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UNIVERSITY OF SAN DIEGO
Hahn School of Nursing and Health Science
DOCTOR OF PHILOSOPHY IN NURSING

Nutritional Status of Patients with End Stage Liver Disease: An Outpatient Assessment

by

Anna Marie Cumming-Browne Hefner, RN, MSN, CPNP

A dissertation presented to the
FACULTY OF THE HAHN SCHOOL OF NURSING AND HEALTH SCIENCE
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Requirements for the degree
DOCTOR OF PHILISOPHY IN NURSING

May, 2013

Cynthia D. Connelly, PhD, RN, Chair

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Abstract

Cirrhosis is the 12th leading cause of death in the United States. It is well documented end stage liver disease drives a patient to a catabolic state thus depleting them of essential nutrients. Malnutrition is often unrecognized and untreated in outpatients. Though BMI, nutritional intake, anthropometric measurements have been used in clinical trials, there still remains no standard nutritional assessment.

The purpose of this dissertation was to (1) identify the incidence of malnutrition in patients with compensated and decompensated liver disease utilizing defined nutritional parameters (Subjective Global Assessment, anthropometric measurements, hand grip strength, and laboratory values) and (2) correlate with care (hospital visits, physician appointments, outcome and quality of life) secondary to viral hepatitis, metabolic and alcoholic liver disease.

The conceptual framework underlying this study is derived from the literature based on the domains of liver function, nutrition, and malnutrition. Nutrition includes the chemical substances in food utilized by the body for growth, maintenance, and repair: the intake, digestion, and assimilation and utilization of nutrients for tissue maintenance and energy provision.

There is no gold standard for proper nutritional assessment of patients diagnosed with liver disease; notably, the traditional assessment tools are invalid with end-stage liver disease. Ascites, edema, and diuretics cause fluctuations in weight and weight changes. Cirrhosis of the liver drives a patient to a catabolic state, thus depriving them of essential nutrients. Simple and easily applied methods are needed to identify the patients approaching the state of malnutrition.

Study findings presented in three papers provides a major contribution in discriminating the nutritional parameters of different etiologies of cirrhosis leading to malnutrition.

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DEDICATION

To my mom and dad, who instilled in their children, education was important. They gave me the tools that made this possible by their expectations and dedication to learning. To my daughters, Kristin and Michelle, for the love and support given as I embarked on this journey. To Scottlyn Rose, the comic relief and pure joy to give her Nana the smiles and encouragement as only a baby can do. To my brother Michael, who picked up the slack when it was needed most. I love you all.

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CHAPTER 1

The Problem and Background

Cirrhosis of the liver is the twelfth leading cause of death in the United States (Heron, Hoyert, Murphy, Xu, Kochanek, & Teejada-Vera, 2009; & Kochanek, Murphy, Anderson, & Scott, 2004). The cirrhotic liver is characterized by fibrosis and the normal architecture is converted to structurally abnormal nodules that lack lobular organization. It involves the entire liver and is irreversible at its late stages. Cirrhosis is a disease of contrasts in etiology and symptomatology. The most common etiology has been alcoholic liver disease and chronic viral hepatitis (Hepatitis C and Hepatitis B). However, fatty liver disease has increasing prevalence across the world and is known to progress to cirrhosis and is becoming one of the leading causes of cirrhosis globally. Cirrhosis can be asymptomatic or presents with manifestations of hepatic decompensation as evidenced by variceal bleeding, ascites, hepatic encephalopathy, and hepatorenal syndrome.

Nutrition is one of the most important factors that can influence overall mortality and morbidity. There are a variety of issues that make it difficult for patients with cirrhosis of the liver to maintain adequate nutritional intakes. At one end of the spectrum, there is severe nutritional deficiencies related to chronic alcoholic liver disease and viral hepatitis which has progressed to cirrhosis. At the other end of the spectrum is nutritional excess related to nonalcoholic steatosis (NASH) or progressive fatty liver disease (NAFLD). Both ends of the spectrum require specially designed nutritional plans.

Severe protein caloric malnutrition (PCM) is common in patients with liver cirrhosis, particularly alcoholics. It seriously undermines the liver's capacity for regeneration and functional restoration. Studies have shown the more severe the malnutrition, the worse the prognosis. Nutritional supplements on an inpatient basis have been shown to improve nutritional status, as well as the liver function for these patients. The prevalence of malnutrition is as high as 80% depending on the cirrhotic population studied (Campillo, Richardat, Scherman, & Bories, 2003; Matos, Porayko, Francisco-Ziller, & DiCecco, 2002).

There is no gold standard for proper nutritional assessment of patients diagnosed with liver disease. Indeed, liver disease also complicates the nutritional assessment (McCullough, 2000). Notably, the traditional assessment tools are invalid with end-stage liver disease. Ascites, edema, and diuretics cause fluctuations in weight and weight changes. It has been well documented cirrhosis of the liver drives a patient to a catabolic state, thus depriving them of essential nutrients. Simple and easily applied methods are needed to identify the patients approaching the state of malnutrition. This study is

designed to provide a major contribution in discriminating the nutritional parameters of different etiologies of cirrhosis leading to malnutrition.

Background

The liver is the largest metabolic organ in the human body and integrates carbohydrate, fat, and protein metabolism. The liver stores vitamins and activates others. It detoxifies and excretes endogenous and exogenous waste products.

The majority of the cells found in the liver are hepatocytes. These hepatocytes are vital in maintaining homeostasis. The functions of the hepatocytes include the synthesis of most essential serum protein including albumin, coagulation factors, carrier proteins, hormonal and growth factors, the regulation of nutrients (glucose, glycogen, lipids, and cholesterol amino acids), the production of bile and its carriers of bile acids, lecithin, and phospholipids, and the metabolism and conjugation of bilirubin, anions, cations, and drugs. Therefore, cirrhosis, a chronic liver disease characterized by replacing normal liver tissue with fibrosis, scar tissue and regenerative nodules leading to the loss of liver function, has major nutritional implications.

Cirrhosis represents the final stage of many chronic liver diseases. It has been associated with hyponutrition despite the etiology. Malnutrition is an important prognostic factor in liver cirrhosis (Campillo, Richardet, & Bories, 2006). There are three common influences which contribute to hyponutrition in the patient with chronic liver disease. These are: 1) a decrease of limit of intake; 2) impairment of nutrient digestion and/or absorption; and 3) the interference of nutrient metabolism. The relevant causes of dietary insufficiency are anorexia, nausea, vomiting, food tastes non palatable due to

protein and salt restriction, early satiety, and reflux disease due to ascites and abnormal gut motility. Pancreatic insufficiency, cholestasis related to fat soluble vitamins, and drug related diarrhea from ingestion of lactulose, antibiotics, and diuretics are some of the causes of malabsorption. Metabolic disturbances due to infections, hemorrhages, protein catabolism, impaired glucose homeostasis, proinflammatory cytokines of interleukins, leptins and TNF alpha, and increased lipolysis and enhanced lipid oxidation contribute to interference of nutrient metabolism(Lee & Nieman 2007; Stratton, Green, & Elia, 2008).

Protein malnutrition is documented in nearly every etiology associated with cirrhosis of the liver(McCullough & Buglani, 1997). As liver insufficiency increases, the prevalence of protein malnutrition increases. Protein needs increase during treatment of malnutrition but in end-stage liver disease, the tolerance is decreased. Low levels of vitamins A, zinc, and magnesium have been associated with protein calorie malnutrition. The literature reflects protein calorie malnutrition as a common finding in patients hospitalized with chronic liver disease; investigations with individuals in an outpatient clinic are sparse.

The purpose of this study is to identify the incidence of malnutrition in patients with compensated and decompensated liver disease utilizing defined nutritional parameters (Subjective global assessment, anthropometric measurements, hand grip strength, and lab values) and correlate to care (hospital visits, ER visits, physician appointments , outcome, and quality of life). The degree of malnutrition will be compared in patients with end stage liver disease secondary to viral hepatitis, metabolic (NASH), and alcoholic liver disease.

Nutritional Assessment

The Joint Commission on Accreditation of Health Care Organizations (JACHO) requires a nutritional screening after hospital admission, but there are no universally recognized or validated standards. The areas routinely assessed are height, weight, weight change, dietary prescriptions, appetite, presence of chewing and swallowing, and major food intolerances. In the outpatient setting, dietary assessment should be done to determine whether the patient's diet contributes to an increase health risk or existing chronic disease related problems.

Nutritional assessment is an integral part of patient assessment as it directly influences clinical outcomes and mortality rates. Malnutrition increases the risk of infections, health care costs, and decrease quality of life, prolongs hospitalizations, recovery after surgery, and life expectancy (Robinson, Goldstein, & Levine, 1987; Sherlock & Dooley, 2005).

The assessment of the nutritional status is very inaccurate in patients with chronic liver disease. The traditional measures used to estimate nutritional status have limitations. Body weight and body mass index (BMI) are insensitive in cirrhotics because of salt and water retention causing abdominal ascites. Abnormalities of lymphocyte and decrease plasma protein resulting from ascites, edema, anasarca, and malnutrition also contribute to the retaining of fluid. Malnutrition is an important prognostic factor which can influence the clinical outcome of patients with end stage liver disease (Campillo et al., 2006; Kondrup 2006).

In summary, end stage liver disease is a significant, chronic health problem. There is much known about the nutritional intake during inpatient stays, in contrast less is known about the nutritional aspects that influence the care on an outpatient basis.

Purpose and Aims

The purpose of this descriptive correlation design study is to examine the relationship between nutritional assessment parameters and care among a sample of outpatient of adult patients with End stage liver disease (ESLD). Specifically, the aims of this study are:

Aim 1:

To identify the incidence of malnutrition in compensated and decompensated liver disease patients with end stage liver disease utilizing assessment parameters (SGA, anthropometric measurements, hand grip and laboratory values) among a sample of adult outpatients with end stage liver disease.

Aim 2

Examine the degree of malnutrition in patients with different etiologies of end stage liver disease (viral hepatitis, metabolic (NASH), and alcoholic liver disease).

Aim 3

Describe the relationships between malnutrition, hospital visits, ED visits, physician appointments, outcome, and quality of life among a sample of adult outpatients with end stage liver disease.

Aim 3'

Describe the relationship of the intensity of care management on education and support lifestyle changes to improve metabolic parameters in patients with fatty liver disease.

Conceptual Framework

The conceptual framework underlying this study is derived from the literature based on the domains of liver function, nutrition, and malnutrition. (Figure 1). Nutrition influences both the physical and psychological well being in a person. There is a growing awareness one's nutritional status may impact the quality of life. Good nutrition is essential for adequate function and survival, but eating also satisfies other needs i.e.s eating, satisfaction, socialization, and structure to a day (McKenna and Thorig, 1995). Nutrition includes the chemical substances in food utilized by the body for growth, maintenance, and repair. It includes the intake, digestion, and assimilation and utilization of nutrients for tissue maintenance and the provision of energy.

Specific dietary components may have an influence on the risk of depression, cognitive impairment, and cognitive decline (Rogers, 2001). Subclinical deficiencies of antioxidants (vitamin C,E, beta carotene, vitamin B 12, B6, and folate) and nutrition related disorders (hypercholesterolanemia, hyper triglycerideanemia, hypertension, diabetes) have been identified as potential nutritional related risk factors (Calvanesi & Bryan, 2001).

The liver plays a key role in supplying nutrition to the body. It delivers the elements needed by the different body tissues in simple, utilizable nutrients such as

glucose, amino acids, fatty liver, and vitamins. Though the daily amounts of food consumed by people vary enormously, the nutrient requirements are relatively constant.

Knowledge of liver physiology is essential to understand the mechanisms at work in end stage liver disease. The liver provides the body's homeostasis. It is through the liver; the blood sugar, cholesterol, and blood urea are maintained. The liver regulates most of the metabolism on the body. It is in charge of transforming foreign substances such as toxins in the intestinal flora and the pollutants brought in with food. It does this through multiple enzymes, which are controlled by numerous hormones.

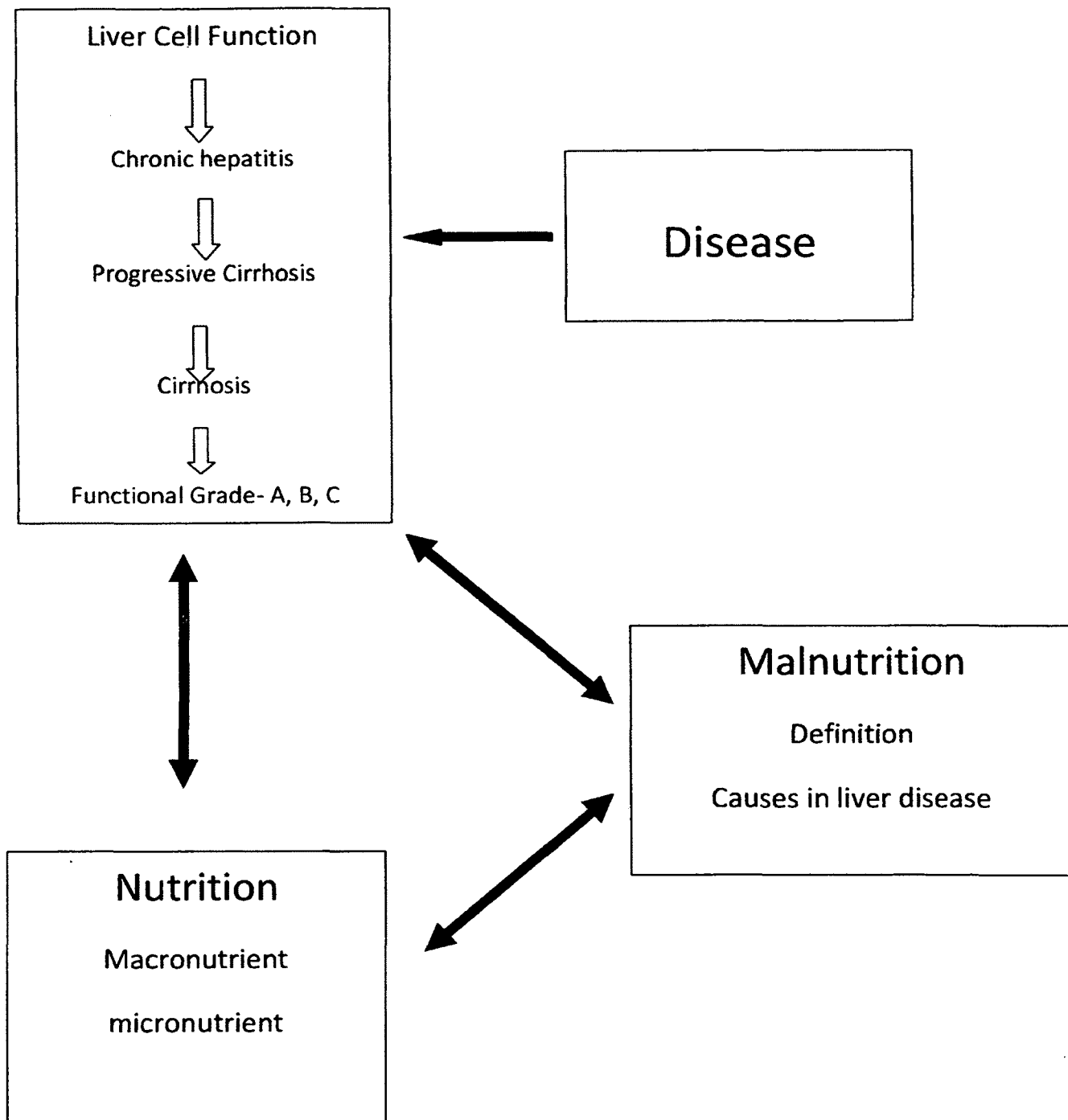
The liver requires a greater metabolic potential than any other organ of the body. It is capable of deriving its own energy through the degradation of carbohydrates and lipids through its enzymes. It must also turn amino acids into proteins. It has specific functions in the digestion of the food we eat. Bile is produced in the liver and is the main means to eliminating cholesterol, and important for the digestion of fatty food. It receives a variety of sugars in the diet and converts them into a single circulating sugar, glucose. The liver transforms endogenous metabolites into soluble compounds easily excreted by the kidneys. The liver detoxifies substances foreign to the body-each requiring different mechanisms for this detoxification. The liver purifies the blood of circulating particles.

Malnutrition implies deviations from normal nutrition in which a deficiency or excess of energy, protein, and other nutrients cause measurable adverse effects on the body and function of the tissues (Elia et al., 2000). It has been divided into primary and secondary malnutrition. Primary malnutrition arises in the absence of disease such as

lack of food due to poverty or social isolation. Secondary malnutrition occurs in a relationship to a disease. In the absence of disease, the rate and magnitude of weight loss affect body function. In the presence of disease, nutritional support affects the function of tissues and cells.

In the presence of disease, nutritional support appears to produce clinical benefits. Nutritional support affects the function of tissues and cells. Recognition of dietary deficiencies and provision of both nutritional support and dietary education are needed to support the patient in achieving fluid and electrolyte balance, decrease frequent hospitalizations, and maintain adequate nutritional stores.

Figure 1: Conceptual Framework Model



Significance

Malnutrition is often unrecognized and untreated in outpatients. Due to the extensive role the liver plays in metabolism and maintenance of homeostasis, liver disorders predispose the patient to malnutrition. Alarming, malnutrition evolves prior to the clinical signs of hepatic insufficiency.

The goals of nutrition are to replenish malnourished individuals, maintain adequate muscle and energy reserves, and manage the patient's symptoms to maximize the quality of life. To assess the overall potential effects of intervention, it is first necessary to assess the frequency of malnutrition and its consequences. With the standard parameters of nutritional assessment often invalid in End Stage Liver disease, it becomes difficult to identify and assess nutritional states. Although there is strong scientific evidence to support aggressive treatment of nutritional deficiencies in cirrhosis, few studies have assessed changes in nutritional status prospectively over the course of liver disease.

This study will add to the empirical base regarding nutritional assessment strategies to improve the nursing care for patients treated for liver disease disorders. This knowledge will facilitate the development of evidence based interventions to improve patient care outcomes (McCullough, 2000; Sobhonslidsuk et al., 2001; & Stratton et al., 2008).

Chapter 2

Literature Review

Cirrhosis of the liver is a complex pathophysiological process representing the final stage of many chronic liver diseases. It results in significant morbidity and eventual mortality in many patients and has been associated with hyponutrition despite the etiology. The prevalence of malnutrition is estimated to be between 65-100% in patients with cirrhosis (Campillo et al., 2003.) The degree of malnutrition is an important prognostic factor in liver cirrhosis (Campillo et al., 2006). Accurate longitudinal data on dietary intake patterns, physical activity, and quality of life would be helpful to the understanding of how these factors may impact on health and functional status.

Malnutrition of the patient with liver disease increases the risk of infections, health care costs and decrease quality of life and life expectancy (Dan, Kallman, Srivastava, Younossai, Kim, & Younossi, 2008). Nutritional assessment of patients with liver disease is critical as it determines interventions that affect clinical outcomes and quality of life. Numerous studies have furthered our understanding of the role of

nutritional status in the hospitalized surgical patient (Figueirido et al., 2006). However the type of nutrition assessment used with the surgical patient underestimates the prevalence and severity of malnutrition with cirrhosis.

The literature reflects protein-energy malnutrition (PEM) as a common finding in patients hospitalized with chronic liver disease (Campillo et al., 2003; Matos et al., 2002). However there is a paucity of literature on patients treated in outpatient clinics. Understanding protein calorie nutrition in outpatients with liver disease is essential because protein needs and tolerance change for these patients as it does for hospitalized patients who are treated for malnutrition. In end stage liver disease, the tolerance for protein is decreased. Protein calorie malnutrition is also associated with low levels of vitamins A, zinc, and magnesium.

The causes of malnutrition in liver disease are complex and multifactorial. There are three common influences which contribute to hyponutrition in the patient with chronic liver disease. These are: 1) a decrease of limit of intake; 2) impairment of nutrient digestion and/or absorption; and 3) the interference of nutrient metabolism. Inadequate dietary intake is attributed to many factors-loss of appetite, anorexia, nausea and vomiting, early satiety, taste abnormalities, reflux disease and impaired expansion of the stomach capacity (Aqel, Scolapio, Dickson, Burton, & Bouras, 2005; Plauth & Shutz, 2002; Sobhonslidsuk, Roongpsiuthipong, Nahtir, Kulapongse, Songchitsomboon, Sumalnop, & Bussagorn, 2001).

Inadequate dietary intake is associated with anorexia, nausea, encephalopathy, and gastritis. Frequently there is restriction of Na and protein due to ascites and edema decreasing the palatability of the food. Reflux disease is associated with increased ascites

causing nausea. Impaired digestion and absorption is a contributing factor to malnutrition. There is a bile salt deficiency, bacterial growth, and altered intestinal motility associated with the antibiotics, lactulose, diuretics, and cholestyramine given the patient to improve liver function and decrease encephalopathy. Portal hypertension changes the intestine, creates mucosal injury, and increases intestinal permeability.

Cirrhosis represents an altered state of starvation. There is hypermetabolism during complications of infections, hemorrhage, ascites and decompensation. An overall protein loss results from a reduced synthesis of urea and hepatic proteins, decrease intestinal protein absorption, increased urinary nitrogen excretion, and a lowered ratio of branched-chain to aromatic amino acids. The protein catabolism causes inflammation and impaired liver synthesis. Impaired glucose homeostasis is a result of hepatic insulin resistance and altered gluconeogenesis, low glycogen stores, and impaired glycogenesis.

Classification of Cirrhosis

The Child Pugh score was based on the Child Turcotte classification (Pugh, Murray Lyon, Dawson, Pietron, & Williams, 1973) and has been widely used as an index of disease severity e.g. Grade A (mild) to Grade C (severe), for patients with end stage liver disease.. There are five factors included in the Child Pugh classification, 2 clinical factors: ascites, hepatic encephalopathy, and 3 laboratory factors: levels of bilirubin, albumin, and prothrombin time. The grading system indicates the degree of hepatic reserve and function. The major criticism of this scoring system is the subjectiveness involved in evaluation ascites and hepatic encephalopathy. This can cause and does cause differences in patients with very similar laboratory markers. However, it remains the most common and feasible method to categorize cirrhotic patients.

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major food intolerances. In the outpatient setting, dietary assessment should also be done to determine whether the patient's diet contributes to an increase health risk or existing chronic disease related problems.

Despite liver disease being the primary cause of malnutrition, it is often unrecognized and is untreated particularly in outpatients. Further insults to the liver at this stage, can lead to decompensation, fluid retention (ascites) and encephalopathy. Clinical detection of malnutrition usually occurs in the advanced stages of deficiencies of nutrients. Biochemical or other tests can identify the deficiency before the specific clinical manifestations become apparent. Detection of subclinical malnutrition has the obvious advantage that a condition can be identified and treated at an early stage to improve or prevent progression of the condition.

Malnutrition is an important prognostic factor which can influence the clinical outcome of patients with end stage liver disease (Campillo, Richard et al., 2006; Kondrup, 2006). Anthropometric tools-MAMC, hand grip strength are known to be predictors of malnutrition in adults with cirrhosis. The use of skin fold anthropometric measurements have been shown to correlate most reliably with malnutrition in liver patients but not with the severity of liver disease. Albertino, Gatta, Amobdio, Merkel, DiPascoli, Bofo, & Caregaro (2001) included mid-arm muscle circumference (MAMC) and triceps skinfold thickness (TST) metrics and found improved prognostic accuracy of the Child Pugh score. Abbott, Thomson, Steadman, Gatton, Bothwell, Kerlin, Wall & Lynch (2001) found advanced Child Pugh scores were associated with diminished muscle status. Malnutrition occurs in all clinical stages, but it becomes more severe related to

the degree of liver injury. Malnourished patients have an increased prevalence in morbidity and mortality (Gunsar et al., 2006).

The assessment of the nutritional status is very inaccurate in patients with chronic liver disease. The traditional measures used to estimate nutritional status have limitations. Body weight and body mass index (BMI) are insensitive because of salt and water retention. Abnormalities of lymphocyte and decrease plasma protein also contribute to the retaining of fluid. Bioelectrical impedance analysis (BIA) is hampered by body water retention. Nonetheless, The European Society for Clinical Nutrition and Metabolism identify the Subjective Global Assessment (SGA) and anthropometric parameters as reliable in assessing the nutritional state of cirrhotic patients (Figueiredo, De Mello Perez, & Kondo, 2005)

The required amounts of essential nutrients differ by age and physiologic state. Energy intake must match energy output to maintain one's weight. Restoring energy expenditure (REE) and physical activity are the major components of energy output. Illness alters the ability of the body to engage in physical activity and its REE.

Sodium concentrations have been recognized as an important prognostic factor in liver cirrhosis. Hepatorenal syndrome, ascites, and death from liver disease are associated with hyponatremia (Arroyo & Colmenero 2003; Borroni, Maggi, Sangiovanni, Cazzaniga, & Salerno, 2000). Kim, Flamm, Di Bissegli, and Bodenheimer (2008) added sodium concentration with the MELD score and found it to be significantly associated with mortality.

The literature reflects protein calorie nutrition is a common finding in patients hospitalized with chronic liver disease. However, investigations of individuals in an outpatient clinic are rare. Most patients are also non patients with chronic alcohol abuse. Protein calorie malnutrition is frequently found in patients with end-stage liver disease. Protein needs increase during treatment of malnutrition but in end-stage liver disease, the tolerance is decreased. Low levels of vitamins A, zinc, and magnesium have been associated with protein calorie malnutrition.

Fat soluble vitamins (A, D, E, and K) are closely associated with lipids. They can be stored and their functions are generally related to structural activities. *Vitamin A.* There are two dietary forms of vitamin A-retinol and carotene. Retinol is found only in animal foods and its compounds are deposited primarily in the liver. Carotene is found both in animal sources as well as in plants. It is converted to vitamin A in the liver. Vitamin A and carotene are absorbed through the intestinal mucosa, entering the blood stream via the lymphatic system and carried to the liver for storage and distribution to the cells. Vitamin A plays a role in iron utilization, humoral immunity, vision adaptation to light and dark, t-cell mediated immunity, natural killer cell activity, and phagocytosis. Vitamin A decreases with cirrhosis and protein energy malnutrition; It increases with hepatosplenomegaly, hypercholesterolemia, and hyperlipidemia.

Vitamin D. There are two compounds with Vitamin D activity-ergocalciferol and cholecalciferol. Vitamin D is involved in the regulation of calcium and phosphorus. It also works with other vitamins- A, C, and K, hormones, and minerals-calcium, phosphorus, and magnesium to affect bone growth. It is found naturally in fish, liver and

oils; it is fortified in dairy products. In liver disease, the concurrent use of thiazide and diuretics can lead to hypercalcemia.

Vitamin E. Vitamin E, also known as tocopherol, is a generic name for a group of compounds with similar physiological activity. It oxidizes very slowly giving it an important role as an antioxidant. It neutralizes free cell radicals and provides a protective role in preventing oxidation of the unsaturated fats. Vitamin E works with a selenium-containing enzyme to provide another mechanism of protection for the cell membrane of fatty acids for the oxidative damage. Vitamin E decreases with malabsorption syndromes with steatorrhea and in protein energy malnutrition.

Vitamin K. Vitamin K is synthesized by intestinal bacteria and can be found in plants. It requires bile salts and pancreatic secretions for absorption. As with vitamin A, it is transported via the lymphatic system to the liver for storage. The major function of vitamin K is to catalyze synthesis of blood clotting factors by the liver. It is essential for maintaining normal levels of four blood clotting factors-prothrombin (factor II), serum prothrombin conversion accelerator (Factor III), plasma thromboplastin component (factor IX), and Stuart-Prower factor (Factor X). Vitamin K activates each of these protein synthesized by the liver. Decreases in vitamin K are seen in patients with liver disease and high phosphates.

Water soluble vitamins cannot be stored, though they are generally distributed through the body tissue maintaining a tissue saturation level. They are easily absorbed and transported to the cells and their function is related to cell metabolism and structure. These are B complex and Vitamin C.

Vitamin C. Vitamin C is also an antioxidant along with Vitamins A and E.

Vitamin C is required to build and maintain body tissues-bone matrix, cartilage, dentin, collagen, and connective tissues. It promotes non-heme iron absorption, carnitine biosynthesis, and conversion of dopamine to norepinephrine. A decrease in vitamin C is seen in alcohol abuse, inflammatory disease, and oxidative damage.

Biotin is a micronutrient involved in gluconeogenesis. It is a coenzyme in metabolism that functions on the tricarboxylic cycle for release of energy. Protein-energy malnutrition can lead to a deficiency in biotin. Clinical signs of biotin deficiency include nausea and depression.

Vitamin B12-cobalmin deficiency is associated with deficiencies in vitamin B6 and folate. It is a coenzyme in the synthesis of hemoglobin, RBC's, and DNA. Folic acid is used in the synthesis of DNA and helps convert vitamin B12 to a coenzyme form in the body. It is needed for growth and development of RBC's, and helps to lower homocysteine levels in the body by breaking down amino acids. It goes through the enterohepatic circulation to be regulated.

Vitamin B6 pyridoxine is a coenzyme in amino acid, lipid, and protein metabolism, erythrocyte function, modulation of hormones, nervous system function, and direct conversion of tryptophan to niacin or to serotonin. Vitamin B2 riboflavin is a coenzyme in protein and energy metabolism and conversion of other vitamins into active forms. The thyroid adrenal hormone controls the conversion to the coenzyme forms. Vitamin B1, thiamin, is a coenzyme in carbohydrate metabolism. A decrease in thiamine may elicit Wernicke-Korsakoff syndrome and Beri-Beri cardiomyopathy.

Nutritional Assessment Measures

There have been a variety of comprehensive assessment tools utilized in an attempt to identify patients at risk of or with malnutrition, yet the literature reflects conflicting information on the patient with End Stage Liver Disease. There is no gold standard for proper nutritional assessment of patients diagnosed with liver disease since liver disease also complicates the nutritional assessment (McCullough, 2000). The traditional assessment tools are invalid with end-stage liver disease. Ascites, edema, and diuretics cause fluctuations in weight and weight changes. Bioelectrical impedance and dual x-ray absorptiometry are altered by fluid retention (Figueiredo et al., 2005; Figueiredo et al., 2006). The search continues for the ideal nutrition marker. Early identification of the malnourished cirrhotic patient, regardless of etiology, is essential to develop effective interventions. The nutritional goals include providing adequate calories, protein, and nutrients to support hepatocyte regeneration within the existing metabolic alterations of liver disease.

Malnutrition can lead to further morbidity with increase rates of septic complications, poorer quality of life, reduced life span. The liver plays a key role in the carbohydrate, lipid and nitrogen metabolism within of our bodies. Therefore, cirrhosis has major nutritional implications. Severe protein caloric malnutrition (PCM) is common in patients with liver cirrhosis. It seriously undermines the liver's capacity for regeneration and functional restoration. Studies have shown the more severe the malnutrition, the worse the prognosis. Nutritional supplements on an inpatient basis have been shown to improve nutritional status as well as the liver function for these patients. Prevalence is as high as 80% depending of the cirrhotic population studied (Campillo et

al., 2002; Matos et al., 2002). Malnutrition affects lean body mass wasting. Decreases in vitamins, metals, and plasma protein may occur before lean body mass wasting (Matos et al., 2002; McCullough & Falck-Ytter, 1999).

Nutrition was used as a prognostic indicator of the Child Turcotte classification for estimating mortality in patients having portocaval shunt surgery (Child & Turcotte, 1964). It has been shown nutrition in alcohol liver disease, decreased infections, enhanced wound healing, and decreased the need for hospitalizations (Hirsch, Bunout, de la Maza, Iturriaga, Petermann, Icazar, & Gattas, 1993).

European Society for Clinical Nutrition and Metabolism argue simple bedside methods for SGA and anthropometric parameters are reliable in assessing nutritional state of cirrhotic patients.

However, the obstacles continue in the evaluation of nutritional status in patients with cirrhosis. Weight is affected in the presence of ascites and edema. Though the patient may increase weight, lean body mass might be reduced. Albumin and pre-albumin are related to low levels of synthesis rather than poor nutritional status, though nutrition does play a role. Indeed, anthropometric measurements may be unreliable due to third spacing. This may result in an over-estimation of these values. Additionally, there may be potential problems associated with poor inter-observer reproducibility. Hand grip strength and respiratory muscle strength may be more useful when taken serially. The SGA has an inter-observer reproducibility rate of 80%. See Table 1 for Studies which Identified level of malnutrition.

Table 1: Prevalence of Malnutrition in Patients with Liver Disease

| Author | Defined malnutrition | Measured | Inclusion/Exclusion criteria | results | reference |
|--|---|--|---|--|--|
| Alberino, F.; Gatta, A.; Amodio, P.; Merkel, C.; Di Pascoli, L.; Bofo, G., and Caregaro, L. | MAMC and/or TSF < 10 percentile | MAMC TSF BMI | Hospitalized with liver cirrhowsis, Child A, B, or C | 54% malnutrition Examined 212 patients in study 143 male, 69 F Mean age 57.4 SD 10.4 years Mean BMI Child A 26.2 (SD 4.2) Child B 25.0 (SD 4.3) Child C 26.0 (SD 4.0) | (2001) Nutrition and survival in patients with liver cirrhosis. <i>Nutrition</i> 17, 445-450 |
| Kalaitzakis, E.; Rolf Olsson, R.; Henfridsson, P.; Hugosson, I.; Bengtsson, R.; Jalna, R.; Bjornsson, E. | Tricep fold and/or mid-arm muscle circumference below 5 th percentile based on age and sex | Anthropometry -tricep skin fold thickness -mid arm muscle circumference Estimation of recent weight change Dry weight-weight after last paracentesis or before ascites development. Expressed as | Liver cirrhosis of any cause Liver cirrhosis was established histologically or based on presence of at least 2 of following: characteristic imaging features, esophageal or gastric varices, ascites or increased international normalized | 128 patients agreed to participate. Not possible to calculate dry weight loss during preveious 3 or 6 months in 11% and 16% respectively. 62% stable weight 7% weight increase Patients with | (2007) Malnutrition and diabetes are related to hepatic encephalopathy in patients with liver cirrhosis. <i>Liver International</i> 1194-1201 |

| | | | | | |
|--|--|---|--|--|--|
| | | <p>percent of actual body weight</p> <p>Weight-light clothing without shoes</p> <p>BMI-calculated.</p> <p>Unintentional weight change of more than 1 kg that could not be explained by ascites or edema during previous 3-6 months was noted</p> <p>Fasting plasma glucose</p> <p>Fasting serum insulin</p> <p>Insulin resistance</p> | <p>ratio (INR) not attributed to any other cause.</p> <p>Swedish speaking</p> <p>Able to give informed consent</p> <p>No patient on dialysis or hepatorenal syndrome.</p> <p>Pts hospitalized because of acute illness were allowed when stable.</p> | <p>or without malnutrition do not differ in proportion of etiology of liver disease or severity of liver cirrhosis (CP or MELD)</p> <p>Malnutrition not found to be related to ascites</p> <p>Muscle mass was related to plasma ammonia level--? Due to skeletal protein catabolism.</p> <p>Association of diabetes with Hepatic encephalopathy. Previous association with hyperinsulinemia and acute hyperglycemia have been proposed to have direct affect on cognition.</p> | |
|--|--|---|--|--|--|

| | | | | | |
|--|--|--|---|--|--|
| <p>Figueiredo, F. A.; Perez, R.; Kondo, M.</p> | | <p>Overnight fasting</p> <p>Anthropometry -height -weight BMI calculated</p> <p>Blood tests -albumin (g/dL) Bilirubin (mg/dL) Prothrombin activity (%) Lymphocytes (cells/mm³)</p> <p>Body composition -DEXA to derive a multicompart ment model consisting of BCM, TBF, ECW, and total body minerals (TBM)- bromide cocktail used -comparison of body composition measures between CP classes was carried out by one-way ANOVA. Tukey's test was used to</p> | <p>Diagnosis of liver cirrhosis based on clinical evidence or liver histology -presence of portal HTN and hepatic insufficiency</p> <p>Severity graded by child-pugh scores</p> <p>Patients with HCC, malabsorption, AIDs excluded</p> <p>Fluid retention defined by presence of peripheral fluid accumulation (edema) and clinically detectable ascites.</p> | <p>17 control patients; 79 patients with CP scores</p> <p>Measurement of body composition essential to assessment of true extent of malnutrition in cirrhosis.</p> <p>Severity of altered body composition profile was related to clinical stage of liver disease.</p> <p>Pronounced loss of body fat initially followed by accelerated loss of BCM in advanced stages of cirrhosis.</p> <p>Significant losses in body composition occur in patients with only mild hepatic dysfunction and no</p> | <p>(2000) Effect of liver cirrhosis on body composition: evidence of significant depletion even in mild disease. <i>Journal of Gastroenterology and Hepatology</i> 20, 209-216</p> |
|--|--|--|---|--|--|

| | | | | | |
|--|---|--|---|---|---|
| | | correct for multiple comparisons Tissue-loss pattern calculated through percentile distribution table by sex. Reduced if <50% | | obvious malnutrition. Changes in ECW (increase) and ICW (decrease) noted before fluid retention was seen clinically. | |
| Alvares-da-Silva, M.; Silveira, T. R. | Malnutrition was defined by a result below the mean +/- two standard deviations in hand grip/ | SGA PNI -visceral proteins -prealbumin -retinol-binding protein Handgrip strength | 145 patients-cross sectional assigned to 1 of 3 groups group 1-50 pts with cirrhosis; group 2-46 pts with HTN; group 3-49 pts with functional gastrointestinal disorders. Inclusion-histologic confirmation with cirrhosis or high suspicion due to medical hx, pe, and complementary tests. Excluded-pts with diabetes mellitus, acquired immunodeficiency syndrome, tuberculosis, chronic renal | Prevalences of malnutrition were 28% by SGA; 18.7% by PNI; 63% by handgrip. Handgrip predicted a poorer outcome Sex did not influence nutritional status according to SGA or PNI Need additional studies to demonstrate that nutritional replacement is reflected by muscle function as measured by dynametry and by | (2005). Comparison between handgrip strength, subjective global assessment and prognostic nutritional index in assessing malnutrition and predicting clinical outcome in cirrhotic outpatients. <i>Nutrition</i> , 21, 113-117. |

| | | | failure, muscle disease, and/or rheumatologic disease | clinical outcome. | |
|--|---|---|--|---|--|
| Campillo m B.; Richardet , J. P.; Bories, P. N. | Malnutrition defined as BMI < 22 for no ascites; < 23 for mild ascites, and <25 for tense ascites | BMI Mid arm muscle circumference Triceps skinfold thickness | 875 study populations and 294 cirrhotic patients | BMI is a reliable parameter to detect malnutrition with BMI cutoffs. | Validation of body mass index for the diagnosis of malnutrition in patients with liver cirrhosis. <i>Gastroenterology in Clinical Biology</i> 30(10), 1137-43. |
| Tai, M.L., Goh, K-L, Mohd-Taib, S.H., Rampal, S., Mahadeva, S. | MAMC <5% SGA indicating malnutrition | Anthropometry- BMI, MAC, TST, handgrip strength, visceral proteins, lean body mass, SGA | Inclusion-18 years or older, admitted to hospital for decompensation of cirrhosis Exclusion- patients with HCC, grade 3 or 4 HE | Malnutrition in 50% of Malaysia patients Fat stores depletion in 30% | (2010) Anthropometric, biochemical and clinical assessment of malnutrition in Malaysian patients with advanced cirrhosis 9, 27-34. |
| Riggio, O., Angeloni, S, Ciufon, L et al. | | Indirect calorimetry Physical activity | | | |
| Houissa, F., Salem, M., Debbeche , R., Mouelhi, | Mid arm muscle circumference (MAMC) and/or Triceps | Anthropometric measurements and biochemical analysis | 44 consecutive cirrhotic patients (21 men, 23 women) hospitalized | High prevalence of malnutrition associated with severity of liver | (2010).Evaluation of nutritional status in patients with liver cirrhosis La Tunisie |

| | | | | | |
|---|--|---|---------------------------------------|---|---|
| L. Bouzaidi, S., Ben Rejeb, M., Mekki, H., Said, Y., Trabelsi, S., Najjar, T. | skinfold thickness (TST) below the 5 th percentile or less than 60% | | Child A=9 Child B=26 Child C=9 | cirrhosis Anthropetric paraments valuable tools for malnutrition diagnosis | Medicale, 88, 76-79 |
| Schneider, A. C, Pinto, R.B, and Silveira, T.R. | Weightage Height/age Body mass index Triceps skinfold thickness Arm muscle circumference | 42 cirrhotic children and adolescents between 3 months and 18 years | Child A=22 Child B=15 Child C=5 | Triceps skinfold thickness best reflected nutritional risk Chronic malnutrition status occurrence greater in Height/age index <10% nutritional risk <3% malnourished | (2007) Nutritional risk and malnutrition determination by anthropometry in cirrhotic children and adolescents Arquivos en Gastroenterologia 44, 345-9 |

Chapter 3

Methodology

The purpose of this study was to examine the incidence of malnutrition in patients with end stage liver disease utilizing defined nutritional parameters (subjective global assessment, anthropometric measurements, hand grip strength, and lab values) and correlate to care (hospital visits, ER visits, physician appointments , outcome, and quality of life). In this chapter a description of the design, sample, data collection, and analytic techniques will be presented. The protection of human subjects and study limitations will also be addressed.

Specific aims:

Aim 1:

To identify the incidence of malnutrition in compensated and decompensated liver disease patients with end stage liver disease utilizing assessment parameters (SGA, anthropometric measurements, hand grip and laboratory values) among a sample of adult outpatients with end stage liver disease.

Aim 2

Examine the degree of malnutrition in patients with end stage liver disease secondary to viral hepatitis, metabolic (NASH), and alcoholic liver disease.

Aim 3

Describe the relationships between hospital visits, ED visits, physician appointments, outcome, and quality of life among a sample of adult outpatients with end stage liver disease.

Aim 3'

Describe the relationship of the intensity of care management by the Advanced Practice Registered Nurse on education and support of lifestyle changes to improve metabolic parameters in patients with fatty liver disease.

Design

A descriptive, repeated measures, correlational design was used to examine the relationship between nutritional assessment parameters and care while an outpatient of adult patients (>18 years) with end stage liver disease (ESLD).

Sample and Sampling

A purposive sample of 50 outpatients with end stage liver disease, secondary by histology or clinical picture to viral hepatitis, metabolic (NASH), and alcoholic liver disease were recruited from a community based hepatology clinic located in Southern California. There are two locations of this clinic-Coronado and San Clemente. These clinics provide specialized care to address the needs of individuals with liver disease in

an effort to manage their liver condition and improve quality of life and survival. The advantage of this sampling is the clinic is a regional site for patients with cirrhosis of the liver. They have over 200 referrals per year to this clinic. End stage liver disease was defined as an irreversible condition that occurs with progressive liver damage. It leads to imminent complete failure of the liver and death.

Inclusion criteria:

Subjects met all of the following inclusion criteria to be eligible for participation in this study:

1. Willing and able to provide written informed consent.
2. Male or female, age eighteen or greater
3. Confirmation of cirrhosis documented by either
 - a. Liver biopsy
 - b. Clinical exam, or
 - c. Non-invasive alternative to liver biopsy such as fibro-test, fibro-scan, or acoustic radiation force impulse imaging.
4. Subject has not been treated with any investigative drug or device within 30 days of the screening visit.
5. A female subject is eligible to enter if she is not pregnant or nursing
6. Subject must be in generally good health as determined by investigator.

Exclusion criteria:

1. History of solid organ transplantation
2. Chronic liver disease of hemochromatosis or Wilson's disease
3. Current history of clinical hepatic compensation (e.g. jaundice, severe ascites, encephalopathy or variceal hemorrhage)
4. Excessive alcohol ingestion defined as >3 glasses per day (1 glass is equivalent to beer [284 ml], wine [125 ml] or distilled spirits [25 ml] for females and >4 glasses for males.
5. Patients with hepatocellular carcinoma or invasive malignancy
6. Malabsorption short bowel syndrome
7. Parental nutrition within the last 3 months,
8. Patient with a comorbidity of AIDS
9. Patients on renal dialysis or renal failure
10. Rehabilitating infections i.e. Tuberculosis, chronic fungal infections
11. Rehabilitating chronic conditions i.e.
12. Severe pulmonary disease (O₂ dependent or FEV <50% predicted value)

13. History of significant cardiac disease (congestive heart failure, myocardial infarction within last 2 years)
14. Pregnant or nursing female

Participants were identified by the physician and directed to the advanced nurse practitioner's clinic.

Instrumentation

Subjective Global Assessment

The independent variable-malnutrition- was measured using the subjective global assessment. It is a general nutritional assessment based on current weight, height, nutritional history, changes on physical examination and existing medical conditions. The patients were classified as being well nourished or having mild, moderate, or severe malnutrition. High specificity (96%) has been reported in the detection of malnutrition in liver patients (Detsky, McLaughlin, & Baker, 1987; Jeejeebhoy, Detsky, & Baker, 1990). Though originally used to categorize surgical patients, this nutritional classification has been shown to be a reliable nutritional assessment tool for renal dialysis and liver failure patients (Hasse, Strong, Gorman, & Liepa, 1993). A single clinician collected this data.

Quality of Life

The Chronic Liver Disease Questionnaire is a disease specific instrument. It is designed to assess the health related quality of life in patients with chronic liver disease. It is a multidimensional construct which includes the psychosocial, social, functional aspects, and physical aspects of chronic liver disease. It was developed by Younossi, Guyatt, Kiwi, & King (1999) for patients with chronic liver disease of all etiologies and

stages of cirrhosis. It produces a summary score and correlates with the severity of liver disease. There is construct validity.

The etiology of the cirrhosis was determined by history and routine tests for Hepatitis. The diagnosis for cirrhosis was determined by history, clinical or liver biopsy and laboratory data.

Dual Energy E-Ray Absorptiometry

The DEXA scan is used to measure relative visceral and subcutaneous fat distribution and bone density. The persons who perform X-Ray Bone Densitometry in California are required to possess a certificate as a California Diagnostic Radiologic Technologist, California Radiography Supervisor and Operator permit, or an X-Ray Technician Limited permit in the X-Ray Bone Densitometry Category.

Laboratory Specimens for Blood Work

The Joint Commission has standards which need to be met for a laboratory to obtain accreditation. The laboratory is required to meet national health and safety standards. Trained and certified technicians and laboratory scientists manage, study, and analyze these blood samples. Regulatory agencies of the government monitor the laboratories through proficiency testing programs for routine quality control tests for equipment and test methods, and validating appropriate handling of the samples collected.

Table 2: Outcome Variables

| Test | Outcome measures | Method |
|--|---|---|
| Demographics, Medical History, Family History, Medications | Age Sex Ethnicity Alcohol use history Current frequency (drinks/day) Maximum consumption (yrs) Tobacco cigarette smoking history Current/former smoker Smoking years Average cigarettes/day End Stage Liver Disease Date of diagnosis Method of Diagnosis Symptoms of Liver Disease Past month Medical/Family history (1 st degree) Diabetes (type I or II) Systemic autoimmune disease Cancer Hypertension Endocrine disease Cerebrovascular disease Hyperlipidemia Coronary artery disease Kidney disease Psychiatric disease Bariatric surgery Medications use within the past 6 months (including vitamins and supplements) | Interview and chart review |
| Clinical Laboratory Measures | Hematology Hemoglobin Hematocrit White blood cell count Platelet Chemistries Electrolytes Blood urea nitrogen | Blood work drawn at Laboratory per standard lab protocol. The lab will provide certification-yearly to meet standards for blood sampling and evaluation of samples. |

| | | |
|--------------------------------------|--|---|
| | Uric acid HbA1C Liver Panel Bilirubin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Albumin Prothrombin time (PT) Fasting lipid profile Triglycerides Total cholesterol HDL cholesterol LDL cholesterol Fasting glucose Fasting Insulin Vitamins B1 B12 Folate Iron Vit D A E K Copper Zinc B6 | |
| Dietary Intake | Total daily calories Daily fat calories Saturated fat calories Unsaturated fat calories Daily protein calories Daily carbohydrate calories Daily mineral intake Daily vitamin intake | 3 day dietary recall |
| Body Composition and anthropometrics | Height Weight BMI Lean body mass Fat mass Bone Mass Tricep skinfold (TSF) Mid upper arm circumference (MUAC) | DEXA Tape measure Calipers Dynamometer |

| | | |
|---|--|--|
| | Hand grip strength | |
| Physical Activity and Sleep Patterns | Total time spent walking (daily) Total time spent exercising (daily) Amount of time spent sleeping (daily) | Self report |
| Quality of Life | Perception of illness and affect on life | Quality of Life Questionnaire Chronic Liver Chronic Disease Questionnaire |

Protocol:

Patients identified with cirrhosis of the liver were assessed per standard medical practice with a review of available medical records, thorough clinical history and physical exam.

1. All patients were seen by physician or nurse practitioner to determine eligibility for study. If eligibility met, patients were asked to participate in study. The study was explained and written consent form all subjects was obtained.
2. On initial visit demographics data was collected or reviewed if the patient was previously seen in the clinic-age, sex, ethnicity, alcohol use history, tobacco history, medical/family history of diabetes, cancer, endocrine disease, hypertension, CVA, hyperlipidemia, liver disease, coronary artery disease, bariatric disease, medications used within past 6 months including vitamins and supplements. IF the patient is a smoker, the number of cigarettes smoked per day and the length of time was also recorded.
3. All patients were evaluated at 1st visit , with 3 months, 6 months ,and 1 year follow-up by dietary evaluation, clinical evaluation and physical examination.

- a. The dietary evaluation included a 3 day dietary intake recall using Diet Analysis Plus software version 7.1 to evaluate and analyze nutrient intake for protein, carbohydrates, fat, vitamin e, vitamin d, zinc, magnesium, vitamin c, vitamin a, calcium and was compared to the recommended dietary intake. The patient completed the diet and quantities were estimated by food diagrams (Nutritional Consulting Enterprises two-dimensional food portion visual chart) and models.
 - i. Sleep patterns-number of hours per night, number of times wake up, naps-length and number
 - ii. Current physical activity-mode, frequency, intensity, and duration
- b. Patients had anthropometric measurements performed-weight, height, body mass index (looking for trends), triceps, and mid arm circumference. Measurement of **standing height** was done using a stadiometer-wall mounted, and standing weight using a balanced beam scale. **BMI** was calculated using weight (kg)/height (m²). The BMI classification is as follows: underweight if BMI<18.5, normal weight if BMI 18.5-24.9, overweight if BMI is 25.0-29.9 and obese if BMI > 30 (WHO, 1998).
Skin fold. Lange Skin fold Calipers were used to measure the triceps and biceps, and the mid arm circumference was measured 3 three times with average used with a tape measure (Paper or plastic better?). Skin fold measurements of the biceps and triceps were measured in millimeters, three times, and the average was recorded at each of these sites. The triceps was measured at the mid-point between the acromiale (lateral edge

of the acromial process) and the radial (approximately the elbow joint, on the mid-line of the posterior surface of the arm. The arm was relaxed with the palm of the hand facing forward. The vertical pinch was parallel to the long axis of the arm. The biceps was measured in the same way as the triceps, but on the anterior surface of the arm.

Muscle strength will be measured using a dynamometer. This is a hand held device designed to measure muscle strength in a simple way. The participant was in a standing position with arms at their sides without touching their body. The elbow was slightly bent. The test was administered on the non dominant hand. The participant did squeeze the dynamometer with as much force as possible, being careful to squeeze it only once. This was done 3 times with a pause of 10-20 seconds between to avoid the affects of muscle fatigue. The results were recorded to the nearest pound or kilogram.

c. **Subjective Global Assessment** was completed by researcher at the time of the visit.

- i. The subjective global assessment(SGA) has been found to be highly predictive of nutritional assessment(Detsky et al., 1987; Jeejeebhoy et al., 1990). Though originally used to categorize surgical patients, this nutritional classification has been shown to be a reliable nutritional assessment tool for renal dialysis patients and liver failure patients(Hasseet al, 1993). It is based on four elements of the patient's history (weight change, dietary intake,

gastrointestinal symptoms, and functional impairment) and three elements of the physical examination (loss of subcutaneous fat, muscle wasting, and presence of edema, and ascites). The information is scored as either A, B, or C which corresponds to the clinical observer's subjective opinion of the patient's nutritional status. The clinician examines the form to obtain a general feel for the patient's status. The more B and C ratings the patient has, the more likely the patient is to be malnourished. After evaluation the patients are categorized into three distinct classes of nutritional status; well nourished, moderately malnourished, and severely malnourished.

- d. Blood work was done after a 12 hour fast for measurements of glucose, insulin, triglyceride, HDL, LDL, total cholesterol, HgbA1C, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, INR, total serum, direct bilirubin, and leptin.
 - i. **Insulin resistance(IR)** was estimated indirectly using the Homeostasis Model Assessment (HOMA) as described by Matthews (1985). It is calculated as follows: $HOMA = [\text{fasting insulin (}\mu\text{U/ml)} * \text{fasting glucose (mmol)/22.5}]$. There is no clearing defining value for IR. Many have used HOMA-IR greater than or equal to 3 as the cut-off value (Cortez-Pinto and Camilo 2004; Marchesini, Bugianesi ,Forlani, Cerreli, Lenzi, Manini,

Natale, Vanni, Villanova, Melchionda, & Rizzetto, 2003; Machado & Cortez-Pinto 2005)

- e. Additional tests at initial visit and 6 months include CBC, with differential including total lymphocytes count, BUN serum creatinine, C-reactive protein, ferritin homocysteine, serum and ionized calcium, TSH, serum zinc, selenium, thiamin, riboflavin, plasma 25-hydroxy vitamin D, plasma vitamin A and retinol binding protein ration.
4. Body Composition and Distribution
 - a. Body composition and distribution was determined using dual energy x-ray absorptiometry (DEXA). The instrument was calibrated according to the manufacturer's guidelines daily. Lean body mass and fat mass was determined from the whole body scan. The percent of fat was calculated. Body mass index was calculated from height and weight. A waist to hip fat ration will be determined between the fat tissues in the android (central) and gynoid (hip and thigh) software defined regions.
 5. Classification clinical staging of cirrhosis. There are two clinical staging methods for cirrhosis that are widely used. The first is Child-Turcotte-Pugh (CTP) and the second is Model for End-Stage Liver Disease (MELD). The CPT method utilizes three quantitative variable: bilirubin, albumin, and platelets or INR and 2 qualitative variables of encephalopathy and ascites. The score ranges from 5 to 15 and is classified as Class A with a score of less than 7, Class B with a score between 7 and 9 points , and Class C with a score of 10 to 15 points. (See Table 3 Child-Turcotte-Pugh Scoring System). A patient with a score of less than 7,

Child A is considered to have compensated cirrhosis and a score greater than 7
(Child B and C) is considered to be uncompensated.

Table 3. The Child-Pugh Score: Grading System for Cirrhosis

| Score | 1 | 2 | 3 |
|------------------------|--------|---------|-----------------|
| Encephalopathy Grade | None | 1-2 | 3-4 |
| Ascites (grade) | Absent | Mild | Moderate-Severe |
| Bilirubin (mg/dL) | <2 | 2-3 | >3 |
| Albumin (g/dL) | >3.5 | 2.8-3.5 | <2.8 |
| Prothrombin Time (sec) | 1-4 | 4-6 | >6 |

Table 4: Timeline for Scheduled Visits and Activities for Each Visit

| | screening | Baseline/day 1 | 3 mos | 6 mos | 1 year |
|--|-----------|-------------------|-------|-------|--------|
| Informed consent | XX | | | | |
| Demographics | XX | | | | |
| Medical history | XX | | | | |
| Vital signs | XX | XX | XX | XX | XX |
| Height | XX | | | | |
| Weight | XX | XX | XX | XX | XX |
| Anthropometrics | | XX | XX | XX | XX |
| Subjective global assessment | | XX | XX | XX | XX |
| Hand grasp strength | | XX | XX | XX | XX |
| Physical exam | | XX | XX | XX | XX |
| Blood work- complete to include all nutritional parameters | | XX | | XX | XX |
| Routine blood work based on condition | | XX | XX | XX | XX |
| DEXA | | XX | | | XX |
| Quality of Life | | XX | | XX | XX |
| 3 day diet | XX | XX | XX | XX | XX |
| Changes in status- hospitalizations, ED visits | XX | XX | XX | XX | XX |

Analysis

Descriptive statistics (means and standard deviations) were calculated for all continuous variables and frequencies and percents were generated for the non-continuous variables. Chi-Square was used to test for differences among groups in nominal categorical outcomes. Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 20.

Primary analysis used one-way analysis of variance (ANOVA) with one between subjects factor (group: Child A, Child B, Child C) examining the differences among cirrhosis groups in nutrients, total body fat (%fat), and muscle strength. When appropriate (significant ANOVA F value), post-hoc pairwise contrasts using the Tukey criteria were examined to determine specifically where group differences occurred.

Human Subjects

Prior to the beginning of the study, Institutional Review Board approval was obtained from all the institutions involved- University of San Diego's Institutional Review Board and the Southern California Liver Center. All participants signed an informed consent and given a copy of the form to keep. Participants were told they could leave the study at any time, and that participation/non-participation did have any effect on their ability to be seen in the clinic. Benefits of participation would include identification of a decrease or increase in biomarkers that potentially brought to within normal limits with nutritional intervention.

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Emerging Health Conditions: Non-alcoholic Fatty Liver Disease

Key Words: Non-alcoholic fatty liver disease; non-alcoholic steatohepatitis

Abbreviations:

NAFLD: non-alcoholic fatty liver disease

NASH: non-alcoholic steatohepatitis

NAFL: non-alcoholic fatty liver

Abstract

This article summarizes the clinical features, pathophysiology, natural history and current treatment of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). The term nonalcoholic fatty liver disease (NAFLD) describes a spectrum of liver diseases ranging from hepatic steatosis to steatohepatitis, fibrosis of the liver and cirrhosis. NAFLD is now recognized as one of the most common liver diseases worldwide and therefore will often be seen by Advance Practice Registered Nurses (APRN). Nonalcoholic fatty liver disease is correlated with visceral obesity, insulin resistance and Type 2 diabetes, metabolic syndrome, and lipid deposition in the

hepatocytes in the liver parenchyma. The pattern of disease is similar to alcoholic liver disease in those without a history of chronic alcohol use. It is estimated that 39 to 95% of obese adults have NAFLD. The prevalence of hepatic steatosis varies with ethnicity. Hispanics have the highest prevalence of fatty liver at 45%, Whites with 33% and Blacks with 24%. Treatment of NAFLD has been focused on treating the underlying metabolic risk factors.

If left untreated, 5-10% of those with NAFLD/NASH develop end stage liver disease, some of them will require transplantation albeit the large majority are not good candidates for liver transplantation (BMI >37). Given the shortage of available organs, it is imperative to identify and treat NAFLD/NASH earlier. Advanced Practice Registered Nurses are seeing obese clients, insulin resistant diabetics clients, and metabolic syndrome clients in primary care settings. We can identify NAFLD/NASH patients early, provide education for our clients and begin management of this progressive disease. We can also identify earlier those patients who will need referral to a liver specialty clinic for further aggressive management. Thus with early detection, we may be able to stop the progression of this liver disease.

Non-alcoholic fatty liver disease (NAFLD) is an alcoholic like liver disease that occurs in individuals who consume less than 20 grams of alcohol per day. NAFLD can inflict heavy burdens on health and well-being (Sandler, Everhart, Donowitz, Adams, Cronin, Goodman, Gemmen, Shah, Advic, & Rubin, 2002). Similar to alcohol-induced liver disease, NAFLD encompasses liver damage, ranging from non-alcoholic fatty liver (NAFL) at the most clinically benign end of the spectrum to cirrhosis on the opposite extreme, where most liver-related morbidity and mortality occur. In NAFL, the liver is steatotic (fat) but generally maintaining its structure and liver function. Non-alcoholic steatohepatitis (NASH) is more severe form than NAFL because there is increased hepatocyte death (steatohepatitis) in addition to steatosis. The liver injury in NASH triggers a repair and regeneration response that sometimes leads to progressive fibrosis and cirrhosis, in which the liver is distorted by regenerating nodules and broad fibrous bands. Persistent abnormal liver enzymes and imaging modalities, however, have limited sensitivity for detecting liver steatosis, steatohepatitis and cirrhosis. In addition, there is no single test that can distinguish NAFLD from other causes of fatty liver disease. Currently, NAFLD is a diagnosis of exclusion (Brunt, 2004; McCullough, 2004; & Neuschwander-Tetri & Caldwell, 2003).

The actual prevalence of NAFLD in the United States is unknown, in part because a liver biopsy is required for a precise diagnosis. Data from the National Health and Nutrition Examination Survey (NHANES III) suggest 24% of American adults may have NAFLD, while other studies suggest that 30% of the population have NAFLD (Sandler et al. 2002). In 2006 liver disease ranking increased from 5th to 15th as the leading cause of death depending on ethnicity (Heron et al, 2009).

Five percent of end stage liver disease has been identified as cryptogenic cirrhosis, a term used to classify cirrhosis of unknown origin. This is currently the third most common indication for liver transplantation (Schreuder, Verwer et al. 2008). NASH can progress to cirrhosis, hepatocellular carcinoma, and liver failure (Browning, Szczepaniak et al, 2004; Harrison & Bisceglie, 2003; Machado, Marquea-Vidal et al, 2006, & Nomura, Kashiwagiet al, 1988). NASH is now identified as a primary cause of 15 to 73% of cryptogenic cirrhosis. The steatosis characteristic of NASH disappears with disease progression, however, making it difficult to identify NASH as the culprit. NAFLD is emerging as the most common cause of liver disease and it is the probable cause when patients present with type 2 diabetes, hyperlipidemia, and obesity after excluding other common causes of chronic liver diseases. Other underlying etiologies are silent autoimmune hepatitis, unidentified viral hepatitis, occult alcohol abuse or other toxins, and cholestasis (Ayata, Gordon et al, 2002; Hubscher, 2009, Maheshwari & Thuluvath, 2006).

Studies have shown a generally low risk of progression but more rapid progression is associated with obesity and diabetes. The risk of progression from NAFLD to cirrhosis is 1-2% over 15 to 20 years, whereas the risk for progression from NASH to cirrhosis is 12-20% over 8 years (Adams, Lymp et al., 2005; Adams, Sanderson et al., 2005; Dam-Lasent, Becker t al.,2009; & Sanyal, Banas et al.,2006).

Limited data suggest that 3% of individuals with NAFLD may have nonalcoholic steatohepatitis (NASH), with rates rising to 37% among the morbidly obese. The progression of cirrhosis to end-stage liver disease is 39-63% in patients with NASH. Of these patients, 22-33% will experience liver disease-related mortality, with a survival

time of 5-7 years. The development of ascites is the most common liver-related morbidity. The mortality rate is higher than in the general population (standard mortality ratio, 1.34; 95% CI: 1.00-1.76; $p = 0.03$) (Adams, Lymp et al. 2005).

Globally, it is estimated the prevalence of fatty liver has increased from 14% in 1988 to 31% in 2005 (Adams, Sanderson et al. 2005). For APRNs, this means approximately 33% of patients have fatty livers. Numerous considerations, however, may complicate the diagnosis. The differential diagnoses one must consider are Wilson's disease, autoimmune hepatitis, hepatitis C virus, galactosemia, and alcohol use/abuse. Additionally, high serum ferritin and transferrin levels need to be evaluated.

The presence of steatosis on histological examination of a liver biopsy is necessary for a diagnosis of NASH. The steatosis is most commonly macrovesicular, although some microvesicular steatosis may be seen. In addition, a mixed inflammatory infiltrate consisting of neutrophils and degeneration and hepatocyte necrosis may be present. Mallory's hyaline bodies may also be seen (Harrison & Bisceglie, 2003). (See table 5.)

Table 5: Histologic Spectrum of Non-Alcoholic Fatty Liver Disease

| Non-alcoholic Fatty Liver Disease (NAFLD) | |
|---|---|
| Histologic Spectrum of Liver Disease | |
| NAFL | type 1-fatty liver (steatosis) |
| | Type 2-steatosis + nonspecific inflammation |
| NASH | Type 3-steatosis + ballooning degeneration and increased hepatocyte death (steatohepatitis) |
| | Type 4-steatosis + fibrosis and/or Mallory bodies |
| Cirrhosis | -complication of Types 3 and 4. |
| | Regenerative nodules + fibrosis |

Multiple risk factors are associated with non-alcoholic fatty liver disease: obesity (high BMI or waist to hip ratio), metabolic syndrome, type 2 diabetes mellitus, alcohol ingestion, female gender and inflammation (including grade and C-peptide). Although most of the studies have been small and they used a variety of histological scoring systems, these are the risk factors identified in the studies (Stengel & Harrison, 2006).

It is questionable whether fatty liver is a risk factor for some of these risk factors or part of a disease complex. Cirrhosis has been found in patients worked up for a gastric bypass and in patients with cardiac failure not doing well, especially with a history of diabetes mellitus. NASH has also been identified in patients with a family history (Rubenstein, Lavine et al, 2008; Younossi, Gramlich et al., 2004).

Obesity related liver disease

Several factors have led to a state of decreased calorie utilization over the past 50 years. Sedentary lifestyle, energy-dense foods, and increased consumption of foods and

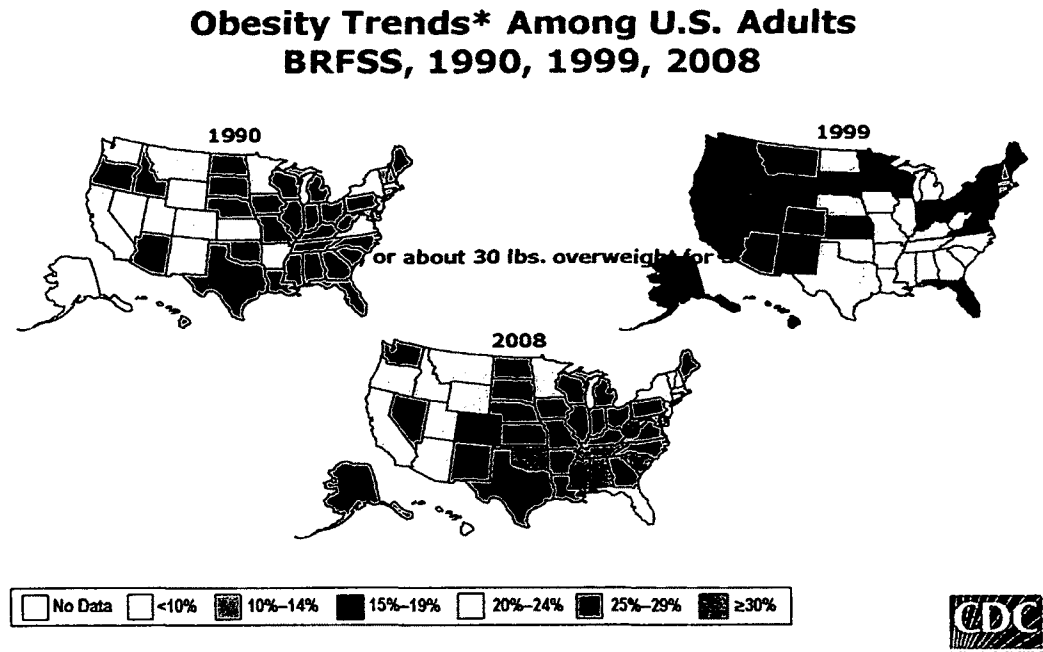
drinks with high fructose have contributed to an increase in adipogenesis. However, while obesity-related chronic inflammation plays a very strong supporting role in the pathogenesis of NAFL and NASH, the mechanisms that drive the progression from NAFL/NASH to cirrhosis remains less well understood.

It is thought to be a two hit process. The first hit is an accumulation of fat in the hepatocytes. Twenty percent of the glucose eaten at a meal is metabolized by the liver, but 100% percent of fructose eaten is metabolized by the liver. With an accumulation of fat in the hepatocytes, there is an increased delivery of fatty acids to the liver, inhibition of β -oxidation of fatty acids, decreased synthesis or secretion of very low density lipids, hyperlipidemia, diabetes mellitus, and obesity. Fat accumulation in NASH is associated with a decrease in insulin and an increase of fat in the diet. Therefore, a decrease in glucose uptake and an increase in free fatty acids are seen.

The second hit is thought to be due to an increase in hepatic oxidative stress, which is greater than the antioxidant defenses. This leads to activation of stellate cells, causing fibrosis and the generation of proinflammatory cytokines. Inflammation, hepatocyte swelling, and ultimately death are a result of the proinflammatory cytokines. This perpetuates the formation of Mallory bodies and fibrosis.

As body mass index (BMI) increases, the fat in the liver increases. Over the past several decades, Americans have become more overweight. Notably in 2008, there was not a state within the country with less than 15% obesity (see Figure 2). A key consequence of obesity is the development of insulin resistance and the metabolic syndrome. This development provides a critical link between obesity and NAFLD.

Figure 2: Obesity Trends Among U. S. Adults



The prevalence of NAFLD and NASH increases among the morbidly obese. Normal transaminase levels do not exclude NASH or fibrosis (Mofrad, Contos et al. 2003). Patients undergoing bariatric surgery have a prevalence of 84-96% NAFLD/NASH, 25-55% progress to NASH. Further breaking down the NASH components, 34%-47% have fibrosis and 2% to 12% have bridging fibrosis or cirrhosis (Clark 2006).

Machado (2006) reanalyzed 12 observational and transversal studies involving 1620 patients who had undergone bariatric surgery. All these 12 studies enrolled patients consecutively and analyzed data prospectively. The prevalence of steatosis averaged 91% (range 85% to 98%), and the prevalence of NASH averaged 37% (range 24% to 98%). The conditions most frequently associated with NASH were diabetes and insulin

resistance. Hypertension was most frequently associated with advanced hepatic fibrosis(Machado, Marques-Vidal et al. 2006). Post-surgery, there appeared to be a decrease in the grade of steatosis and in most cases a decrease in the grade of hepatic inflammation and stage of fibrosis (Barker, Palekar et al. 2006; de Almeida, Rocha et al. 2006).

Steatosis

Numerous studies have found an increase in alanine aminotransferase (ALT), triglycerides, and body mass index (BMI) were the most sensitive markers of steatosis. In the Dallas Heart Study (Browning, 2006), hepatic triglycerides content was determined by proton magnetic resonance spectroscopy (MRS) in a multiethnic cohort of 2287 subjects. The median hepatic triglycerides content was 3.6% but it varied widely from 0% to 41.7% (Browning, Szczepaniak et al. 2004). Overall, nearly a third of the study population had hepatic steatosis, but the prevalence varied by ethnicity: among Hispanics the prevalence was 45%, among Caucasians 33%, and among Blacks 24% (Browning, Szczepaniak et al. 2004; Weston, Leyden et al. 2005). The higher prevalence of hepatic steatosis in the Hispanic population was related to the higher prevalence of insulin resistance and obesity. However, the lower prevalence of hepatic steatosis in Blacks was not explained by ethnic differences in BMI, insulin resistance, alcohol consumption, or medication use(Browning, Szczepaniak et al. 2004). The National Institutes of Health (NIH) are currently investigating genetic risk factors for NAFLD and this provides evidence of a genetic component to NAFLD.

Metabolic Syndrome

The American Heart Association and the National Heart, Lung, and Blood Institute Scientific Statement (Alberti, et al, 2009; Grundy, 2005) have identified the metabolic syndrome as a group of interrelated metabolic risk factors. The presence of these factors identifies a person at risk for atherosclerotic cardiovascular disease and type 2 diabetes mellitus. Key risk factors include abdominal obesity and insulin resistance. Additionally three of five of the following risk factors constitutes a diagnosis of metabolic syndrome: abdominal obesity (waist circumference of >102 centimeters in men and >88 centimeters in women), elevated fasting glucose of > 100 mg/dL, elevated triglycerides of >150 mg/dL, low HDL of <40 mg/dL in men and <50 mg/dL in women, and hypertension, defined as a systolic pressure of >130 mm Hg and a diastolic pressure of >85 mm Hg. Metabolic syndrome is associated with a variety of conditions, including fatty liver (Grundy, Cleeman et al. 2005).

Using the criteria of the National Cholesterol Education Program's Adult treatment Panel III guidelines, Marchesini and others (2003) found the prevalence of metabolic syndrome to be 36% in 304 consecutive non-alcoholic fatty liver disease patients without overt diabetes. The prevalence of metabolic syndrome increased with increasing BMI, from 18% in normal weight individuals to 29% in overweight individuals to 67% in obese individuals. Metabolic syndrome was also significantly associated with female gender (OR =3.02; 95% CI: 1.57 to 6.02) and age (OR = 1.54; 95% CI 1.23 to 1.93 for every 10 years). Eighty eight percent of the subjects diagnosed with NASH by liver biopsy (120 subjects out of 163 subjects obtaining liver biopsies) had metabolic syndrome. The other 43 patients had pure fatty liver disease. Clearly the

presence of metabolic syndrome places patients at risk of NASH and further progression to fibrosis and cirrhosis.

Dietary and Lifestyle Habits

Dietary habits may contribute to the development of NASH. When food intake was reviewed in a cohort of 25 NASH patients and a healthy control matched group for BMI, age, and gender, the NASH patients were found to consume a diet higher in saturated fat and cholesterol and lower in polyunsaturated fat, fiber, and antioxidant vitamins C and E (Capristo, Meiele et al. 2005). In another study, NASH patients were found to consume a diet higher in total calories (energy) than healthy controls (Musso, Gambino et al. 2003). Musso (2003) also examined the relationship of dietary habits to insulin sensitivity and postprandial triglyceride metabolism. They found the insulin sensitivity index was significantly lower in NASH patients and was correlated with saturated fat intake and postprandial rise of triglycerides. There was also a suggestion of a defect in ApoB secretion since the apolipoprotein (Apo) B48 and APO B100 responses were flat and dissociated from the triglyceride response in NASH patients. Musso and colleagues concluded dietary habits may promote steatohepatitis directly by modulating hepatitis triglyceride accumulation and antioxidant activity, or indirectly, by affecting insulin sensitivity and postprandial triglyceride metabolism.

Much work has been done on the association of dietary intake and metabolic syndrome, but few studies have focused on dietary habits associated with NAFLD. Tendler et al. (2007) found in a study of five patients a low carbohydrate, ketogenic diet led to significant improvements in liver histology in patients with NASH/NAFLD. There

were improvements in both steatosis and necroinflammatory grade and there was also reduction in the fibrosis pattern in three patients. One patient experienced histological worsening. However, this patient was not compliant with the diet, nor did he lose weight. It was difficult to determine whether histologic changes were due to a low carbohydrate diet to the weight loss experienced by participants. This study suggests decreased carbohydrate intake may have an independent beneficial effect on fatty liver.

Zelber-Sagi et al. (2007) examined the dietary habits of 349 Israeli volunteers, findings indicated the NAFLD group (diagnosed by ultrasound) consumed less fish rich in omega-3, almost twice the amount of soft drinks and 27% more meat. The higher intake of soft drinks and meat was associated with an increased risk of NAFLD, independent of age, gender, BMI and total calories. Studies have also shown that a fructose-enriched diet leads to development of macrovesicular and microvesicular fat deposits and increases in hepatitis triglyceride and cholesterol levels. These findings suggest high carbohydrate diets may contribute to NAFLD ((Ackerman, Oron-Herman et al. 2005).

Medications for NAFLD

There is no definitive pharmacotherapy for the treatment of NAFLD. This is a multifactorial disease in which insulin and insulin resistance plays a fundamental role. Fat accumulation in the liver is a consequence of lipids in the liver, adipose tissue, muscle and gut. Anti-oxidants in the hepatocytes are lacking, but this is thought to be due to increasing oxidative stress. Together these problems cause inflammation and fibrosis reducing the activation of Kupffer and stellate cells.

Ongoing studies are looking at pharmacology interventions to prevent disease progressions. The drugs currently being used are insulin sensitizers (metformin, pioglitazone, and posiglitazone), antioxidants (vitamins E, C and silymarin), hepatoprotective agents (betaie, s-adenosyl, and ursodeoxycholic), hypolipidemic drugs (fibrates, statins, and omega 3 fatty acid), anti-tumor necrosis factor regimens (pentoxifylline and adiponectin) and angiotensin receptor blockers (losartan) (Belfort, Harrison et al, 2006; Harrison, Torgerson et al, 2002; Neuschwander-Tetri, Brunt et al., 2003; Promrat, Lutchman et al., 2004; Schwimmer, Middleton et al., 2005).

The thiazolidinediones class improves insulin sensitivity primarily in adipose tissue by activating the nuclear transcription factor-perioxisome proliferator-activated receptor- γ (PPAR- γ) through binding ligands. Treatment with pioglitazone along with changes in diet has found to significantly improve hepatic insulin sensitivity and glucose clearance. Hepatic fat content declined by 54% after treatment for 6 months with pioglitazone and diet while it remained unchanged in a group treated with placebo and diet. Pioglitazone appears to have direct anti-fibrotic effects on the liver by preventing the activation of hepatic stellate cells, resulting in reduced expression of type 1 procollagen, smooth muscle actin and transforming growth factor- β 1 (TGF- β 1) (Belfort, Harrison et al. 2006).

Metformin has not shown consistent results in the trials. It improves insulin sensitivity primarily in the liver, but histologic improvement has been generally limited (Bugianesi, Gentilcore et al., 2005; Goodarzi & Bryer-Ash, 2005; Loomba, Luchmann et al., 2006; Nair, Diehl et al., 2004).

Combining vitamin E with pioglitazone significantly improved metabolic parameters and reduced steatosis, cytologic ballooning, Mallory's hyaline bodies and pericellular fibrosis from baseline (Sanyal, Mofrad et al. 2004). These findings are promising, however they must be interpreted with caution due to the limited sample size.

Evaluation of the Individual for the Presence of NAFLD

A thorough history of the individual and a physical examination begin the process of identifying NAFLD. NAFLD is the most common cause of asymptomatic elevated liver enzymes, found in 77% of patients (Cortez-Pinto & Camillo, 2004). The most frequent symptoms expressed by the individual are right upper quadrant pain, fatigue, and abdominal discomfort. The examiner may find hepatomegaly and abnormal liver tests. A complete hepatic panel with gamma-glutamyl transferase, AST, ALT, and total bilirubin is needed. However, the NIH criteria differ from the laboratory values found on lab tests. Normal liver enzymes for a woman are ALT of 19 and for a male, 30. Results higher than these are considered elevated (Prati, Taioli et al. 2002). In NAFLD, ALT is greater than AST ((Huber 2004).

Additional laboratory tests are needed to exclude alternate causes of abnormal liver enzymes. A hepatitis panel to rule out viral hepatitis, and iron studies and ferritin to rule out hereditary diseases such as hemochromatosis are needed. A thyroid panel, especially thyroid stimulating hormone (TSH), needs to be checked since thyroid abnormalities may alter liver function. Anti-liver-kidney microsomal antibodies, antinuclear antibodies, and anti-smooth muscle antibodies will indicate whether autoimmune hepatitis is a culprit. Primary biliary cirrhosis is identified by a greater than

1:4 positive antimitochondrial autoantibody titer. Alpha-1 antitrypsin antibodies help identify hereditary enzyme deficiency that leads to both lung and liver disease.

There are also noninvasive studies to identify the presence of steatosis.

Sonography is the most commonly used method. Computerized tomography and MRI have also been used, though none of these are ideal. No imaging study to date has been able to distinguish between simple fatty liver and NASH or with fibrous NASH.

However, this area continues to be investigated for the ability to assist in the diagnosis of NASH.

Liver biopsy remains the “gold standard” for the definitive diagnosis of NAFLD. It completes the work-up in individuals without significant coagulopathy and who are at high risk for having bridging fibrosis based on other clinical and laboratory parameters. The decision to perform a biopsy continues to be debated, though a biopsy makes it possible to predict a patient’s clinical pathway based on the findings of the biopsy. Simple steatosis has a low likelihood of progression to advanced liver disease. NASH is more likely to progress to advanced disease, with or without fibrosis. The biopsy, however, has potential risks related to the procedure itself and the current lack of treatment for NAFLD.

NAFLD: Therapeutic Approach

Based on the data, it is possible to construct a therapeutic algorithm that can be used to treat patients with NAFLD. Treatment of NAFLD has focused on the underlying metabolic risk factors. Those with overt features of metabolic syndrome (obesity, diabetes, hypertension and dyslipidemia) should have those diseases treated according to

standard approaches. Regardless of whether or not patients exhibit other features of metabolic syndrome, all individuals with NAFLD should have some form of therapy for their liver disease. Fatty liver may be categorized as primary or secondary depending on the pathogenesis. Distinction between primary and secondary types is important since these have different treatment and prognosis.

Treatment is guided by the severity of the liver damage, and the degree of proof of therapeutic efficacy and safety. Patients with simple steatosis should be encouraged to reduce caloric consumption and increase physical activity, using an approach that improves insulin sensitivity in diabetes (Andersen, Gluud et al. 1991; Drenick, Simmons et al. 1970; Rozenthal, Brava et al. 1967). Patients with steatohepatitis should be given similar advice and may also be encouraged to enroll in one of the several treatment trials underway. Patients with cirrhosis should receive standard therapy for portal hypertension and undergo routine screening for hepatocellular carcinoma. If hepatic decompensation ensues, patients without contraindications for surgery should be considered for orthotopic liver transplant (OLT).

Once NAFLD has been diagnosed, periodic monitoring to assess disease progression is needed. NAFLD can reoccur after liver transplant, and aggressive efforts are needed to prevent and treat metabolic syndrome post-OLT (Sutedja, Gow et al. 2004; Ghali and Lindor.2004). If diet contributes to NASH, then weight loss may help reduce fat deposits. In women with gestational diabetes, a weight loss of 8% was associated with significant reduction in liver fat content (39+ or - 5%)(Tiikkainen, Bergholm et al. 2003).

Summary

Dietary treatment to prevent and control NAFLD has not been clearly defined. The diet for weight loss remains debatable, though a diet enriched with unsaturated fatty acids is theoretically reasonable. Restricting calories is known to achieve weight loss. Foods with a low glycemic index may reduce mean incremental blood glucose. In summary, lifestyle modifications incorporating a gradual weight loss and increased exercise are an important component of patient management and are associated with improved liver histology.

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Facilitating Lifestyle Changes to Manage Progressive Fatty Liver Disease

Abstract:

Background: With the increase in obesity in the United States, and the rising incidence of metabolic syndrome, more patients are presenting with abnormal liver injury tests related to fatty liver. There is no standard therapy for fatty liver disease other than lifestyle changes to combat the metabolic derangement and avoid the progression to NASH/cirrhosis. The aim of this study was to describe the relationship of the intensity in care management by the nurse practitioner on education and support of lifestyle changes to improve metabolic parameters in patients with fatty liver. **Methods:** Seventeen patients were identified with a diagnosis of Fatty Liver disease-13 adult patients and 4 pediatric patients. Patients were identified through elevated liver enzymes, and exclusion of all other possible liver diseases. Patients were followed every 2-3 months initially and then tailored to the individual patient needs resulting in 1 month to 3 month follow up. Each structured clinic visit lasted 30-45 minutes to assess patients and discuss lifestyle changes. **Results:** Thirteen adults-8 females (62%) and 5 males (38%), age range 29-72

years and four pediatric subjects-3 males and 1 female, age range 12-17 years were in the study. The adult participants had an initial BMI of 30.93 ± 3.7 , AST 49.5 ± 27.8 , and ALT 71.5 ± 43.8 , while the pediatric participants had a BMI of 33.33 ± 6.3 , AST of 42.3 ± 14 , and ALT 66.65 ± 36.6 . During the follow-up period, the adult participants self-selected to increase frequency of visits to monthly or every other month for self-accountability. Diet changes were more difficult in adults since 85% of the adult's skipped either breakfast or lunch. The adult averaged 4 medications-including antihypertensives, and cholesterol medications. The pediatric participants continued with every 3 months but increased their physical exercise to 5 times a week-1-1/2 hours per session. Their diets included more fruits and vegetables previously lacking. By self-report, they made better choices through the school lunch program. The BMI remained relatively stable for 6 months for both groups, though at three months ALT and AST was normal in the adult group in 55% and 44% respectively. In contrast, 100% of the pediatric participants achieved normal AST and ALT levels by 3 months. Adolescent growth in height facilitated the mild changes in the BMI, whereas in the adult, the BMI changes were based on actual weight loss. Conclusions: Outside clinical trials; (1) management of fatty liver is feasible; (2) improvement occurs with dedicated time and a contract with the patient-listening to their individual needs, (3) albeit chemical and metabolic improvement occurs, it is slow, and (4) pediatric patients require full participation and family support in lifestyle changes of the patient to achieve the goals of therapy. The trial showed to be labor intensive and this model could be the most cost effective.

Introduction

Non-alcoholic fatty liver disease is emerging as an increasingly important cause of liver disease. It is associated with obesity, diabetes, and insulin resistance. Non-alcoholic fatty liver disease (NAFLD) can lead to cirrhosis and may result in significant morbidity and eventual mortality. Though there is no specific therapy, exercise and nutritional intervention appears to improve and prevent these inter-related conditions.

The risk of progression from NAFLD to cirrhosis is 1-2% over 15 to 20 years, whereas the risk for progression from NASH to cirrhosis is 12-20% over 8 years (Adams, Lymp et al. 2005; Adams, Sanderson et al. 2005; Sanyal, Banas et al. 2006; Dam-Larsen, Becker et al. 2009). Additionally, there is a more rapid progression of fatty liver disease when obesity and diabetes confound the health issues.

The changes to the CDC-Behavioral Risk factor surveillance system, which provides the prevalence of self-reported obesity among United States adults have resulted in a new baseline. Traditionally the telephone survey was based on land lines, and this year cell phone users were surveyed to obtain data that better represents the diverse population (CDC, 2011). This expanded and improved way to gather and process information does not accurately compare to previous findings. More than one-third of United States Adults are obese. In fact there is not a state less than 20% obesity. The Southern States have the highest obesity rate at 29.5% (Table 6). Our clinic population in Southern California is primarily Hispanic/Latino and the obesity rate is around 40%.

Table 6: Prevalence of Self-Reported Obesity Among U.S. Adults, 2011

Obesity Prevalence



Numerous studies have found that an increase in alanine aminotransferase (ALT), triglycerides, and body mass index (BMI) were the most sensitive markers of steatosis. In the Dallas Heart Study, hepatic triglycerides content was determined by proton magnetic resonance spectroscopy (MRS) in a multiethnic cohort of 2287 subjects. The median hepatic triglycerides content was 3.6% but it varied widely from 0 to 41.7 percent. Overall, nearly a third of the study population had hepatic steatosis, but the prevalence varied by ethnicity: among Hispanics/Latinos the prevalence was 45%, among Caucasians 33%, and among blacks 24% (Browning, Szczepaniak et al. 2004; Weston, Leyden et al. 2005). The higher prevalence of hepatic steatosis in the Hispanic/Latino population was related to the higher prevalence of insulin resistance and obesity. However, the lower prevalence of hepatic steatosis in Blacks was not explained by ethnic differences in BMI, insulin resistance, alcohol consumption, or medication use (Browning, Szczepaniak et al. 2004). The National Institutes of Health (NIH) are

currently looking into genetic risk factors for NAFLD which may provide evidence of a genetic component to NAFLD.

Metabolic Syndrome

The American Heart Association and the National Heart, Lung, and Blood Institute Scientific Statement have identified the metabolic syndrome as a group of interrelated metabolic risk factors. The presence of these factors identifies a person at risk for atherosclerotic cardiovascular disease and type 2 diabetes mellitus. Key risk factors include abdominal obesity and insulin resistance. Additionally three of five of the following risk factors constitutes a diagnosis of metabolic syndrome: abdominal obesity (waist circumference of >102 centimeters in men and >88 centimeters in women), elevated fasting glucose of > 100 mg/dL, elevated triglycerides of >150 mg/dL, low HDL of <40 mg/dL in men and <50 mg/dL in women, and hypertension, defined as a systolic pressure of >130 mm Hg and a diastolic pressure of >85 mm Hg. Metabolic syndrome is associated with a variety of conditions, including fatty liver .

The economic impact of chronic illnesses, specifically fatty liver disease and obesity, is a burden to the health care system. While these diseases are often associated together, they are also linked with a higher risk for several other serious health conditions such as hypertension, type 2 diabetes, hypercholesterolemia, and coronary artery disease. Direct medical costs and indirect costs such as absenteeism from work, decrease productivity, and disabilities are increasing with the rise of obesity and fatty liver disease. Baumeister et al (2008) reported an increase of 26% in health care costs of a patient

diagnosed with fatty liver disease. There were reports the cost of obesity in 2008 to be estimated as high as \$147 billion.

The current treatment of fatty liver disease remains diet, exercise and weight loss, though there is little data to support the intensity. Maintaining weight loss in clinical practice is difficult despite the benefits.

Aim:

The aim of this study was to describe the relationship of the intensity of care management on education and support lifestyle changes to improve metabolic parameters in patients with fatty liver disease.

Methodology

A repeated measures non experimental feasibility study design was used for this study. The sample was recruited from patients referred to Southern California Liver Centers with elevated liver enzymes. Between September 2011 and January 2012, 17 (13 adults and 4 adolescents) patients were identified with a diagnosis of fatty liver disease. Inclusion criteria were elevated liver enzymes and the exclusion of all other liver disease. Patients were both English and Spanish speaking. The study procedures, including the protocols for health care and obtaining informed consent were reviewed and approved by the administrative and University institutional review boards.

Demographic Data:

Demographic data was obtained through the clinic directed questionnaire and chart review.

Medical History:

Co-morbidities were assessed through medical record audits, diagnostic (ICD9 codes), health care utilization (outpatient, inpatient, and emergency room encounters), patient history. All medication and pharmacy information was taken at each visit as standard procedure in the clinic. Patients were/are asked to bring in all medications to verify dosage and frequency. At the initial visit personal and family history are taken including diseases related to liver, diabetes, cancer, cardiovascular, and obesity and risk factors for such diseases.

Clinical Criteria:

NAFLD was diagnosed based on a combination of clinical features, blood profile, and radiological imaging or liver biopsy. The blood profile included evidence of elevated liver enzymes, gamma-glutamyl transpeptidase, and alkaline phosphate. Radiological features identified fatty infiltrations or fibrosis. A liver biopsy identified the percent of steatosis or provided a NAFLD Activity Score (NAS).

Nutritional Assessment:

Nutritional assessment was based on the following: anthropometry, 24 hour diet recall, and laboratory values of vitamins and minerals. All measurements were taken by the same investigator to avoid any inter-observer variation.

Anthropometry:

All patients had a baseline body mass index (BMI) calculated at each clinic visit. BMI was calculated by dividing weight in kilograms by height in meters squared and

calculated according to the Centers for Disease Control and Prevention adults charts. BMI was used as a baseline comparison. The waist circumference was taken at the level of the iliac crest, placing a tape measure in a horizontal plane (parallel to the floor) with participant standing. The measurement was taken at the end of expiration and snug but not compressing the skin. Additional anthropometric measurements include the following midarm circumference (MAC), triceps skin fold thickness (TST), biceps skin fold thickness (BST), and handgrip strength. MAC was measured midway between the tip of the shoulder and the tip of the elbow (olecranon process and the acromium) to the nearest millimeter with a measuring tape for both the right and left arm. The participants palm was facing the thigh. TST and BST, established measures of fat stores, was measured to the nearest millimeter on both arms using the Harpenden skin fold calipers in a standard manner. Each measurement was taken three times and the average values calculated and recorded (Lee & Nieman, 2007).

Visceral proteins

Serum albumin concentration is the most frequently used laboratory measure of nutritional status. It has been used to assess change in nutritional status and stratifying the risk of malnutrition. Serum proteins are affected by capillary permeability, drugs, impaired liver function, and inflammation. In a dehydrated patient, albumin levels may be falsely high due to decrease plasma volume. Because of a relatively long half-life of approximately 14-20 days, albumin has been identified as a marker of chronic nutritional status. Albumin is expected to return to normal as the inflammatory response resolves.

Dietary intake and assessment

The assessment of the individual patient's intake was determined by the dietary recall method of the patient. The patient was instructed to write down the daily intake and time of intake in a provided food diary. If they did not bring this diary, the provider reviewed the previous 24 diet recall of the patient at the time of the visit. The objective was to determine the categories of food eaten based on the pyramid.

Lifestyle Changes

The changes in lifestyle were determined by self-reported modifications of diet and exercise. The patient set goals at each visit and reviewed at subsequent visits with the APRN. The goals set involved changes or modifications in diet, exercise, and sleep patterns.

Statistical Analysis

All data was entered into Statistical Packages for the Social Sciences (SPSS) version 16.0 (Chicago, Illinois, USA) software for analysis. Descriptive statistics were calculated for all analysis variables.

Results

Seventeen patients with diagnosed fatty liver disease were identified during September 2011 through January 2012. There were 13 adults and 4 adolescents. The mean age of the adults was 58.8 ± 12.9 (range 29-72 years) and the mean age of the adolescents was 16 years ± 2.9 (range 12-17 years). The majority of patients (n=15) chose to respond to the assessment interviews in English. All participants had a diagnosis of elevated liver enzymes for referral to the specialist. Obesity was seen in 100

% of the participants; not surprising given that obesity is a risk factor for NAFLD. The initial laboratory values indicated a mild to moderate increase in liver injury tests. The hepatic function was intact. There was no biochemical evidence of cirrhosis. The laboratory results indicated non cirrhotic liver patients, without infection or anemia. The liver enzymes were elevated in all the adults and adolescents. The basic demographic and clinical features are presented in Table 7.

Table 7: Basic Demographic and Clinical Features

Demographic Data and Clinical Features
adults n=13, adolescents n=4 unless otherwise stated

| | Adults | Adolescents | Normal Values |
|----------------|-----------------|------------------|----------------------------------|
| WBC | 6.4 ±1.4 | 6.9±1.4 | 3.8-10.8 thousand/uL |
| HGB | 14.25±1.4 | 13.7±0.73 | 11.7-15.5 g/dL |
| Plts | 242.8±59.6 | 277.75±41.7 | 140-400 thousand/uL |
| ALT | 71.5±43.8 | 66.65±396.6 | 6-40 U/L |
| AST | 49.5±27.8 | 42.3±14 | 10-35U/L |
| GGT | 201.5±262.2 n=6 | 30.5±26.2 n=2 | 0-45 U/L female 0-65 U/L male |
| Albumin | 4.29±0.39 | 4.5±0.21 | 3.6-5.1 g/dL |
| INR | 1.03±0.9 | 1.05±0.07 n=2 | 9.0-11.5 sec |
| DM | 5/13 | 1/4 | |
| HTN | 4/13 | 0/4 | |
| CAD | 0/0 | 0/0 | |
| Hyperlipidemia | 6/13 | 1/4 | |

Patients were followed every 2-3 months but tailored to the individual patient needs and preferences. Each structured visits lasted 30-45 minutes to assess patient clinical condition, discuss lifestyle changes and develop and evaluate goals. At the initial visit, the laboratory tests include a CBC, CMP, lipid panel, fasting insulin, hemoglobin A1C, vitamins E, B6, K, D, and folate, and minerals Calcium, phosphorus, zinc, copper,

iron, selenium, and magnesium. At subsequent visits, laboratory values of CBC and CMP, and other labs as directed by patient evaluation and calculated BMI were done.

Both the adult and adolescent groups had co-morbidities. There was almost 50% of Diabetes type 2, hypertension, and hyperlipidemia seen in the adults. Surprisingly, one adolescent patient was diagnosed as pre-diabetic and borderline hyperlipidemia. At the time, he was not placed on medications. Diet and exercise were prescribed by his primary physician for treatment.

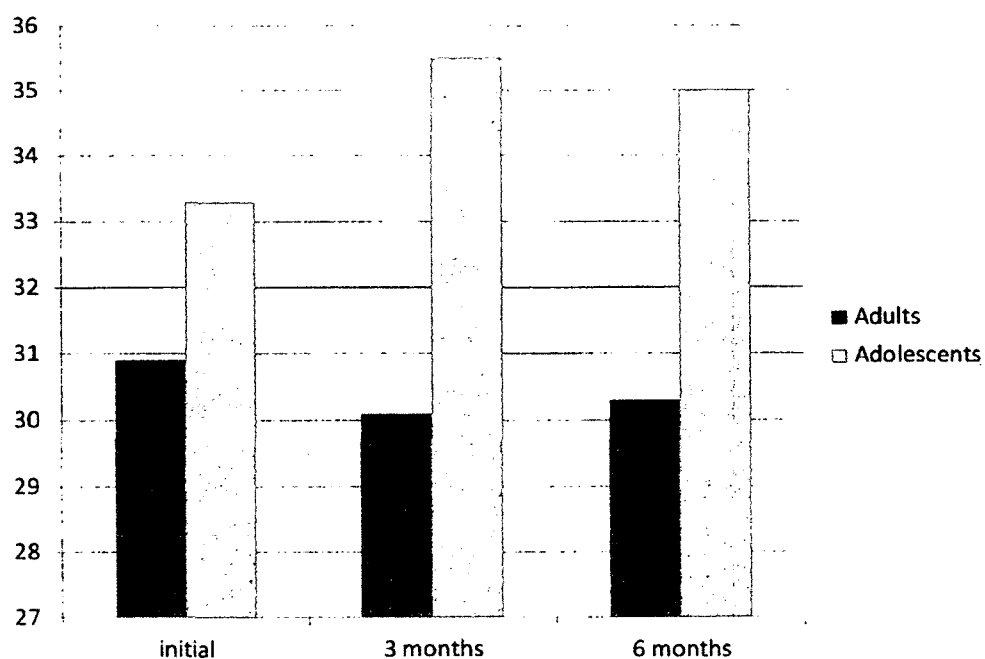
Initial anthropometric measurement of waist, arm circumference, bicep and tricep skin fold, and BMI were increased in both groups (Table 8). The waist measurement of the adults was 41.5 inches \pm 2.68 and the adolescent waist was 43 inches \pm 6.14. The mid arm circumference of the right side was 32.5 cm \pm 1.64 for adults and 37.3 cm \pm 1.43 for adolescents. The left mid arm circumference was 34 cm \pm 1.86 and 37 cm \pm 1 .53, adults and adolescents respectively. The triceps was measured for both right and left in the adults and adolescents. The results were 20.5 mm \pm 3.83 and 21.4 mm \pm 4.65 in adults and 29.5 mm \pm 2.12 and 27.4 mm \pm 6.22 in adolescents. The biceps in the adults and adolescents were also measured on the right and left side. The adults biceps for the right was 19.6mm \pm 5.68 and for the left was 20.17mm \pm 4.54. The adolescent right and left bicep was 28 mm \pm 9.89 and 33.5 mm \pm 9.19, respectively.

Table 8: Initial Anthropometric Measurements

| | Adults | Adolescents | Normal values |
|--|--------------|--------------|--|
| Waist | 41.5 ± 2.68 | 43 ± 6.14 | <35 inches |
| Mid arm circumference, left non dominant | 13.35 ± 1.86 | 14.66 ± 1.53 | >22 |
| Triceps, left non dominant | 21.4 ± 4.65 | 27.4 ± 6.22 | Range 13.8-14.2 males based on age Range 22.3-24.9 females based on age |
| BMI | 30.93 ± 3.7 | 33.33 ± 6.3 | 18-25 |

Over the six months of assessment, the adults lost weight, decreasing their body mass index (BMI) from 30.9 initially to 30.3 at six months. The adolescents increased their BMI initially at 33.3 to 35 at six months. During this time period, the height of the adolescent remained unchanged. At six months, 2 of the adolescents began to increase in height (Table 9).

Table 9: Body Mass Index changes over 6 months in Adults and Adolescents



Laboratory studies indicated both groups were non cirrhotic (Table 7). Albumin levels were 4.29 ± 0.39 and 4.5 ± 0.21 in adults and adolescents respectively. The GGT was initially high 20.1 ± 206.2 ($n=6$) in the adults and 30.5 ± 26.2 ($n=2$) in the adolescents. Initial elevated liver enzymes of ALT 71.5 ± 43.8 and 66.65 ± 39.6 , and AST 49.5 ± 27.8 and 42.3 ± 14 in the adults and adolescents respectively were found (Table 10). At three months, the ALT and AST were normal in the adolescents. While in the adults, the ALT and AST were normal in 55% and 44% respectively.

At six months, the ALT and AST remained normal in the adolescents (Table 11). While in the adults, the ALT and AST continued to decrease to normal levels.

Table 10: Initial Liver Function Tests and BMI of Adults and Adolescents

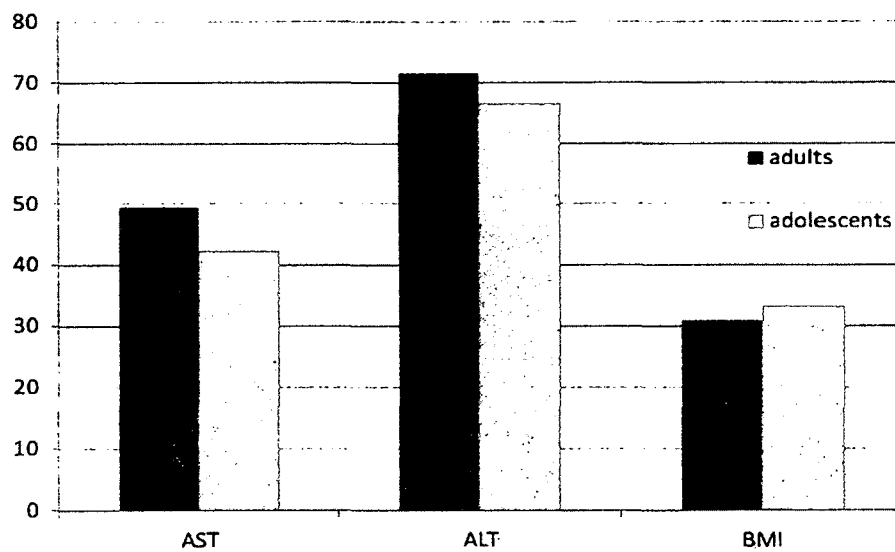
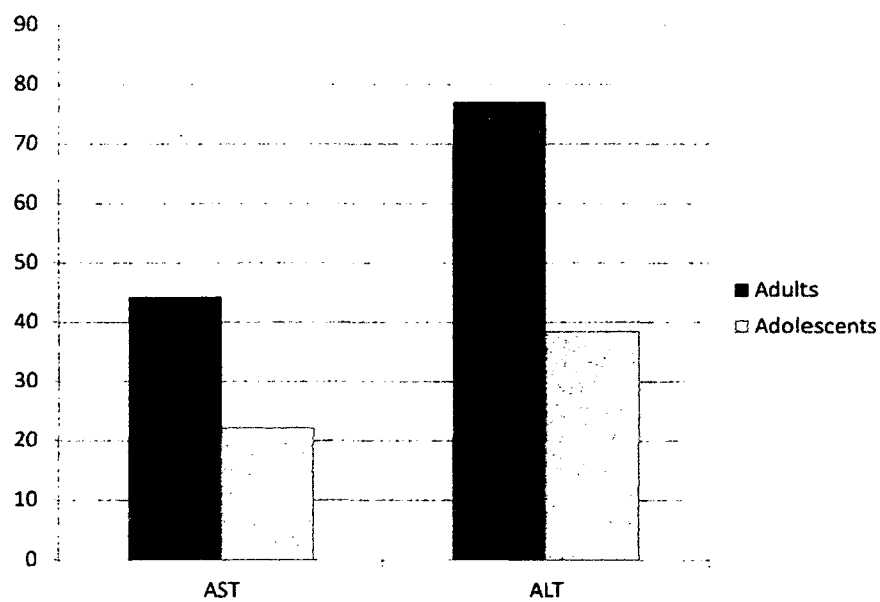
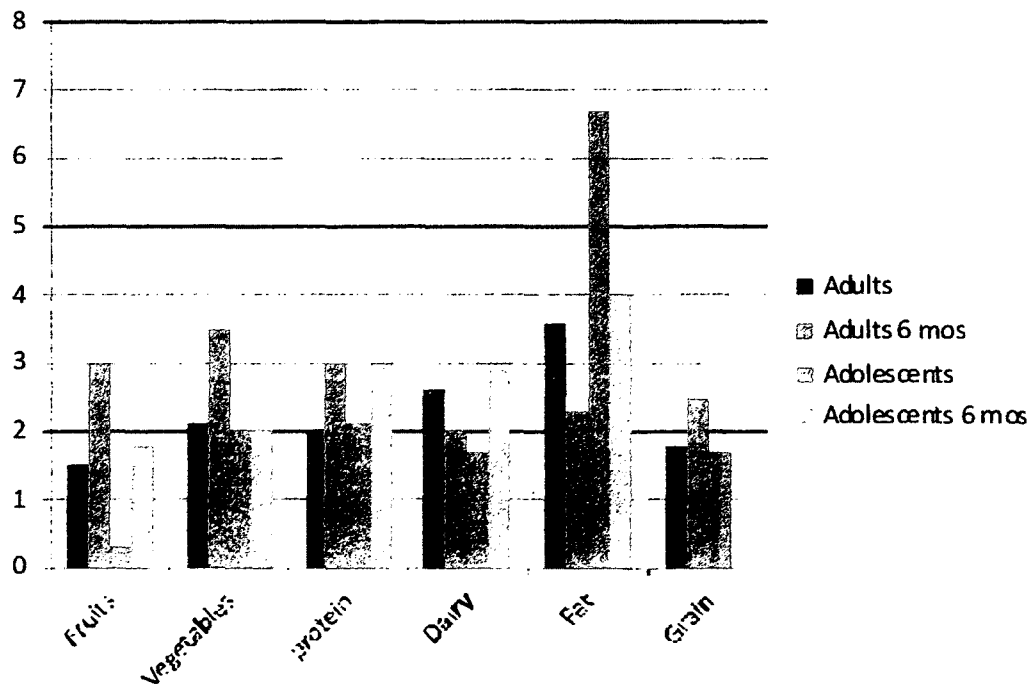


Table 11: Liver Function Tests at 6 Months in Adults and Adolescents



A healthier choice of foods over the six month period emerged. For the adults, diet changes were more difficult since 85% of the adults skipped either breakfast or lunch. There were two adults who skipped both breakfast and lunch. Initially both groups did not meet the required number of servings. The adults did consume the better diet, through poor, and the adolescents consumed higher fat content. At six months, though not adequate, improvement was noted in the food choices made (Table 11). The participants increased fruits and vegetables to an average of 6 servings in the adults and 2 $\frac{3}{4}$ servings in the adolescents. Adults increased their servings of protein, and grains, while decreasing their fat intake at six months. Adolescents reported an increased awareness of better food choices through the school lunch program. They found ways to improve their school lunch program by removing breading off the chicken tenders and adding more vegetables to the salad, a choice they had rarely done before.

Table 12: Diet analysis at onset and 6 months



Exercise was addressed at each visit. The adults found exercise to be difficult to schedule in their daily activities. However, they did increase their exercise times to twice a week for an average of 30 minutes. They stated it was hard to incorporate exercise into their lives as they usually exercised by themselves. The adolescents increased their physical exercise to 5 times a week lasting 1 to 1.5 hours per session. The family became part of the exercise team.

Discussion

The current study was designed to address the intensity of care management as evidenced by length of scheduled visits, time spent developing new goals and reviewing previous identified goals, needed on education and supporting of lifestyle changes to improve metabolic parameters in patients with fatty liver disease. In this study, the protocol was for visits every three months, The adults self-selected for monthly visits for weight checks and provider visits every 2-3 months. The adolescents chose to continue with every 3 month visits citing family constraints. We did not add medication to either group.

Each visit was/is a re-evaluation of where the participant has been and where they are headed in their changes of lifestyle. Goals are evaluated, modified, and created with the participant. Listening to your patient, becoming an advocate and cheerleader for their successes and celebrating the successes-small or big, help the patient. The goal is a healthy lifestyle-it takes work and commitment.

Though most clinical trials have used a balanced diet with restriction, we focused on the food pyramid and healthy choices of complex carbohydrates and a decrease of fats in the diet. Adults increased their servings of fruits and vegetables, proteins, and grains. Though the adolescents presented with a higher BMI, the adults presented with higher ALT and AST.

A major finding in this study was that frequency and time allocated of visits and mutual goal setting improved the outcome of the liver enzymes. Outside of clinical trials, management of fatty liver is feasible, but intense. Improvement occurs with dedicated time and a contract with the patient, listening to the patient, allows for tailoring the program albeit, chemical and metabolic improvement is slow, it does occur. Modifications of diet and increased exercise were aimed to promote weight loss. Lifestyle changes were initiated and discussed. Adolescents require full participation and family support in lifestyle changes of the patient to achieve the goals of therapy. One adolescent stated it gave her time with her mother to talk on their daily walks.

Though our results are similar to the literature suggesting a lifestyle change is needed to manage fatty liver disease, this study of a small sample size, provides additional data supporting the need for intensive dedicated time to the patient. It supports the need for the patient to be part of the structuring of their lifestyle changes. Education and listening to the patient becomes a key component to each visit. The guidelines for dietary intake were taken from myplate.com. Though simple, it was user friendly for this population.

Conclusion:

Fatty Liver Disease is a difficult disease to treat. The United States culture provides an environment of high-calorie food, “super-sized” portions, and busy daily routines that seem to preclude time for exercise. As the risk of this chronic liver disease becomes more common, insulin resistance, type II diabetes, and cardiovascular disease increases. Though pharmacologic intervention continues to be explored, there remains no consensus for the use of any single drug or combination of drugs for the treatment of fatty liver disease.

Uneo, Sugawara and Sujaku (1997) found a three month restrictive diet and exercise program led to a decrease in liver enzymes, improved cholesterol and blood glucose levels in patients with NAFLD. St. George et al. (2009) reported increased physical activity reduced aminotransferase levels and weight loss in a three month study.

The literature describes a 5-8% weight loss is needed to improve liver function tests. Yet, in this small study, the adolescents did not demonstrate weight loss, yet improved liver function tests at three months. Not every patient with fatty liver disease requires aggressive therapy, but every patient should be started on a healthy diet and regular exercise program. Practical considerations for follow up is scheduling a longer clinic visit and listening to your patients. It is labor intensive, it could be cost effective for the patient, and the APRN can run this clinic.

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A Descriptive Study of Nutritional Parameters in End-Stage Liver Disease

Abstract:

Nutrition is one of the most important factors which can influence overall mortality and morbidity. It is well documented, liver cirrhosis, end-stage liver disease (ESLD), drives a patient to a catabolic state thus depleting them of essential nutrients. With the standard parameters of nutritional assessment often invalid in ESLD, it becomes difficult to identify and assess nutritional status. Simple and easy methods are needed to identify the patients approaching the state of malnutrition.

The purpose of this study was to (1) identify the incidence of malnutrition in patients with compensated liver disease utilizing defined nutritional parameters (anthropometric measurements, hand grip strength, and laboratory values) and (2) examine the degree of malnutrition patients with end stage liver disease secondary to viral hepatitis, metabolic (non alcoholic steatohepatitis) and alcoholic liver disease.

The results of this study provide a description of nutritional parameters of cirrhosis based on the etiologies of Hepatitis C virus (n=15), Non-Alcoholic Steatohepatitis (n=9), and Alcoholic Liver Disease (n=9). Thirty three (33) subjects were included in this retrospective study. The disease severity was Child A-14 and Child B-11. Diabetes type II and hypertension were the most common comorbidities. The BMI average across the groups was 31. Clinical assessment shows a trend toward increase in malnutrition. Identification of the earlier stages of malnutrition is challenging, it develops insidiously and maybe masked by edema, however this information is critical for intervention to prevent further complications in the progression of liver disease.

Introduction:

The liver plays a fundamental role in our body and influences the nutritional status. When a liver injury occurs, malnutrition may be exacerbated. Malnutrition has been reported as high as 90% depending on the patient population studied and the disease severity (Italian Multicentre Cooperative Project, 1994). Protein energy malnutrition is a frequent finding in patients with liver cirrhosis, and malnutrition represents a risk factor influencing both short term and long term survival (Campillo, Richardet, Scherman, & Bories, 2003; Matos, Porayko, Fransisco-Ziller, & DiCecco, 2002; & Roongisuthipong, Sobbonliduk, Nantiny, & Songchitsomboon, 2001). In the cirrhotic patient, lean patients with a Body Mass Index (BMI) of less than 18.5 kg/m² has been associated with protein energy malnutrition (PEM), though obese patients with a greater than 25 kg/m² has a higher prevalence and increases the risk for hepatocellular cancer (Callee, Rodriguez, Walker-Thurmond, & Thun, 2003; Inoue, Iwasaki, Otani, Sasazuki, Noda, Tsugane, 2006; Muto, Watanabe, Moriwaki, Suzuki, Kato, Kato, M., Nakamura, Higuchi, Nishiguchi, Kumada, Ohashi, 2006; Yoshiji, Noguchi, Kitade, Ikenaka, Namisaki, Yoshii, Yanase, Yamazaki, Tsujimoto, Akahane, Kawaratani, Uemura, & Fukui, 2009).

Due to the multiple causes of cirrhosis, there are a variety of dietary habits from PEM to over nourishment. However, most of these studies regarding nutritional intake have focused on hospitalized patients (Muto et al, 2006; Albertino, Gatta, Amodio, Merkel, DiPascoli, Boffo, & Caregaro, 2001; Italian Multicenter Cooperative Project on Nutrition in Liver Cirrhosis, 1994). Though not fully understood, there are multifactorial

mechanisms contributing to malnutrition in cirrhosis: poor dietary intake, malabsorption, increased protein losses in the intestine, low protein synthesis, hypermetabolism, and disturbances in substrate utilization. (The diet often recommended is low sodium to control the peripheral edema and ascites. Food may become unpalatable leading to decrease in intake. A low zinc or magnesium level can distort or decrease taste sensation (Madden, Bradbury, & Morgan, 1997; & Yang, Lai, Chiang, Chen, & Chen, 2004).

Poor nutritional status is the single reversible prognostic marker in cirrhosis. Multiple studies have suggested a causal relationship between malnutrition and survival (Alberino et al, 2001; Norman, Kirchner, Lochs, & Pirlich, 2006). Notably, malnutrition has been associated with impaired immunity and increased susceptibility to infections.

There is currently is no gold standard for clinical assessment. Body weight is influenced by ascites and peripheral edema in the patient with liver disease, though it was validated in one study (Campillo Richardet, & Boris, 2006). Nitrogen balance has been associated with improved outcome during critical illness, but rarely measured outside clinical trials (McGhee, Henderson, & Millikan, 1983). Plasma protein and anthropometry are common bedside assessments but have significant drawbacks.

The purpose of this study was to identify the incidence of malnutrition in patients with compensated liver disease utilizing defined nutritional parameters (anthropometric measurements, hand grip strength, and laboratory values) and examine the degree of malnutrition patients with end stage liver disease secondary to viral hepatitis, metabolic (NASH) and alcoholic liver disease.

Methods:

A retrospective study was conducted to identify malnutrition in outpatients with liver cirrhosis and to compare the differences in the nutritional status of the patients with NASH, HCV, alcohol, and combinations of diseases using a variety of objective measures including clinical examinations, anthropometric measurements and dietary intake. One hundred five charts were reviewed and the sample included thirty three subjects meeting the criteria of diagnosis cirrhosis, nutritional data available and not currently in a clinical trial. Secondary data analysis was conducted on data abstracted from the medical record of patients receiving services from Southern California Liver and GI Centers in San Diego and Orange Counties. The Institutional Review Board of the University of San Diego approved the study protocol and Southern California Liver and GI Center agreed to allow the review of patient's chart. The data collected was routine clinical procedure for the clinic.

Nutritional Assessment

The nutritional assessment was conducted through 24 hour patient recall. For each patient the following data were included: anthropometric measurements, evaluation of diet through food on my plate, and laboratory tests.

Anthropometric measurements

Each patient was weighed on a balance beam scale. Height was taken standing in bare feet with a stadiometer. Body mass index was computed as body weight (kg)/height (m^2). Mid-arm circumference was measured at the midpoint between the tip of the acromion and the olecranon process using a flexible tape measure. The arm was relaxed

with the palm of the hand facing forward. The vertical pinch was parallel to the long axis of the arm. Skin fold measurements were determined at triceps and biceps areas (mm), according to standardized protocol. All the measurements were taken using Harpender skin fold calipers with a pressure of $10\text{g}/\text{mm}^3$ applied to the surface area. The same operator completed the readings to reduce measurement errors. Triceps skin fold thickness and mid arm circumference can be measured and is used in patients with advanced liver disease. These anthropometric measurements are only mildly affected by fluid retention (Matos, Porayko, Francisco-Ziller, & Di Cecco, 2002). Muscle strength was measured using a dynamometer. This is a hand held device designed to measure muscle strength in a simple way. The participant was in a standing position with arms at sides without touching their body. The elbow was slightly bent. The test was administered on the non dominant hand. The participant squeezed the dynamometer with as much force as possible, being careful to squeeze it only once. This was done 3 times with a pause of 10-20 seconds between to avoid the affects of muscle fatigue. The results were recorded to the nearest pound or kilogram.

Dietary Intake

Twenty-four hour recall was evaluated through dietary interviews with the patient.

Laboratory values

Laboratory values were measured by established laboratory methods. The laboratory examination included alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase, total

bilirubin, total, HDL and LDL cholesterol, triglyceride, hemoglobin, hematocrit, glucose, insulin, serum ferritin, thyroid stimulating hormone (TSH), Prothrombin time (PTT), PT, INR, platelets, magnesium, uric acid, hgbA1C, vitamin d, vitamin a, and vitamin e.

Severity of Cirrhosis

Both the Child-Pugh (Child & Turcotte, 1964) and the MELD (Kamath, Wiesner, Malinchoc, 2001) scores were used to classify the severity of cirrhosis. The Child-Pugh score and the MELD score was derived from laboratory parameters.

Analysis:

Descriptive statistics were calculated for all analysis variables. Chi-square tests for categorical variables and one-way anova for continuous variables were used to examine bivariate relationships. Comparisons of measured values among the Child-Pugh classifications-Grade A, B, And C and etiology of cirrhosis were performed using one-way anova, Schiffe Post hoc..

Results:

The sample was comprised of 33 patients with diagnosed cirrhosis of the liver (17 men, mean age 56.4 ± 9.4 and 19 woman, mean age 56.8 ± 12.2) undergoing follow up between June 2012 to March 2013. Liver cirrhosis was diagnosed by clinical and laboratory profiles. All the subjects had liver biopsies or ultrasounds to confirm cirrhosis. The etiology of cirrhosis was Hepatitis C virus (n=15), non-alcoholic steato-hepatitis (NASH) (n=9), alcohol (n=9), and a combination of liver diseases (n=3). The disease severity was categorized by Child-Pugh classification revealing Score A in 14

cases and Score B in 11 cases. The subjects have an average of 2.7 co-morbidities ranging from 0-4. The most frequently seen co-morbidities were diabetes mellitus and a history of hypertension. Ten percent of the subjects were taking 1-3 kinds of prescribed medication and 90% were taking 4 or more medications. The demographic data and clinical profile of the patients is presented in Table 13 and 14.

Table 13: Demographic Data of Participants.

| | Hepatitis C | NASH | Alcohol | HCV/NASH | Alcohol/HCV |
|--|--------------------|--------------------|--------------------|--------------------|--------------------|
| N= | 15 | 9 | 9 | 2 | 1 |
| Age | 58.1±9.4 | 56.4±13.9 | 44±11.1 | 54±1.4 | 56 |
| Sex | Female-8 Male-7 | Female-7 Male-2 | Female-2 Male-7 | Female-2 Male-0 | Female-0 Male-1 |
| Weight-mean 190.79±46.2 | 188.6±45.8 | 195.7±43.3 | 189.4±56.9 | | |
| Exercise routine yes/no | 5yes | 6 yes | 0 | | |
| Co-morbidity 0/1-3/>4 | <3-13 >3-2 | <3-3 >3-9 | <3-7 >3-2 | <3-2 | <3-0 >3-1 |
| Alcohol drinking – no, current drinking, past drinker | 0 | 0 | 2-current 7past | 0 | 0 1 past |
| No of prescribed meds 0/1- 3/>4 | 8.3±2.4 | 5±2.8 | 8.8±2.3 | 10 | 0 |

Table 14: Clinical Profile of Participants

| | Normal values | Hepatitis C | NASH | Alcohol | HCV/NASH | Alcohol/HCV |
|-----------------|-----------------|-------------|-----------|----------|-----------|-------------|
| Child-Pugh A | | 4 | 6 | 4 | | |
| Child Pugh B | | 7 | 2 | 2 | | |
| Child Pugh C | | | | | | |
| MELD | | 9.3±3.4 | 9.5±3.2 | 9±2.3 | 12±4.24 | 9.4 |
| Total Bilirubin | 0.2-1.2 mg/dL | .95±.69 | .96±.94 | 1.16±.87 | 1.1±1.06 | 1.8 |
| INR | 0.9-1.1 sec | 1.9±2.7 | 1.2±.33 | 1.2±.12 | 1.15±.21 | 1.3 |
| Albumin | 3.6-5.12 g/dL | 3.7±.63 | 4.01±.56 | 3.48±.52 | 3.95±.35 | 3.1 |
| HGB | 11.7-15.5 g/dL | 13.01±2.5 | 12.6±1.14 | 12.3±1.8 | 12.9±1.2 | 14.3 |
| Creatinine | 0.15-1.05 mg/dL | 1.27±.52 | .79±.31 | .75±.2 | .75±.21 | .83 |
| Sodium | 135-146 mmol/L | 137.4±3.7 | 139.7±1.8 | 134±3.5 | 138.5±3.5 | 139 |
| Potassium | 3.5-5.3 mmol/L | 4.1±.72 | 4.1±.26 | 3.9±.48 | 3.9±.14 | 3.7 |

The nutritional parameters were identified by triceps skin fold thickness and hand grip of the non-dominant hand, waist circumference, albumin, total protein, and my plate categories of fruits, vegetables, protein, dairy, and empty calories, identified the subjects with HCV with a higher waist circumference (43.0 inches±8.5) than the subjects with NASH (35.17 inches±23.85) and subjects with alcohol as etiology of cirrhosis (32.01±19.91). Tricep skin fold thickness, was decreased in all etiologies as was hand

grip strength, five to 10 percent in the participants with each etiology. The subjects with NASH cirrhosis consumed more fruits, average 1.33 than either the HCV subjects or alcohol subjects, 0.77 and 0.5 respectively. Vegetables and Protein, albeit low, was consistent across groups ranging from 1.3 to 1.75 and 1.75 to 2.2 respectively. Differences were shown in dairy with the HCV subjects consuming at least one dairy product a day and the alcohol subjects consuming less than a quarter of a dairy product daily. Interesting to note, two of the subjects with alcohol cirrhosis continue to drink actively. Alcohol intake was not noted in any of the other subjects or groups (see table 15 and 16 for details).

Table 15: Nutrition Intake of Patients According to Etiology.

| | Normal values | HCV | NASH | Alcohol |
|----------------|--|----------|-----------|-----------|
| Fruits | 1 ½ -2 cups daily | .77±.83 | 1.33±1.03 | .5±1.0 |
| vegetables | 2-3 cups daily | 1.6±1.0 | 1.3±1.0 | 1.75±.957 |
| protein | 46-56 grams daily | 2.2±1.39 | 2.0±.63 | 1.75±.5 |
| Dairy | 3 cups daily | 1.0±1.41 | .66±.81 | .25±.5 |
| Empty calories | 120-260 calories depending on gender daily | 1.9±1.67 | 3.0±2.5 | 3.3±1.5 |

Table 16: Nutritional Profile According to Etiology

| | Normal values | HCV | NASH | Alcohol |
|-------------------------------|--|-------------|-------------|-------------|
| Tricep Skin fold-non dominant | Range 13.8-14.2 males based on age Range 22.3-24.9 females based on age | 17.8cm±1.58 | 22.9±1.07 | 19.6±1.4 |
| Hand grip-non dominant | Range 30.2-57.7 males based on age Range 17.2-35.3 females based on age | 14.6±9.8 | 27.07±48 | 9.66±10.59 |
| Waist Circumference | <35 inches | 43.0±8.5 | 35.17±23.85 | 32.01±19.91 |
| Albumin | 3.6-5.1 g/dL | 3.7±.64 | 4.01±.56 | 3.48±.52 |
| Total Protein | 6.2-8.3 g/dL | 7.2±.86 | 6.9±.37 | 6.87±.46 |

A one way anova between groups of analysis of variance was conducted to explore the impact of Child Pugh scores on selected laboratory parameters-albumin, total bili, alanine transferrase, prothrombin time, and anthropometric measurements of body mass index and etiology. As expected, significance at 0.3, 0.32, and 0.001, respectively, the higher the body mass index, the lower the albumin and the higher the total bili, the higher the Child Pugh score, indicating the subject was worsening. Once cirrhotic, etiology made no difference (see table 17).

Table 17: Comparisons of Selected Measures with Child-Pugh Classifications

| | Normal values | f | P |
|------------------------------------|---------------|-------|-------|
| Body mass index | 18-25 | 4.118 | 0.03 |
| Etiology (NASH/HCV/Alcohol/Others) | | .556 | .581 |
| Albumin | 3.6-5.1 g/dL | 3.985 | .031 |
| Total Bilirubin | 0.2-1.2 mg/dL | 8.864 | 0.001 |
| ALT | 6-40 U/L | 1.232 | .309 |
| Prothrombin time | 9.0-11.5 sec | .540 | .590 |

A one-way anova between groups analysis of variance was conducted to explore the impact of disease etiology on nutritional intake, as measured by a 24 hour nutritional recall and laboratory values of albumin, INR, and total protein. Subjects were divided into 3 groups according to the etiology of cirrhosis- Group 1-HCV, Group 2-NASH, and Group 3-alcoholic cirrhosis. There was no statistical significance (see table 18).

Table 18: Comparisons of selected nutritional parameters with Etiology of HCV, NASH, and Alcohol

| | Normal Values | F | P |
|-----------------|---------------------------------|-------|-------|
| Albumin | 3.6-5.1 g/dL | 1.251 | .312 |
| INR | 0.9-1.1 sec | .354 | .787 |
| Grains | 5-10 servings daily | 2.086 | .145 |
| Veg | 2-3 cups daily | .362 | .782 |
| Fruits | 1 ½-2 cups daily | 1.022 | .409 |
| Oils | 15 percent of calories consumed | 8.533 | .001 |
| Protein | 46-56 grams daily | .494 | .692 |
| Dairy | 3 cups daily | .556 | .653 |
| Empty calories | 120-260 depending on gender | .784 | .479 |
| Skips breakfast | 0 | 6.870 | .003 |
| Skips lunch | 0 | 2.831 | 0.071 |
| Skips dinner | 0 | .241 | .867 |

Discussion:

Identifying the earlier stages of malnutrition is challenging. It develops insidiously and maybe masked by edema. The earlier the diagnosis of malnutrition, the earlier interventions can be started. It has been well documented complications of liver disease increases with malnutrition (Cabre & Gassull, 1998). The nutritional status of patients with liver cirrhosis has shown great diversity and there is no gold standard for early diagnosis. Some have identified protein energy malnutrition and others have excessive nutrition and obesity. Evaluating the nutrition from the perspective of management of the underlying cause of cirrhosis may prevent additional liver injury. This study categorized subjects with cirrhosis according to the top three disease entities of cirrhosis. Laboratory evaluations, anthropometric measurements, 24 hour diet recall, etiology of cirrhosis, ascites, edema, anasarca and Child Pugh score was completed on 33 patients.

Anthropometric measurements and handgrip strength have correlated well with the dual-energy x-ray absorptiometry (DEXA) (Alvares-da-Silva, & Reverbel, 2005; Figueriredi, Dickson, & Pasha, 2000; & Flore, Merli, & Andreoli, 1999). NASH subjects had a higher handgrip strength than either the HCV or alcohol subjects. Alvares-da-Silva and colleagues (2005) found handgrip strength as an easy and effective tool in assessing nutritional risk in patients with end stage liver disease. When taken serially, it may become very useful in clinical practice. In this study the tricep skin fold thickness and the hand grip strength of the non-dominant hand was decreased in all etiologies indicating decrease muscle tone and strength. Serially measurements need to be taken to validate the findings. One is cautioned the overuse of handgrip strength may

overestimate the prevalence of malnutrition. The BMI was found to be higher in the subjects with HCV, but all three groups averaged BMI of 31.13 ± 8.57 . As expected, the NASH subjects had the highest BMI at 33.91 ± 6.1 and the lowest BMI was the subjects of alcoholic cirrhosis with a BMI of 29.1 ± 7.1 . Ascites and peripheral edema was minimally reported in this population of subjects.

Early identified poor diets may offer opportunities for nutritional counseling. In this study, the subjects were not taking adequate nutrients. Consistently the subjects who consumed fewer fruits, vegetables, protein, and dairy had an increase in empty calories. Meals were skipped-breakfast the most common meal skipped. Previous research has shown in healthy adults; breakfast is the most important meal of the day, setting the tone for activity, wellness, and energy.

Muscle wasting and easy fatigability is well recognized in cirrhosis. Exercise is relevant as the impact of physical fitness can be improved. However, in this study, the subjects overall did very little exercise, citing fatigue and lack of energy as the source of limited exercise. Discussion of exercise was documented in the patient's record and encouragement of walking was encouraged.

Clinical Assessment demonstrates a trend towards more malnourishment with increasing clinical severity. A larger study sample is required to support these findings. The goals of nutrition are to replenish malnourished individuals, maintain adequate muscle and energy reserve, and manage patient's symptoms to maximize quality of life. With the standard parameter of nutritional assessment often invalid in end-stage liver disease, it becomes difficult to identify and assess nutritional status.

The results of this study must be interpreted in the context of limitations including a cross sectional design, a small sample, and nutritional parameters documented in the clinical chart. This data could form a baseline for future prospective studies and change the practicing standards of operating practice in clinical practice. As there is no longitudinal data available, continued analysis of nutritional parameters is warranted on an outpatient status of persons with end-stage liver disease.

Conclusions:

Cirrhosis is considered a risk for malnutrition, but needs to be looked through the lenses of etiology. Obesity may change the revision of nutritional standards (Shiraki, Nishiguchi, Saito, Fukuzama, Mizieta, Kaibori, Hanai, Nishimura, Shimizu, Tsurumi, & Moriwaki, 2003). Nutritional support may improve clinical outcomes in those with early cirrhosis. Preventing further nutrient and muscle depletion, correcting vitamin and mineral deficiencies may minimize the risk of infection, debility, and deconditioning (Campos, Matias, Coelho, 2003). Additional studies are needed to provide information and nutritional therapies for patients with liver cirrhosis. Nutritional education is important and recommended for patients with liver cirrhosis to help them in the balance and selection of foods with protein and nutrients.

This study continues to collect data identifying the nutritional parameters of the patient with cirrhosis of the liver. This data is part of a longitudinal study looking at the parameters of nutrition in the patient with end stage liver disease.

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PROPOSED PLAN OF RESEARCH

My dissertation has only touched the surface of my projected research plan. There are many threads to pursue.

1. What is the relationship between hospital visits, ED visits, physician visits, quality of life and outcome of the patient with fatty liver disease and end stage liver disease.
2. What is the impact of disease state on the lifestyle changes over time?
3. How do we improve strategies to assess the liver patient? What is the dry weight versus the wet weight (having edema and ascites)?
4. Is a change in chemical injury tests and/or BMI a predictor of liver disease regression or progression?
5. What are the characteristics of malnutrition with respect to etiology of cirrhosis?

This process of learning about research, a novice understanding of research and statistics, has only increased my thirst of finding questions. The patients are the winners in this thirst for knowledge. It is their experiences, their laboratory values, their anthropometric measurements, which when collected and analyzed will help shape the knowledge known and only lead to more questions.