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RESEARCH ARTICLE

VITAMIN D STATUS IN CHILDREN FOLLOWING LIVER TRANSPLANTATION VERSUS NORMAL POPULATION IN KUWAIT

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Abstract

Background: We look at the serum vitamin D levels of patients who underwent liver transplantation and compare that with the normal population residing in the same area and in similar age distribution. Vitamin D is a pro-hormone that is essential for normal absorption of calcium from the gut and the deficiency of vitamin D is associated with rickets in children and osteomalacia in adults.

Aim of the study: To compare vitamin D status in pediatric liver transplant patients versus the normal pediatric population.

Method: A retrospective cross-sectional cohort study comparing vitamin D levels between transplanted patients of at least 2 years post-transplant and those of the control group of the same age. Patients who were on steroids or vitamin D supplements at the time of assessment were excluded.

Results: 42 liver transplant patients and 42 control group patients were studied - with a median age of 8.5 years in both categories. The male to female ratio was 18:24 in the non-transplanted group and 20:22 in the transplant group. The mean vitamin D values of transplanted patients were 57.5 nmol/L (median 45.6 nmol/L) and for non-transplanted patients were 44.5 nmol/L (median 39.6 nmol/L). The median vitamin D levels were insufficient according to the global evidence-based consensus recommendation in all categories[1]. There was a significant difference in vitamin D values for female transplant and non-transplant patients (57.5 nmol/L vs. 40.5 nmol/L; p-value of 0.01), and no significant difference for male patients (57.5 nmol/L vs. 49.7 nmol/L; p-value of 0.40).

Conclusion: Despite the high morbidity and use of multiple medications in liver transplanted patients, their vitamin D status does not differ significantly from the general population. Although in female patients we see a significant difference in vitamin D distribution in both categories. This implies that the immunosuppressants used in those patients are not detrimental to bone metabolism.

Introduction:-

Vitamin D status may be affected significantly after any transplant due to multifactorial causes like a high dose of immunosuppressants, steroids, and high infection rates, and it also depends on the organs transplanted, especially the

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liver, kidney, and bone marrow. Vitamin D deficiencies are observed with malignancies, type I diabetes, inflammatory bowel disease, multiple sclerosis, and cardiac diseases [2][3]. Drugs, mainly steroids, affect transplanted patients, which influences their vitamin D catabolism. And the add-on effect of lack of sun exposure and social customs are likely to worsen it. Sunblock creams, which are mostly prescribed for transplanted patients, can reduce up to 95% of vitamin D absorption. [4][5].

Other organ transplant patients like patients who underwent renal transplants have a higher prevalence of vitamin D deficiency,mainly as the kidney is the site of activation of vitamin D. This is cited in studies done by Stavroulopoulos et al., where they have shown that there was an insufficient amount of serum vitamin D in renal transplant patients [6]. Very few studies have evaluated the vitamin D levels at the time of transplantation. Liver transplant patients had a significantly lower level of vitamin D than heart transplant recipients due to malabsorption and impaired hydroxylation of vitamin D [7].

Vitamin D is a pro-hormone that is essential for normal absorption of calcium from the gut and the deficiency of vitamin D is associated with rickets in children and osteomalacia in adults. Vitamin D is a fat-soluble steroid hormone precursor that is mainly produced in the skin, by exposure to sunlight. Vitamin D is biologically inert and undergoes successive hydroxylation in the liver and kidney to become 1,25 dihydroxy vitamin D. In man, vitamin D is bound to vitamin D binding protein and transported to the liver where it undergoes 25 hydroxylations, and this is the metabolite to determine the overall status of vitamin D. The global evidence-based consensus recommendation on vitamin D [1] are sufficiency > 50 nmol/L, insufficiency 30-50 nmol/L, deficiency <30 nmol/L and Toxicity >250 nmol/L.

Vitamin D deficiency confers significant risk for both skeletal and non-skeletal disorders. And vitamin D deficiency has been reported in transplant candidates with congestive cardiac failure, end-stage pulmonary disease, liver failure, and chronic kidney disease [8]. Vitamin D deficiency is not uncommon, and an estimated 26-33% of patients develop severe deficiency after organ transplantation [8].

The effects of 1,25 dihydroxy vitamin D on the immune system may reduce the risk of infection and preventallograph rejection after transplantation. Vitamin D potentiates the innate immune system and protects against bacterial infections and tuberculosis[9]. When 1,25 di-hydroxy vitamin D is produced by monocytes and macrophages in sufficient quantities it interacts with T and B lymphocytes in the local environment. The ability of monocytes and macrophages to synthesis 1,25 di-hydroxy vitamin D is dependent on serum vitamin D concentration and increases in response to vitamin supplementation[10]. Recent studies have demonstrated the role of vitamin D in the regulation of immune cell proliferation, differentiation, and responsiveness [11]. Evidence from animal studies suggests that administration of 1,25 di-hydroxyvitamin D can prevent allograft rejection after liver, kidney, and heart transplantation but there are only limited data from human studies [12][13].

The role of calcineurin inhibitors in causing bone loss in post-transplant patients is unknown. Tacrolimus suppresses T cell activation and releases IL-2 and other cytokines. In a research of 360 patients with liver transplants done due to chronic cholestatic liver disease, the post-transplant bone gain was lower and the number of fractures was higher in patients treated with cyclosporine than with Tacrolimus in an adult study [14].

As there has been very little study showing vitamin D status in liver transplanted patients, we wanted to do a cross-sectional cohort study to evaluate the vitamin D levels in liver transplanted pediatric patients and compare that with the normal pediatric population. The study included an analysis of vitamin D distribution between liver transplanted patients and normal patients in males and females. And also the role of immunosuppressant medication in causing bone loss in post-transplant patients.

Methods:-

A retrospective cohort study of 42 liver transplant patients who were more than 2 years post-transplant was collected from the medical records of Al-Amiri Hospital, Kuwait, which is a territory center that caters to almost all liver transplanted patients in Kuwait. Along with this, data of normal patients, who attended the accident and emergency (A&E) for minor illnesses, were collected from the same hospital. The cut-off age was up to 15 years, with age and sex-matched controls of the general population. The liver transplanted patients were enrolled only after two years post-transplant, to avoid the confounding factors given repeated infections, use of high steroid doses, and high morbidity associated in the immediate post-transplant period. The exclusion criteria in both groups included those

on anticonvulsants, steroids, and those on vitamin D supplementation at the time of the study. Multi-organ transplant patients were also excluded. Vitamin D levels were collected and analyzed statistically. The study included patients living in Kuwait. All transplanted patients were on either FK-506 (38 patients), Sirolimus (2 patients), Azathioprine (2 patients), or a combination of FK and mycophenolatemofetil (6 patients) or a combination among them. Vitamin D assay was done using electrochemiluminescense binding assay on Cobra immune essay analyzer in nmol/L. None of the patients in the general population group were on any medications. Results were determined via a calibration curve by two-point calibration and a master curve provided by a reagent bar code.

Statistics

The general statistics of the Vitamin D values for males and females in both categories – where we find mean and median values to be higher for transplanted patients, with higher variance (details in table 1). In the statistical study, we consider the null hypothesis (H0) as there is no difference in vitamin D values between transplanted and non-transplanted patients for both males and females. We used the python programming language and its scipy toolkit to compute the general and T statistics shown in the Results section.

Results:-

A set of 42 liver transplant patients and control group patients each were studied with an average age of about 9 years for transplanted patients and 8 years for non-transplanted patients (median age of both categories being 8.5 years). The male to female ratio was 18:24 in the non-transplanted group and 20:22 in the transplant group. The mean vitamin D values of transplanted patients were 57.5 nmol/L (median 45.6 nmol/L) and for non-transplanted patients were 44.5 nmol/L (median 39.6 nmol/L). We look at these values in more detail including male and female distribution and significant differences. The median vitamin D levels were insufficient according to the global evidence-based consensus recommendation in all categories. And on performing statistical analysis on the sample set, we were able to find a significant difference in vitamin D values for female transplant and non-transplant patients (with p-value 0.01 – average vitamin D values of 57.5 nmol/L for transplant patients and 40.5 nmol/L for non-transplant female patients), and no significant difference for male patients (average vitamin D values of 57.5 nmol/L for transplanted patients and 49.7 nmol/L for non-transplanted male patients).

On considering the test statistics for both males and females comparing between transplanted and non-transplanted patients, the p-value for males (0.41) is not significant at 0.05 level, however, for females the p-value (0.01) is significant at the 0.05 level, indicating that it is highly unlikely that these results would be observed under the null hypothesis and hence we hypothesis the higher vitamin D values in transplanted patients compared to non-transplanted patients is significantfor females considering the sample set.

Table 1:- General Statistics and T-Test for Male Patients.

Sex		**Male**	
Transplant		**No**	**Yes**
AGE	**count**	18.00	20.00
	mean	7.61	8.95
	std	3.27	3.80
	min	2.00	3.00
	25%	5.00	7.00
	50%	8.50	8.00
	75%	10.00	11.25
	max	14.00	15.00
VIT. D	**count**	18.00	20.00
	mean	49.68	57.52
	std	27.56	31.34
	min	20.00	28.40
	25%	28.60	38.63
	50%	36.75	44.64
	75%	81.32	62.60
	max	93.18	144.20

T-Test on Vitamin D Values for Transplant and Non-Transplant Male Patients	
T Statistic	0.82

P-Value	0.41

Table 2:- General Statistics and T-Test for Female Patients.

Sex		Female	
Transplant		No	Yes
AGE	count	24.00	22.00
	mean	8.21	9.55
	std	3.67	3.11
	min	2.00	4.00
	25%	5.75	7.00
	50%	9.00	10.00
	75%	11.00	12.00
	max	15.00	15.00
VIT. D	count	24.00	22.00
	mean	40.60	57.51
	std	17.77	25.15
	min	7.59	30.86
	25%	29.20	40.46
	50%	42.40	46.21
	75%	46.13	72.60
	max	89.90	124.90
T-Test on Vitamin D Values for Transplant and Non-Transplant Female Patients			
T Statistic			2.61
P-Value			0.01

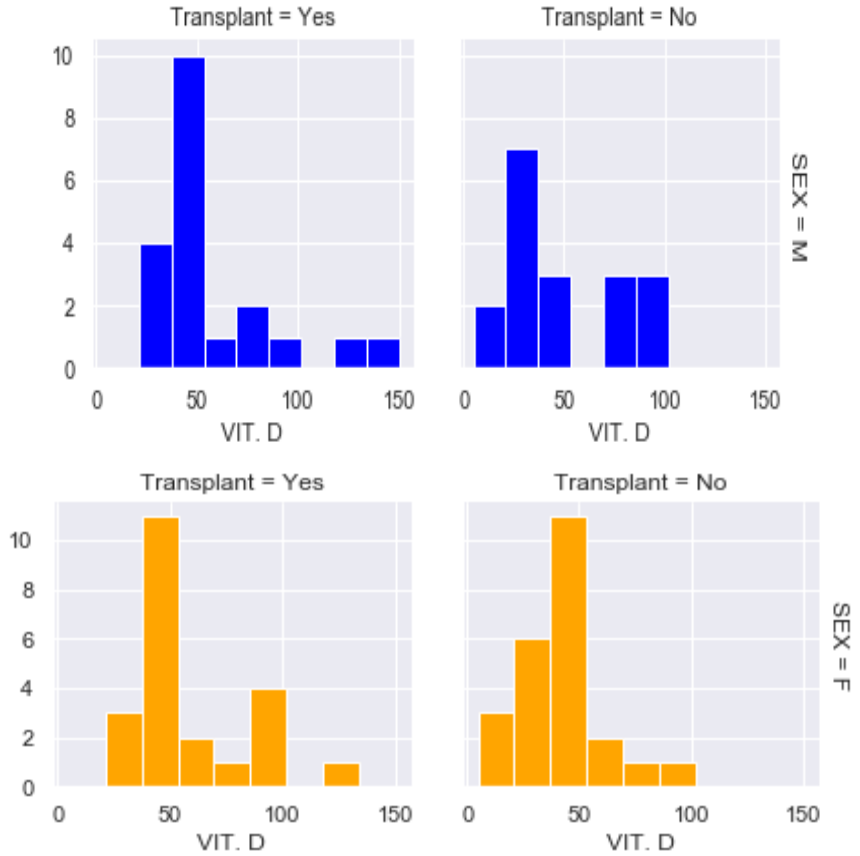

Figure 1:- Histogram showing the distribution of Vitamin D values among Transplant and Non-Transplant Male and Female Patients.

Conclusion:-

Vitamin D deficiency is prevalent in both transplant and normal patients. On comparing both transplant and non-transplant patients – for males there is no significant difference based on their expected (mean) Vitamin D values, however, for females, there is a significant difference. This could be because females get insufficient sun exposure and less physical activity compared to males in Kuwait. However, the immunosuppressants used are not detrimental to the bone metabolism besides close monitoring of these patients aids in early detection and control of any abnormality in vitamin D status after transplant.

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