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Original Research Paper

General Medicine

A STUDY OF VITAMIN D LEVELS IN PATIENTS WITH CHRONIC LIVER DISEASE

Md Ziauddin Ex-sr, Department Of General Medicine, Jnmch, Amu, Aligar

Abeer Masood* Department Of Physiology, Jnmch, Amu, Aligarh *Corresponding Author

Sheelu S. Siddiqi Rajiv Gandhi Centre For Endocrinology, Jnmch, Amu, Aligarh, U.p, India.

ABSTRACT

INTRODUCTION- Chronic liver disease (CLD) is major sources of morbidity and mortality all over world, it accounts for about 2% of all deaths in Europe (170,000/year) with increasing mortality rates in several countries. Recent study on multiethnic cohort at United States has shown non alcoholic fatty liver disease (NAFLD) is the most common cause of CLD in all ethnic groups combined (52%), followed by alcoholic liver disease .Since, liver contributes an important role in the metabolism process of Vitamin D , consequently chronic diseases of the liver interfere with production of the active metabolites of vitamin D,.

AIM- To study and examine the status of Vitamin D in relation to patients presenting with Chronic liver diseases

METHODOLOGY - The present study was undertaken from July 2012 till June 2014 at, Department of medicine, Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University and Rajiv Gandhi Centre for Diabetes and Endocrinology, AMU, Aligarh. In the present study we examined 100 patients with diagnosed chronic liver diseases and /or cirrhosis .The patients recruited in our present study were enrolled after taking informed consent from them. Vitamin D was also estimated.

CONCLUSION - Our findings suggest that periodic screening of serum vitamin D and supplementation should be considered in routine care of CLD patients, with emphasis given to patients with cirrhosis, however, safety and cost effectiveness need to be evaluated

KEYWORDS :

INTRODUCTION

Chronic liver disease (CLD) is major sources of morbidity and mortality all over world, it accounts for about 2% of all deaths in Europe (170,000/year) with increasing mortality rates in several countries (McCullough AJ et al 2004). Recent study on multiethnic cohort at United States has shown non alcoholic fatty liver disease (NAFLD) is the most common cause of CLD in all ethnic groups combined (52%), followed by alcoholic liver disease (Marchesini G et al 2005). Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of clinicopathologic entities that have in common the presence of fat accumulation in the liver in the absence of significant alcohol consumption. According to its severity, NAFLD may present with pure steatosis, steatohepatitis (NASH), cirrhosis and, rarely, hepatocellular carcinoma (Adams LA et al, 2007). NAFLD is increasingly diagnosed worldwide and considered to be the commonest liver disorder in Western countries (McCullough AJ et al, 2005; Farrell GC et al, 2006), affecting approximately 15 to 30% of the general population, and its prevalence increases steadily to 70–90% in people with obesity or type 2 diabetes (Marchesini G et al, 2005; Neuschwander-Tetri BA, 2005). The major risk factors for NAFLD, central obesity, Type 2 diabetes mellitus, dyslipidemia, and metabolic syndrome, are now widely prevalent and are increasing geometrically in the Asia–Pacific region (Yoon KH et al. 2006; Fan JG et al 2005). Cirrhosis is a condition that is defined histopathologically and has a variety of clinical manifestations and complications, some of which can be life-threatening. IL-6 and TNF- are the major stimuli responsible for increased hepatic production of C-reactive protein (CRP), fibrinogen and other acute-phase proteins. It has been shown that fibrinogen and CRP levels, which are known CVD risk factors, are increased in NAFLD patients, particularly in those with NASH (Yoneda M et al 2006).

Vitamin D is important for cell growth, immunity, and metabolism. Vitamin D deficiency has classically been associated with rickets and decreased bone density and more recently with increased risk and severity of autoimmune diseases, cancers, myocardial infarction, diabetes, and infectious diseases. (Mehta S et al. 2010). The liver plays an important role in metabolism of vitamin D. Vitamin D from the skin and diet is hydroxylated in the liver into 25-hydroxyvitamin D [25(OH)D]. 25(OH) D, the major circulating form of vitamin D, is used to determine a patient's vitamin D status. 25(OH) D, in turn, is transported to the kidney, undergoes a second hydroxylation in proximal convulated tubule, and is converted into 1,25(OH)D, the active form. Since, liver contributes an important role in the metabolism process of Vitamin D , consequently chronic diseases of the liver interfere with production of the active metabolites of vitamin D, thus resulting in abnormal calcium and bone metabolism. (Holick et al 2007).Chronic liver disease in the clinical context is a disease process of the liver that involves a process of progressive destruction and regeneration of liver parenchyma leading to fibrosis and cirrhosis. Also, Tumor necrosis factor-α (TNF-α) has been associated with NAFLD (Feldstein AE et al, 2004; Hui JM et al,2004), however, this inflammatory pathway is also shared by cardiovascular disease (Schram MT et al, 2005; Maumus S et al, 2005; Lopez-Garcia E et al, 2005).

Blood levels of 25-hydroxyvitamin D (Calcidiol) are the best measure of vitamin D deficiency (Borderi et al 2010).

	European (SI) measurement (nanomoles per litre)	US measurement (nanograms per millilitre)
Sufficient	≥75 nmol/L	≥30 ng/mL
Insufficient	0–75 nmol/L	20-30 ng/mL
Deficient	<50 nmol/L	<20 ng/mL

AIM

To study and examine the status of Vitamin D in relation to patients presenting with Chronic liver diseases

MATERIAL AND METHODS –

The present study was undertaken from July 2012 till June 2014 at, Department of medicine, Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University and Rajiv Gandhi Centre for Diabetes and Endocrinology, AMU,

Aligarh. In the present study we examined 100 patients with diagnosed chronic liver diseases and /or cirrhosis .The patients recruited in our present study were enrolled after taking informed consent from them. The subjects were either admitted in medical wards or were attending Medicine OPD, Gastro OPD of the Department of Medicine, J.N. Medical College and Hospital and Endocrinology OPD, AMU, Aligarh from July2012 to June 2014, and were recruited if they fulfilled the criteria for inclusion and exclusion.

The study design was non-randomised, cross-sectional, observational cohort study . The study had institutional ethics committee permission, and the procedures followed in the study were in accordance with institutional guidelines.

DIAGNOSIS OF CHRONIC LIVER DISEASES

NAFLD according to the Recommendations of the Asian–Pacific Working Party for diagnosis for NAFLD (**APWP-NAFLD**) **in 2007** summarized the definition of NAFLD for operational purposes as presence of fatty liver on abdominal ultrasonography (defined by at least two of three abnormal findings: diffusely increased echogenicity ('bright') liver with liver echogenicity greater than kidney or spleen, vascular blurring, and deep attenuation of ultrasound signal). NAFLD is highly likely provided that the other causes of liver disease have been rigorously excluded, particularly significant alcohol intake and medication.

Routine liver function tests and serological assays for the detection of HBV antigens (HBsAg and HBeAg) and antibodies (anti-HBs, anti-HBc and anti-HBe) should be performed to assess the phase of chronic hepatitis B. Also Anti-HCV antibodies for chronic hepatitis C were assessed.

By definition, chronic hepatitis is a necrosis and inflammatory process that may be complicated by fibrosis.

One grading system used for assessing inflammation and fibrosis is that of

Batts and Ludwig Grading System- Batts and Ludwig (Am J Surg Pathol 1995)

TABLE NO 1

STAGE	DESCRIPTION	CRITERIA
0	No fibrosis	Normal connective tissue
1	Portal fibrosis	Fibrous portal expansion
2	Periportal fibrosis	Periportal or rare portal-portal septa
3	Septal fibrosis	Fibrous septa with architectural distortion; no obvious cirrhosis
4	Cirrhosis	Cirrhosis

TABLE NO 2

GRADE	DESCRIPTION	PIECEMEAL NECROSIS	LOBULAR INFLAMMATION AND NECROSIS
0	No activity	None	None
1	Minimal	Minimal, patchy	Minimal; occasional spotty necrosis
2	Mild	Mild; involving some or all portal tracts	Mild; little hepatocellular damage
3	Moderate	Moderate; involving all portal tracts	Moderate; with noticeable hepatocellular damage
4	Severe	Severe; may have bridging fibrosis	Severe, with prominent diffuse hepatocellular damage

ALCOHOLIC LIVER DISEASE

Diagnosed on basis of history of alcoholism (Quantity and duration of alcohol intake are the most important) with clinical features of CLD or/and cirrhosis and laboratory findings.

1. *LIVER FUNCTION TEST (LFT)*:

a) Total serum bilirubin: estimated by Van den Bergh method of calorimetry.

b) AST/ALT: Serum Aspartate amino transaminase (AST) and Alanine amino transaminase (ALT) were estimated by simplified calorimetric test at 505nm.

c) Alkaline phosphatase: Estimated calorimetrically by the test described by E.J. King.

2. SERUM VITAMIN D ANALYSIS

We measured total serum 25-(OH)-D by Diasorin competitive radioimmunoassay (RIA) (AID Diagnostika, GmbH, Strasburg, Germany).

STATISTICAL ANALYSIS:

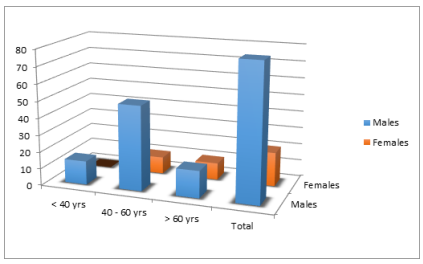
All statistical data were analysed by using SPSS software version 17.0, Statistical package for windows (Chicago. Inc.). Statistical significance was set at two-sided p-value≤0.05. Results are reported as the mean ± standard deviation (SD) or n (%) for continuous variables and as frequencies for categorical variables. In comparison of patient's data, one-way ANOVA and t-test was used for quantitative variables and chi-squared test for qualitative variables. The relationship for continuous variables was examined by Pearson's correlation coefficients and categorical variables by Spearman correlation analysis. Multivariate modeling was done by linear regression analysis.

RESULTS:

TABLE NO 3- Age and sex characteristics of study group

Age (years)	No. of patients (%) (n=100)	Male (n=80)		Female (n=20)	
		Number (n)	% of males	Number (n)	% of females
< 40	14 (14%)	14	17.5%	0	0
40-60	60(60%)	50	62.5%	10	50
> 60	26(26%)	16	20%	10	50

FIGURE NO 1



LIVER FUNCTION TESTS

TABLE NO 4

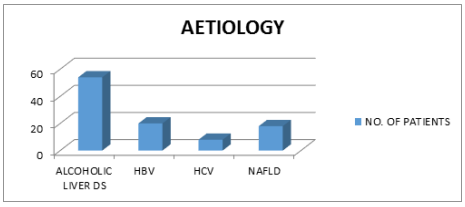
Test	Vitamin D <25nmol/L (Mean ± SD)	Vitamin D >25nmol/L (Mean ± SD)	P value
AST	48 ± 33	66 ± 66	NS
ALP	121 ± 67	103 ± 46	NS
INR	1.13 ± 0.13	1.15 ± 0.42	NS
ALBUMIN	3.5 ± 0.7	3.5 ± 0.7	0.0147
BILIRUBIN	5±2.1	3.2±1.6	<0.001

The Liver function tests suggests that the mean levels were 48, 121, 1.13 with standard deviation being 33, 67, 0.13 for of AST, ALP, INR respectively among patients having vitamin D levels<25 nmol/L, mean levels were 66, 103, 1.15 with standard deviation being 66, 46, 0.42in patients with vitamin D>25 nmol/L f of AST ,ALP, INR respectively.

The mean value and standard deviation of bilirubin in patients with vitamin D levels<25 nmol/L were 5±2.1 and those with vitamin D levels>25 nmol/L were3.2±1.6. By applying t test the value of p=0.001 which is (p<0.05) significant. Bilirubin has strong negative relation with severity of vitamin D deficiency.

The mean value and standard deviation of albumin in patients with vitamin D levels<25 nmol/L were 3.5 ± 0.7 and those with vitamin D levels>25 nmol/L were 3.5 ± 0.7. By applying t test the value of p= 0.0147 which is (p<0.05) significant. This shows albumin has strong positive relation with severity of vitamin D deficiency

FIGURE NO 2

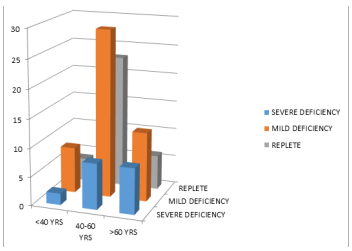


Most of the cases in present study, 62 (62%) has history significant of chronic alcoholism to be attributable to as a cause of chronic liver disease. Whereas among 100 patients HBV was tested positive in 20 (20%) and HCV among 8 (8%) patients. 4 patients of each category HBV (out of 20) and HCV (out of 8) were also having chronic alcoholism, rest of the patients (18%) were diagnosed as NAFLD.

VITAMIN D LEVELS IN VARIOUS AGE GROUPS
TABLE NO 6 PATTERN OF VITAMIN D STAUS

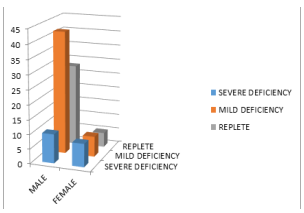
AGE	SEVERE DEFICIENCY (<25nmol/L)	MILD DEFICIENCY (25-54 nmol/L)	REPLETE (>54 nmol/L)	TOTAL
<40 YRS	2(14.29%)	8(57.14%)	4 (28.57%)	14
40-60 YRS	8(13.33%)	29(48.34%)	23(38.33%)	60
>60 YRS	8(30.77%)	12(46.15%)	6(23.08%)	26

FIGURE NO 3



The study population was further categorised according to vitamin D level with severe deficiency (<25nmol/L) , mild deficiency (25-54 nmol/L) and replete (>54 nmol/L). It was found that 18(18%) patient had severe deficiency , 49(49%) had mid deficiency and 33(33%) had been classified as replete. By applying chi-square test the p-value is 0.31 (p>0.05) which is insignificant, no relation between the age and vitamin D levels.

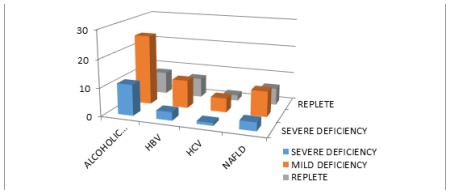
VITAMIN D LEVELS IN BOTH SEXES
FIGURE NO. 4



Among males (80 in no.), 10 (12.5%) were with severe deficiency (<25nmol/L), 42(52.5%) with mild deficiency (25-54 nmol/L) and 28(35%) were in replete (>54 nmol/L). Among females (20 in no.), 8 (40%) were with severe deficiency (<25nmol/L), 7(35%) with mild deficiency (25-54 nmol/L) and 5(25%) were in replete (>54 nmol/L).

By applying chi-square test the p-value is 0.017 (p>0.05) which is significant, showing vitamin D subnormal levels is positively related to female population in chronic liver disease.

VITAMIN D LEVELS IN DIFFERENT AETIOLOGIES OF CHRONIC LIVER DISEASES
FIGURE NO- 5



The total patients (n=100) of chronic liver diseases, has maximum (n=54) patients of ALD of which 11(20.37%) in severe deficiency (<25nmol/L), 25(40.3%) in mild deficiency (25-54 nmol/L) and 8(33.33%) in replete (>54 nmol/L).

There were 20 patients of HBV in which 3(15%) in severe deficiency (<25nmol/L), 10(50%) in mild deficiency (25-54 nmol/L) and 7(35%) in replete (>54 nmol/L).There were 8 patients of HCV in which 1(12.5%) in severe deficiency (<25nmol/L), 6(62.5%) in mild deficiency (25-54 nmol/L) and 2(25%) in replete (>54 nmol/L). There were 18 patients of HBV in which 3(16.67%) in severe deficiency (<25nmol/L), 9(50%) in mild deficiency (25-54 nmol/L) and 6(33.33%) in replete (>54 nmol/L).

DISSCUSION:-

The majority of patients in the study population belonged to age group of 40-60 years (62%). The distribution of rest of the cases was 14% below 40 years age group and 26% in >60 years age group. There were 80 males 20 female among the patients. In 80 males 52 (65%) were deficient and among females 15 (75%) were deficient.

Since duration of CLD is important in development of cirrhosis, younger patients are expected to have lower incidence of cirrhosis, these trends are seen to support our findings. Most of the cases in present study, 54 (54%) has history significant of chronic alcoholism to be attributable to as a cause of chronic liver disease and cirrhosis. Whereas among 100 patients HBV was tested positive in 20 (20%) and HCV among 8 (8%) patients. 4 patients of each category HBV (out of 20) and HCV (out of 8) were also having chronic alcoholism. The 15(15%) of the patients were diagnosed for NAFLD. This finding also coinciding with findings of other studies [Heidelbaugh JJ et al 2006]. Fisher L, Fisher A etal 2007 A recent study analysed 100 patients with noncholestatic CLD, showed that 91% of these subjects had vitamin D deficiency (<80nmol/L), this was similar to our result.

Crawford BA, Kam C, McCaughan GW 2003. They conducted study of heterogeneity of bone disease in cirrhosis suggesting high frequency of vitamin D deficiency in patients of CLD. Also, Mikkel Malham, Jørgensen, Søren Peter et al 2010They conducted a retrospective study in alcoholic liver cirrhosis (89 patients) and primary biliary cirrhosis (34 patients) with 85% and 55% vitamin D deficiency respectively suggesting vitamin D defiency is related to liver dysfunction rather aetiology.

In S. Fourlanos, A. Nicoll etal 2010, There study comparised of 158 patients of different aetiology of CLD Suboptimal

25[OH]D levels were present in 101 patient(64%) and 24 (15%) had severe vitamin D deficiency. Vitamin D deficiency was seen in liver disease across all etiologies including in subgroups with a low incidence of cirrhosis. A similar study of J Arteh, S. Nair et al 2008 which included 118 patients , 43 with hepatitis C cirrhosis, 57 with hepatitis C but no cirrhosis, 18 with non hepatitis C related cirrhosis) attending the University of Tennessee Hepatolog Clinic had their 25hydroxy vitamin D level measured. Vitamin D deficiency found in (92%) among patients with chronic liver disease, and one third of them suffer from severe vitamin D deficiency.

CONCLUSION:-

Our findings suggest that periodic screening of serum vitamin D and supplementation should be considered in routine care of CLD patients, with emphasis given to patients with cirrhosis, however, safety and cost effectiveness need to be evaluated. Given the high frequency of hypovitaminosis D found in this study, there is a need to work more on health promotion activities to this community targeting the importance of physical activities, exposure to sunlight and use of diets rich in vitamin D.

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