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Nutritional intervention could improve long term outcome post LDLT in limited resources university hospital in Egypt

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***Abstract*---**Introduction: liver transplantation (LT) is considered as salvage therapy for those with irreversible liver failure. Malnutrition is prevalent in transplanted patient's pre and post transplantation. Objective: to analyze the nutritional status of patients post living donor liver transplantation (LDLT) by using different nutritional assessment tools with nutritional modification in order to improve the outcomes post liver transplantation. Materials and methods: Our prospective cohort study was conducted on 30 who underwent liver transplantation before the study, they were nutritionally assessed through different nutritional scores and anthropometric parameters with application of nutritional modification. Results: ALT and AST decreased significantly and normalized at 6 months with p-value .025,

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.036; respectively. HbA1c, fasting blood sugar and post prandial blood sugar levels decreased after 6 months. There was statistically significant improvement in lipid profile after 3 and 6 months with nutritional modification. There was significant improvement (p= 0.017) in metabolic syndrome. There is correlation between numbers of years from transplantation and appearance of metabolic syndrome Regarding dyslipidemia, there was significant improvement after 6 months (p< 0.001).CAP study showed improvement (p= 0.014). Conclusions: It is essential to provide proper nutritional assessment and modifications post liver transplantation, in order to improve the outcomes after LT through ameliorating the effect of pre transplant malnutrition and prevent newly developed malnutrition state.

***Keywords*---**Nutritional, living donor liver transplantation, malnutrition, metabolic syndrome, recommended dietary allowances.

Introduction

Prevalence of malnutrition has been reported in a significant proportion of patients with cirrhosis and ranges from 10% to 100%, contingent on the severity of hepatic decompensation in the setting of cirrhosis (Maharshi, Sharma, & Srivastava, 2015; Marr et al., 2017), and it's related outcomes have been recognized with many studies that show the negative impact after LDLT, such as longer hospital and intensive care unit stay, graft impairment, infections up to mortality (Ferreira, Santos, Anastácio, Lima, & Correia, 2013). Nutritional status also affected post liver transplantation by different etiological factors including change in the liver gut brain axis., increased calorie intake and immunosuppressive therapy (Hou et al., 2013) (Giusto et al., 2014) (Kohli, Cortes, Heaton, & Dhawan, 2018)

The most common nutritional issues post liver transplantation including new onset diabetes mellitus, non-alcoholic fatty liver, dyslipidemia and weight gain with post-transplant sarcopenia. Thus, proper nutritional assessment and management are required not only pre liver transplantation, but also has an important role in preserving graft function post liver transplant. The aim of this study was to analyze the nutritional status of patients post living donor liver transplantation (LDLT) by using different nutritional assessment tools with nutritional modification in order to improve the outcomes post liver transplantation.

Materials and Methods

Our prospective cohort study was conducted on 30 who underwent liver transplantation before the beginning of the study from May 2018- April 2020, they were nutritionally assessed for the first time at the base line with starting of nutritional modification continued 6 months with follow up in El-Manial Specialized hospital, Cairo University, liver transplantation unit. Study was approved by Tanta University Institutional Review Board and written informed consent was obtained from each participant in the study.

Exclusion criteria
Patients less than 18 years with contraindications for liver transplantation and patients underwent dual organ transplantation.

Methods of evaluation:

All patients after informed consent were subjected to the following at the baseline of study and after 3 and 6 months of nutritional management: Medical history, complete clinical examination, laboratory investigations, radiological investigations include: Abdominal-pelvic ultrasonography and transient elastography for hepatic fibrosis detection and assessment of liver steatosis (CAP study).

Evaluation of nutritional status had been done using different assessment tools including Anthropometric measurements: Body mass index (BMI), Triceps skinfold thickness (TSF), Mid upper arm circumference (MUAC), Mid arm muscle circumference (MAMC), Handgrip strength method (HGS). Also, evaluation of nutritional status had been done using Subjective global assessment (SGA), Creatinine height index (CHI), and 24-hour dietary recall at the base line and at 3 & 6 months with nutritional management. Nutritional intervention was done and tailored for each patient according to nutritional status based on published guidelines (European Association for the Study of the Liver, 2019; Plauth et al., 2019).

Statistical analysis

Analysis of the data was done using statistical program for social science (SPSS) software version 22, 2015 USA. Categorical data were presented as number and percent while numerical data were presented by mean± standard deviation for normally distributed data. For skewed data, median and inter-quartile ranges were used. The qualitative variables are described in the form of frequency and percentages. Chi square test (X2 value) and Mann-Whitney U test were used to compare a qualitative variable between two independent groups. P value (which is either non-significant if > 0.05, significant if ≤ 0.05, or highly significant if < 0.001) was calculated. Association between different parameters and degree of malnutrition was tested using Spearman's rho correlation to obtain correlation coefficient(r).

Results

Patients who were recruited for the study were transplanted from 2-15 years ago with mean± SD (6.07± 2.73) and median 6 (4- 7). Patients who were recruited for the study were transplanted from 2-15 years ago with mean± SD (6.07± 2.73) and median 6 (4-7). At the base line of study there was 9 (30%) diabetic cases and 1 (3.3%) prediabetic from those 2 (6.7%) cases in prediabetic range of HBA1c and 8 (26.7%) cases in diabetic range. HbA1c, fasting blood sugar and post prandial blood sugar levels decreased after 6 months with net result of 6 (20%) diabetic cases and 4 (13.3%) prediabetic.

As shown in (Table I), there was statistically significant improvement in lipid profile after 3 and 6 months with nutritional modification. There was no statistically significant difference during follow up regarding creatinine height index (p= 0.063) as at the base line of study there were about 11 (36.7%) patients had mild malnutrition with creatinine height index less than 80%, decreasing in number with nutritional modification after 6 months to 4 patients (13.3%).

At the base line of study before starting nutritional modification 11 patients (36.7%) were overweight and the same ratio were obese, while after follow up with nutritional modification normal weight patients increased up to (46.7%), over weight were increasing to (40.0%) and obese were decreasing to (13.3%), but there was no statistically significant difference during follow up regarding weight (P=0.285) (Table II).

Regarding anthropometric examination through, there was statistically significant decrease in weight (p=0.002) and BMI (p=0.018) values post nutritional modification. After 3 and 6 months' post nutritional modification, triceps skin fold thickness, MUAC and MAMC in both right and left side showed no statistically significant difference with slight decrease in TSF, MUAC and more or less constant MAMC. Hand grip strength in both right and left side showed little insignificant increase with nutritional modification (Table III).

At the base line assessment, 10 (33.3%) patients had sarcopenia, only one (3.3%) patient had severe sarcopenia and 3 (10%) patients had dynapenia. Later on, dynapenia and severe sarcopenia were improved and became absent 3 and 6 months with nutritional management, but sarcopenia was decreased and was observed in 8 (26.7%). The patients were assessed by subjective global assessment of nutritional status (SGA). The majority of cases (29, 96.7%) had A classification and one (3.3%) patient had classification B that became SGA class A with nutritional management. There was significant improvement (p= 0.017) in metabolic syndrome as only 2 (6.7%) patients after 6 months were found to have metabolic syndrome compared to 11 (36.7%) patients at the base line. Regarding dyslipidemia, there was significant improvement after 6 months (p< 0.001) as there were 21 (70%) patients had dyslipidemia at base line assessment compared to 3 (10%) patients after 6 months with nutritional management. There is correlation between numbers of years from transplantation and appearance of metabolic syndrome p <0.001 (Table IV).

CAP study was performed on 27 patients other 3 patients were restricted because of high BMI at the base line assessment. Prevelance of steatosis was about 48.1% and no steatosis in 14 patients 51.9 %, steatosis catagorized as grade 1 steatosis 6 patients(22.5%),grade 2 steatosis 6 patients(22.2%)and grade 3 steatosis 1 patient (3.7%),with nutritional management after 3 months CAP study done on 10 patients and were categorized as no steatosis in 3 patients (30%), grade 1 steatosis 4 patients 40%,grade 2 steatosis 3 patients (30%),after 6 months CAP study done on 29 patients from 30 with increasing in normal CAP study as shown (Figure II). Analysis of nutrients intakes are displayed in (Table V), patients' nutrient intake was assessed relative to the recommended dietary allowances.

Discussions

Advances in post-transplantation care and the management of graft rejection have greatly improved the outcomes of patients after orthotopic liver transplantation (OLT). The clinical features of declining liver function tend to normalize following successful organ replacement, but preventing and treating malnutrition in these patients requires more attention (Yap, Vara, & Morais, 2020). In general patient's nutritional status can worsen rapidly during the post-operative period due to preoperative malnutrition, surgical stress, immunosuppressive therapy, post-interventional complications, post-operative protein catabolism and fasting period (Nawaz & Chopra, 2017).

This suggests the need for early nutritional management with tailored nutritional intervention with follow up including the needed amounts of carbohydrates, fat and proteins according to nutritional status for each patient after proper nutritional assessment (Kaido et al., 2017). The role of patients and guardians' education in methods of diet management had turned out by comparing the rate of malnutrition after one year post transplant with nutritional advice (Lim, Kim, Park, & Kim, 2015). At the base line of our recent work before starting nutritional modification 11 patients (36.7%) were overweight and the same ratio were obese, while after follow up with nutritional modification normal weight patients increased up to (46.7%), over weight were increasing to (40.0%) and obese were decreasing to (13.3%), but there was no statistically significant difference during follow up regarding weight (P=0.285).

In 1999, **Keogh & co-authors** used dual energy X-ray absorptiometry to assess the changes in bone mineral density and body composition after liver transplantation. The timing of the evaluation of body composition in this study was extremely heterogeneous (range, 3-44 months after surgery) (Keogh et al., 1999). The result of this study showed that body weight increased in patients didn`t receive pre-transplantation nutritional management by 12% after transplantation due to an increase in the fat mass (from 24.1% ± 2.0% to 35.1% ± 1.8%) and a decrease in the fat free mass (-5.7% ± 1.4%) which is considered similar to our results before starting nutritional intervention in study group.

Other studies have primarily focused on the increase in body weight and BMI after liver transplantation as one of the most common long-term complications after LT, which may lead to a diagnosis of obesity in some patients. One of these studies was that performed retrospectively on 597 patients transplanted between 1996 and 2001 found that by 1 and 3 years, 24% and 31% of the patients, respectively, showed BMI > 30 kg/m^2 (Richards, Gunson, Johnson, & Neuberger, 2005). Another smaller study, 23 patients were followed for 9 months after transplantation. At the end of the observation period 87% were classified as overweight or obese due to a significant increase in fat mass this in contrast to our study in group B who started nutritional intervention before LT and completed it after LT for 6 months, also this is in agreement with our first base line assessment in study group A pre -nutritional management (Richardson, Garden, & Davidson, 2001).
In a long term follow up study for 4 years after liver transplantation on 143 patients, 58% of the patients were observed to be overweight, and 21% were

observed to be obese (Anastácio et al., 2011). In spite of the nutritional modification and advice that introduced to our patients, sarcopenia not totally vanished as improvement was more in hand grip strength and physical performance that explores other important factors in management of sarcopenia as exercise and pharmacological therapy as mentioned in EWGSOP2 (Cruz-Jentoft et al., 2019) which are lacked in our study and also was confirmed by study that reported incomplete restoration of protein stores and respiratory muscle strength did not reach normal predicted levels in patients underwent liver transplantation on standard nutritional therapy pre- and post-transplant and followed up for 12 months (Plank et al., 2001).

As regards to dyslipidemia in our study, total number of patients with dyslipidemia were 21(70.0%) in study group pre nutritional intervention, respectively, that were improved after 6 months of nutritional management to 3 (10%) that is withstanding with other studies that estimated the prevalence of hyperlipidemia in liver transplant (LT) recipients to vary from 27% to 71% (Laish et al., 2011; Mells & Neuberger, 2007). Gisbert C et al., studied hyperlipidemia pre and post LT and reported hyperlipidemia occurred in 8% pre-LT and 66% post LT which was similar to the prevalence in our study pre nutritional modification [24].

The previous study reported the prevalence of hyperlipidemia started to increase from the first month and continued rise during the follow up for one year post LT compared to follow up in our study the prevalence showed significant decrease with nutritional management (Gisbert et al., 1997). It is worthy to know that hyperlipidemia isn`t only resulted from improper nutrition, but also can result with some immunosuppressive therapy as sirolimus in patients with some genetic alterations as reported by Sam et al. (Sam et al., 2012)

Management of this dyslipidemia in our study was similar to study reported that treatment of hyperlipidemia after liver transplantation consists of life style modification, modifying the dose or type of immunosuppressive agents and use of lipid lowering agents when needed with special attention to drug interactions (Hüsing, Kabar, & Schmidt, 2016). Another metabolic problem that considered as one of the most frequent complications after liver transplantation is the development of Post Liver Transplantation Diabetes Mellitus (PLTDM). In addition to all well-known complications of DM, PLTDM is associated with reduced graft function, increased risk of transplant loss and worsened patient survival (Lv et al., 2015). This metabolic derangement better managed in our study with nutritional modification in both groups.

PLTDM can be defined as a degree of hyperglycemia that is consistent with current definitions of DM in a patient who has received a LT. A reliable diagnosis of PLTDM must be made after the patient has been discharged and doses of immunosuppressive agents have been tapered and are stable (Sharif et al., 2014). However, discrepancies in the definition of PLTDM still persist among studies. Additionally, since some cases of PLTDM may be transient, the length of the follow up and the time of diagnosis, the overall reported incidence varied between studies (Khalili et al., 2004) (Hartog et al., 2015; Honda et al., 2013; Soule et al., 2005).

The cumulative incidence of PLTDM during the first year after transplantation ranges from 10.8 to 33%, which represents a remarkable burden to any health system (Peláez-Jaramillo, Cárdenas-Mojica, Gaete, & Mendivil, 2018). PLTDM develops in liver transplant recipients owing to multiple risk factors including factors that are similar to general population older age, male sex, high body-mass index (BMI)], pre transplant impaired fasting glucose, family history of DM and African American or Hispanic ethnicity (Peláez-Jaramillo et al., 2018).

Other risk factors include conditions that predispose particularly to development of DM after a LT include hepatitis C virus (HCV) or cytomegalovirus infection and immunosuppressive therapy with high dose corticosteroids [or calcineurin inhibitors (CNIs; tacrolimus or cyclosporine). Also, nonalcoholic steatohepatitis (NASH) is a strong risk factor for the development of type 2 diabetes (T2DM) in the general population and there is no reason to believe that this association would be any different in patients who have received a LT Donor characteristics also play a key role in predisposing or protecting from PLTDM. Factors associated with increased risk are age > 60 years, male gender and diagnosed liver steatosis (Peláez-Jaramillo et al., 2018).

Because of these multiple risk factors nutritional intervention in our study partially participated in improvement of PLTDM, and at least contributed in decreasing the number of new emerging diabetic cases. Dyslipidemia, DM together with obesity and hypertension are elements of metabolic syndrome diagnosis. In our recent study we found that pre nutritional management 11 patients (36.7%) had metabolic syndrome that improved with nutritional intervention to become (6.7%).

While, another study carried out by Fussner et al., as a retrospective review of 455 consecutive LT recipients with an 8 to 12 year follow up showed the prevalence of patients with MS increased post LT as MS prevalence at the beginning of the study was 8%- 22% , but the prevalence of post-LT metabolic syndrome at 1 year remaining between 30% and 50% similar to estimated prevalence in our study group pre nutritional management .The study reported also increased prevalence of MS with increasing the duration from timing of transplantation this was inconsistent with our study results (Fussner et al., 2015).

Another meta-analysis included 16 articles comprising 3539 patients and showed post-transplant mean prevalence for metabolic syndrome was 39% (range = 14–64%) similar to prevalence in our study pre nutritional intervention (Thoefner, Rostved, Pommergaard, & Rasmussen, 2018). Metabolic syndrome, hyperlipidemia and obesity are common in patients after the first 6 months post LT, especially those with immobility, and are associated with 42% cardiovascular disease related mortality, diabetes mellitus, and hypertension. Also, PTMS can affect 1 out of 2 transplant recipients. These conditions contribute to the long-term morbidity and mortality. Thus, proper assessment and management of metabolic syndrome in LT recipients is considered highly important issue in post LT follow up (Johnston, Morris, Cramb, Gunson, & Neuberger, 2002; Stegall et al., 1995).

Additionally, the presence of post transplantation metabolic syndrome (PTMS) has been associated with a rapid progression to fibrosis in individuals transplanted for HCV cirrhosis (Hanouneh et al., 2008). NAFLD was assessed in our study using transient elastography with Controlled Attenuation Parameter (CAP). There was statistically significant difference as regarding steatosis with nutritional management. Nonalcoholic fatty liver disease is closely associated with features of metabolic syndrome and likely represents the hepatic manifestation of the metabolic syndrome. The risk of developing de novo NAFLD after liver transplant is associated with pre transplant obesity, and a higher post-transplant BMI (Siddiqui & Sterling, 2012). Thus, with improving BMI in our study group, the prevelance of NAFLD had decreased as previously showed.

Patients with greater than 10% increase in pre transplant BMI had a significantly higher risk of developing de novo NAFLD compared to those without weight gain, so proper nutritional management is essential in pre and post LDLT (Siddiqui & Sterling, 2012). Chayanupatkul et al., used transient elastography (TE) with controlled attenuation parameter (CAP) to estimate prevelance of steatosis post liver transplantation on 150 allograft patients and revealed that (70%) had steatosis with 40% of these had severe steatosis that was higher than our results, this differeance possibly due to sample size with usage of lower cutoff value for steatosis than our study (Chayanupatkul, Dasani, Sogaard, & Schiano, 2021)..

Another study included retrospective review of 588 adult liver transplant (LT) recipients) and showed that two hundred fifty-four transplant recipients had imaging or biopsy evidence of allograft steatosis beyond 2 months post liver transplant. Of those, 215 (84.6%) had de novo allograft steatosis. At 10 years, 48% of all transplant recipients had evidence of allograft steatosis (Narayanan et al., 2019). The importance of NAFLD assessment and management resulted from being one of the most common causes of LT in the last 20 years. It is the second leading indication for LT among adults in the United States, with (21.5%) LTs performed in 2018. Also, it can be one of the most important preventable mechanisms in development of HCC (Anstee, Reeves, Kotsiliti, Govaere, & Heikenwalder, 2019; Cotter & Charlton, 2020).

After LT, patients with NAFLD are more prone to development peri-surgical complications such as infections), whereas in the long term, they have a higher incidence of malignancies (33%) and cardiovascular events (24%) compared to patients transplanted for other reasons (Adam et al., 2003; van den Berg, Douwes, de Meijer, Schreuder, & Blokzijl, 2018). Some limitations that we had met in our study were as small sample size, short duration of follow up, the study was one center study, lack of integration of exercise as a part of life style modification, lack of some facilities as specific software for muscle mass assessment, calorimetry, DEXA and BIA for exact analysis.

Conclusions

accurate assessment of the nutritional status and adequate intervention are prerequisites not only for peri-operative nutritional treatment in patients who undergo LT but also, in post liver transplant phase along with immunosuppressive therapy as it can affects the long-term outcomes with

improving steatosis and decreasing the prevalence of metabolic syndrome, sarcopenic obesity and post-transplant diabetes mellitus. Further studies are still needed to overcome our limitations in the study.

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