.Y. et al., 2006).***Royal Free Hospital–Subjective Global Assessment (RFH-SGA), including measures of BMI calculated from estimated dry weight, MAMC, and details of dietary intake. Intakes were categorized as adequate if they met estimated requirements, inadequate if they failed to meet estimated requirements but exceeded 500 kcal/day, or negligible if they provided fewer than 500 kcal/day.

AIM OF THE WORK

The aim of this prospective study is to:

1. Assess the nutritional status of chronic liver disease Egyptian patients before Living Related Liver Transplantation.

2. Assess the impact of Liver Transplantation on nutritional status of chronic liver disease Egyptian patients.

MALNUTRITION IN CHRONIC LIVER DISEASE

Patients with end-stage liver disease (ESLD) frequently have diverse abnormalities of carbohydrate, lipid, and protein metabolism that cause progressive deterioration of their clinical condition and malnutrition.

- **Changes in metabolism in chronic liver disease:-**

The pathophysiology of PEM (protein energy malnutrition) in ESLD is not clearly understood. Patients with ESLD can have altered carbohydrate, lipid, protein, and energy metabolism, which deplete muscle and fat stores, and can be present even before obvious malnutrition develops***(Greco et al., 1998).***

- **Carbohydrates:**

Patients with ESLD may develop glucose intolerance and insulin resistance. The prevalence of diabetes mellitus in cirrhotic patients has been reported to be 38%***(Nishida T et al., 2006).*** Patients with ESLD tend to use fat as a major substrate for energy after fasting and may develop a catabolic state of starvation in the morning because of a lack of glycogen stores***(Yamanaka H et al., 1999).***This "accelerated starvation" phenomenon with increased gluconeogenesis may exacerbate further muscle wasting.

Accelerated starvation phenomenon:

Patients with hepatic failure have "accelerated starvation", with an early recruitment of alternative fuel sources. Cirrhotic patients demonstrate significantly increased fat oxidation and gluconeogenesis with protein catabolism after an overnight fast. It would take a healthy adult approximately 72 hours of starvation to reach the same level of fat oxidation and protein catabolism as occurs in an overnight fast in cirrhotic patients***(Wei-Kuo et al., 1997).*** It is believed that the diminished hepatic and muscle glycogen stores that occurs with cirrhosis is a factor in this accelerated rate of starvation. Patients without adequate glycogen stores utilize increased fat and muscle protein for fuel even during short-term fasting. This contributes to the loss of subcutaneous fat and muscle wasting that the hallmark of malnutrition.

- **Lipids:**

The liver is an important site for lipid metabolism. Patients with ESLD may have impaired synthesis of polyunsaturated fatty acids from their essential fatty acid precursors. Decreased polyunsaturated fatty acids have been associated with the severity of malnutrition in liver disease***(Cabre et al., 1993).***

- **Protein:**

Reduced hepatic synthesis of transport proteins may result in low serum albumin and transferrin values in these patients. Therefore, albumin and transferrin levels are not accurate indicators of visceral protein status in patients with CLDs.

Likewise, reduced synthesis of serum proteins, which can decrease serum oncotic pressure, is the most probable cause of ascites and oedema***(Lieber, 2000).***

Hepatic synthesis of clotting factors is also reduced, interfering with blood coagulation, as evidenced by an abnormal prothrombine time and partial thromplastin time (***Hasse and Matarese, 2000)*.**

Blood urea and nitrogen levels are reduced with increased plasma ammonium levels in liver diseases because of decreased hepatic urea synthesis. The failure to detoxify ammonia and the abnormal amino acid profile (increased aromatic amino acids and decreased branched chain amino acids) seen in patients with cirrhosis may raise their risk of hepatic encephalopathy ***(Kondrup and Müller, 1997).***

Abnormal metabolism of proteins and amino acids is common in patients with ESLD. Increased protein catabolism occurs early in cirrhosis, and protein deficiency worsens as liver disease progresses. Patients with ESLD have an imbalance of branched-chain amino acids (leucine, isoleucine, and valine) and aromatic amino acids (phenylalanine, methionine, and tyrosine). The expected ratio should be 3.5:1; however, this ratio falls to 1:1 in patients with ESLD allowing increased cerebral uptake of aromatic amino acids, promoting the synthesis of false neurotransmitters (octopamine, phenylethylamine, and

phenylethanolamine) which in turn may affect neurocognitive function by competing with endogenous neurotransmitters.

Muscle wasting is an important clinical manifestation of ESLD and is almost always present in patients waiting for LT***(Andersen et al., 1998).*** Patients with chronic liver disease should have adequate protein in their diet, as tolerated, to avoid aggravating protein deficiency.

- **Energy Metabolism:**

Liver transplantation candidates often present with disturbances in body composition and, consequently, in the metabolic rate***(Campos et al., 2002).*** The human body composition is represented by 2 components: lean body mass, and fat mass. Lean body mass is composed of muscle mass, visceral proteins, glycogen, and intracellular water. Body cell mass represents the active metabolic body compartment and is responsible for basal energy expenditure (BEE). Energy expenditure is determined by the measurement of BEE, which can be predicted with several formulas, such as the Harris-Benedict equation, or measured with indirect calorimetry. Measurement of BEE in patients with ESLD is variable, and up to 34% can be hypermetabolic ***(Yamanaka et al., 1999),*** which, in conjunction with a poor nutritional state, has been associated with decreased survival after LT***(Selberg et al., 1997).***

The most common formula to calculate BEE used in clinical practice is the Harris-Benedict equation. For men: 66.5 _ [13.8 _ wt (kg)] _ [5.0 _ height (cm)] _ [6.8 _ age (y)] _ kcal/d. For women: 655.1 _ [9.6 _ wt (kg)] _ [1.8 _ height (cm)] _ [4.7 age (y)] _ kcal/d. Since the formula is based on weight, which may be affected by fluid retention, predicted values based on the Harris-Benedict equation may differ from measured values in patients with ESLD, and its accuracy has been questioned***(Madden AM.1999).***Consequently, BEE should be measured and not predicted in liver transplant candidates with fluid retention manifested by ascites and oedema.

- **Prevalence and Consequences of Nutritional Alterations in Patients With End-stage Liver disease:**

Malnutrition is frequently associated with chronic liver disease: the prevalence may range from 20% to 80% depending on the methods used for the nutritional assessment and the severity of liver disease***(Campillo et al., 2003).*** A large multicenter study has shown that the prevalence of malnutrition is considerably higher in patients with a more severe liver impairment (20–25% in Child A–B patients but >50% in Child C)**.** The correlation between malnutrition and the origin of liver cirrhosis is controversial. Some authors have suggested a higher prevalence of malnutrition in patients with post alcoholic disease***(Caly et al., 2003)***; alcohol abuse may in fact represent a cause of malnutrition per se due to the replacement of nutrient

foods with empty calories, or secondary to the conditions of maldigestion and malabsorption, induced by the reduction of the bile and pancreatic enzyme secretion, which can lead to increase nutrient losses***(DiCecco et al., 2006).*** Malnutrition, however, is not limited to post-alcoholic cirrhosis and a number of studies have demonstrated that the prevalence of malnutrition is similar in patients with non-alcoholic liver disease***(Sarin et al., 1997).*** Concerning the gender, a more pronounced loss of body fat has been described in woman while men experience more frequently depletion in the lean body mass. This alteration may be present even in the early stages of liver cirrhosis and is further accelerated in the advanced stages of the disease***(Figuerido et al., 2005).***

Malnutrition in cirrhotic patients is known to be associated with a higher prevalence of complications, such as hepatic encephalopathy, ascites, hepatorenal syndrome, and bacterial infections***(Merli et al., 2010)***; furthermore, malnourished patients may experience deterioration in the quality of life. The independent role of malnutrition on survival in patients with liver disease has been extensively documented; patients comparable for the severity of liver insufficiency show a higher rate of mortality when nutritional status is severely impaired***(Alberino F et al., 2001).***

- **Sequelae:**

Malnutrition is associated with increased morbidity and mortality rates in patients with chronic liver disease. Patients with

cirrhosis who are malnourished have a higher rate of hepatic encephalopathy, infection, and variceal bleeding***(Moller et al., 1994).*** They are also twice as likely to have refractory ascites***(Lautz et al., 1992).*** Although numerous studies have found a correlation between poor nutritional status and a decreased survival rate, there is debate as to whether the increased mortality rate is caused by malnutrition or by the advanced liver disease itself***(Alberino et al., 2001).***

Nutritional status has prognostic implications in liver transplant candidates. Malnutrition before transplantation is associated with a higher rate of post-transplant complications, including infection and variceal bleeding***(Figueiredo et al., 2000).*** Patients who are severely malnourished require more blood products intraoperatively, remain on ventilatory support longer postoperatively, and have an increased length of hospital stay and a higher incidence of graft failure***(Stephenson et al., 2001).*** Ultimately, patients with poor nutritional status before transplant surgery have a decreased survival rate after liver transplantation***(Selberg et al., 1997).***

- **Factors contributing to malnutrition in chronic liver disease:**

1. **<u>Abnormal Nutrient Intake:</u>**

Patients with chronic liver disease frequently have anorexia and early satiety, which contribute to Decreased food intake

leading to malnutrition ***(Davidson et al., 1999).*** Important factors in the progression of anorexia include zinc deficiency, hyperglycemia, and unpalatable diets related to sodium and protein restriction. Increased proinflammatory cytokine levels (tumor necrosis factor, interleukin 1b, and interleukin 6) have been described in patients with chronic liver disease and may have an anorexic effect***(Aranda-Michel, 2001).***

2. Decreased Intestinal Absorption (Malabsorbtion):

Malabsorption is another important factor in the development of malnutrition in this patient population. A number of mechanisms contribute to malabsorption. There might be a reduction in the bile-salt pool in patients with advanced liver disease, leading to fat mal absorption***(Vhlachevic et al., 1971),*** which is particularly problematic in patients with cholestatic liver disease. Another potential mechanism that contributes to mal absorption in patients with advanced liver disease is bacterial overgrowth resulting from impaired small-bowel motility***(Gunnarsdottir et al., 2003)***. The presence of portal hypertension has also been implicated as a cause of mal absorption and gastro intestinal protein loss***(Conn et al., 1998).*** An additional factor is the administration of medications that lead to malabsorption, such as neomycin, which is used in the treatment of hepatic encephalopathy***(Thompson et al., 1971).*** Fat mal absorption not only contributes to undernourishment, but also results in a deficiency in fat-soluble vitamins.