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Vitamin D_3 deficiency in babies and children with cholestasis

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ABSTRACT

Background: Cholestasis, also known as prolonged jaundice, is characterized by a reduction in bile flow. Vitamin D_3 is a fat-soluble vitamin whose absorption is affected by bile acids passing through the bile ducts. The primary objective was to determine the clinical utility of serum vitamin D_3 in infants and children with cholestasis. *Materials and Methods:* Using an enzyme-linked immunosorbent assay, vitamin D_3 levels in the blood serum of sixty patients with cholestasis, twenty patients with non-cholestatic causes, and twenty-five healthy subjects ranging in age from one day to fourteen years were determined. *Results:* Comparing intra- and extra-hepatic cholestasis groups to the control group, intra- and extra-hepatic cholestasis groups showed a highly significant decrease in serum vitamin D_3 ($P<0.001$), while there was no significant difference between the control and non-cholestatic jaundiced groups ($P= 0.069$), and there was no significant difference between the old and newly diagnosed intra-hepatic cholestatic groups ($p = 0.627$). *Conclusion:* The amount of vitamin D_3 in the serum of those with extra-hepatic cholestasis is lower than those with intra-hepatic cholestasis, indicating a poor prognosis for cholestasis illness.

Keywords: Extrahepatic Cholestasis, Fat-soluble Vitamins, Intrahepatic Cholestasis, Obstruction of Bile flow, Vitamin D_3

1. INTRODUCTION

The most common manifestation in newborns is jaundice, typically caused by direct or unconjugated hyperbilirubinemia. Jaundice must be evaluated to determine if it is of recent onset, early-onset (less than 24 hours of life), sustained beyond fourteen days of life, or jaundice with a sharp increase in serum bilirubin levels. When neonates' total blood bilirubin level exceeds 2.5 - 3.0 mg/dL (42–51 mmol/L), it is evaluated for severe causes, such as the development of hepatobiliary dysfunction or infection is determined whether immediate therapeutic intervention is required. This condition manifests as yellowing of the oral mucosa or scleral icterus. Although jaundice in newborns is common and to be expected, persistent jaundice at 14 days of age may indicate a pathogenic condition (Lane & Murray, 2017). Because many kinds induce newborn cholestasis, this study focused on the following types: Biliary atresia is biliary blockage caused by gradual fibrosis of intra-hepatic and extra-hepatic bile ducts with unknown pathophysiology. If biliary atresia is not corrected, it will lead to liver cirrhosis and failure and afflict patients

will usually die within twelve to eighteen months after birth (Song et al., 2012; Squires et al., 2020).

Furthermore, biliary atresia can be a clinical characteristic of several hereditary disorders (Sanchez-Valle et al., 2017), including Mitchell Riley syndrome (Calcaterra et al., 2021), Fanconi anaemia complementation group Q (Bogliolo et al., 2013), Zimmermann Lab and syndrome 1, Alagille syndrome (Diaz-Frias & Kondamudi, 2022) and Kabuki syndrome 1 (Masui et al., 2019). Progressive familial intra-hepatic cholestasis and biliary hypoplasia are two other bile duct anomalies that mimic the medical signs of obstructive jaundice with biliary atresia (Gomez-Ospina et al., 2016; Sambrotta et al., 2014). Between two and five weeks and sometimes peaking at seven to eight weeks, biliary atresia is frequently associated with cholestasis (Ling et al., 2021). In infants, Alagille syndrome and biliary atresia are the most common concurrent causes of cholestatic liver disease (Kriegermeier & Green, 2020).

Alagille syndrome is a type of intra-hepatic cholestasis is characterized by ductopenia; however, in early infancy, ductular proliferation may be primary and suggest a diagnostic dilemma. Biliary atresia is more likely to happen when there is a sign of biliary duct obstruction in the splendid duct. Intraoperative cholangiography can assist in distinguishing ductal involvement (Kriegermeier & Green, 2020; Lin et al., 2017). Progressive familial intra-hepatic cholestasis is a group of unrelated monogenic diseases caused by mutations in one of the genes involved in canalicular hepatobiliary transport, resulting in cholestasis and liver damage(Fawaz et al., 2017).

According to research, prolonged bile acid buildup in the liver promotes fibrosis, the development of portal hypertension, and cirrhosis, eventually necessitating liver transplantation (Hohenester et al., 2020) or, in rare cases, fatal bleeding due to vitamin K shortage (Lane & Murray, 2017; Srivastava, 2014). Vitamin D is a steroid that plays a crucial role in calcium and phosphorus metabolism. Its primary functions include renal calcium reabsorption and intestinal calcium absorption and a direct effect on osteoblast and chondrocyte development and bone production (Wu et al., 2022). In infants and children with cholestatic liver illness, absorption of ingested vitamin D_3 was decreased. Several fat-soluble vitamin deficiencies, notably vitamin D_3 insufficiency, were frequent in cholestatic patients and were inversely related to blood total bilirubin levels (Dong et al., 2017).

The presence of an adequate plasma level of vitamin D depends on the absorption of vitamin D_2 and D_3 and the cutaneal production of vitamin D_3 following ultraviolet light exposure. Good bile flow promotes absorption, which occurs in the ileum and jejunum, transported as chylomicrons to the liver. It is 25-hydroxylated in this organ, resulting in 25-hydroxy vitamin D (25- OHD). The 25-hydroxyvitamin D then enters the circulation system and is excreted to the renal system, where it suffers another hydroxylation reaction to generate 1,25-dihydroxyvitamin D_3 (1,25 [OH2] D_3) or 24,25-dihydroxyvitamin D_3 (24,25 [OH2] D_3) depending on the sufficiency of vitamin D_3; as a result, any decrease in bile flow caused by either an intra-hepatic or extra-hepatic problem, such as bile duct blockage, leading to a reduction in plasma vitamin D_3 levels (Sun et al., 2021; Veraldi et al., 2020).

2. MATERIALS AND METHODS

The study was carried out during the term from January 2022 to March 2022 study, it included 60 patients with different causes of cholestasis diseases (Biliary atresia, Alagille syndrome, Progressive familial intra-hepatic cholestasis). It was divided into the intra-hepatic cholestasis group containing 40 patients, the extra-hepatic cholestasis group containing 20 patients, and 20 patients with non-cholestasis jaundice diseases who suffer from hepatitis C and neonatal jaundice, and 25 healthy subjects without liver disease or any other chronic illness and is age-matched. The subjects ranged in age from one day to fourteen years; the intra-hepatic cholestasis group was divided into new (recently) and old (previously) diagnosed groups. If they took medication, the last group must stop it two times weeks before the blood sample was drawn. Al-Imameen Al-Kademen Medical City, the Digestive Center at Medical City, and Child's Central Teaching Hospital provided samples.

Exclusion criteria included individuals who did not have dyslipidemia, diabetes mellitus, or any other condition that might restrict the study, as well as patients who did not receive any medication, such as ursodeoxycholic acid or vitamin D_3 supplementation that was ceased two weeks before to the trial. Collecting approximately five milliliters of blood from the veins of cholestasis patients and healthy control volunteers yielded blood samples. Serum was separated by centrifugation at 3000 rpm for 10 minutes and kept at -20 °C until vitamin D_3 levels were determined using an enzyme-linked immunosorbent assay (ELISA) kit manufactured by the Chinese kit Kono Biotech.

The data that obtain were analyzed using SPSS version 18 and Microsoft excels 2010. Numeric data was expressed as median and range. Mann Whitney test was used to calculate individual P-value between normal subjects and patients correlated between each sample of vitamin D_3 level. P value < 0.05 was considered significant.

3. RESULTS

Serum Vitamin D_3 was measured for all cholestatic, non-cholestatic jaundice, and control groups. The median serum Vitamin D_3 in the control and patients' groups was displayed in the table (1). Serum Vitamin D_3 has reduced significantly in intra- and extra-hepatic cholestatic patients when compared with control ($P<0.001$) and non-significantly diminished when equated to the non-cholestatic jaundiced patients with the control group ($P= 0.069$), as display in the table (1).

Table 1 Comparison of three study groups versus the control group using the Mann Whitney test

Parameter		Control Number (25)	Intra-hepatic cholestasis Number (40)	Extra-hepatic cholestasis Number (20)	Non-Cholestatic Jaundice Number (20)
Vit.D_3 (µg/L)	Median	407	185	164	323
	Range	268 - 5977	67 - 5909	102 - 372	69 - 4590
	P value		<0.001	<0.001	0.069

Assessment of Parameter in an intra-hepatic cholestatic Patients according to Time of Diagnosis

In this study, the intra-hepatic cholestatic patients are subclassed into newly diagnosed patients' group in which the patients have newly developed disease and newly diagnosed after investigation and clinical data collected and oldy diagnosed patients' group in which patients previously had the disease and making follow up with their state. Serum Vitamin D_3 levels did not differ significantly between previously diagnosed intra-hepatic cholestatic patients and newly diagnosed intra-hepatic cholestatic patients ($p = 0.627$), as shown in table (2).

Table 2 Assessment of parameter in intra-hepatic cholestatic patients according to time of diagnosis by Mann Whitney test

Parameter		Newly Diagnosed Number (10)	Old Diagnosed Number (30)	P-value
Vit.D_3 (µg/L)	Median	204	184	0.627
	Range	67 - 5593	80 – 5909	

Assessment between non-cholestatic jaundice Patients with Intra- and Extra Hepatic Cholestatic Patients

There was no arithmetical difference in Serum Vitamin D_3 when a comparison was made between intra-hepatic cholestatic patients and non-cholestatic jaundice patients ($P = 0.406$). Also, the serum levels of Vitamin D_3 are low in these groups. However, there was a significant reduction in extra-hepatic cholestasis compared with the non-cholestatic jaundice patients ($P= 0.043$) by Mann Whitney test, as shown in Table (3).

Table 3 Comparison of non-cholestatic jaundice patients with intrahepatic and extrahepatic cholestatic patients using the Mann Whitney test

Parameter		Non Cholestatic Jaundice Number (20)	Intra-hepatic cholestasis Number (40)	Extra-hepatic cholestasis Number (20)
Vit.D_3 (µg/L)	Median	323	185	164
	Range	69 - 4590	67 - 5909	102 - 372
	P value		0.406	0.043

4. DISCUSSION

Children with the cholestatic liver illness have decreased vitamin D_3 absorption due to the absence of bile in the intestine, which is fat-soluble vitamin D_3 absorption dependent, resulting in steatorrhea with the signs and symptoms caused by malabsorption and must be treated earlier to balance the malabsorption that caused by this deficiency (Sun et al., 2021). Several fat-soluble vitamin deficiencies, notably vitamin D_3 insufficiency, were frequent in all types of cholestatic patients, as this article found in old and newly diagnosed intra-hepatic cholestatic patients (Dong et al., 2017). This article found that a low level of vitamin D_3 was associated with a poor prognosis of cholestatic status, which is consistent with the significant relationship between a low level of vitamin D_3 and the vital signs of cholestatic patients, which may be due to impaired absorption of vitamin D_3 (Sun et al., 2021; Veraldi et al., 2020).

Non-cholestasis jaundice classifies into two types: Hepatitis C is an infection caused by the hepatitis C virus that primarily causes liver damage and jaundice. People frequently have mild or no symptoms during the early illness. A fever, stomach ache, darker urine, and yellowish tinted skin are the most acute symptoms of jaundice. The virus remains in the liver in around 75% to 85% of first-infected people. There are usually no symptoms early on in chronic infection (Ghany et al., 2020; Jin, 2020). Lower serum vitamin D_3 concentrations were proved to be associated with poor prognosis in hepatitis patients. They worsened liver disease outcomes as this article agrees with recent results in Hu et al., (2019).

Neonatal jaundice is common and can be physiologic and resolve independently; however, if jaundice persists after fourteen days of age, there is a risk of a pathologic abnormality (Fawaz et al., 2017; Rosli et al., 2021). Uncertain causes of physiologic jaundice have been associated with vitamin D_3 deficiency in newborns. This article concurs with a recent study that may be due to its biosynthesis in the liver, affecting bilirubin levels in physiologic jaundice neonates (Bhat et al., 2021). A recent study shows that patients with the hepatitis C virus have decreased vitamin D_3 serum levels. It is prevalent in chronic hepatitis C virus cases in the non-cholestasis group compared to the intrahepatic cholestasis group in Table 3 (Ladero et al., 2013).

5. CONCLUSION

It concluded that vitamin D_3 deficiency in cholestatic and non-cholestatic patients referred to a poor prognosis of disease, so all patients must undergo supplemental vitamin D_3 treatment due to their lack of absorption of any fat-soluble vitamins due to impairment of bile flow at any stage of disease or any disruption in liver metabolism, so medical advice must be given to moms to make an early check for their babies if they have any jaundice and the causative disease may last for long term and causing malabsorption for nutrients.

Ethical standards

With registration number 5/34/587-01102022, the Ethics committee of the institutional board review of the medical college at Alnahrain University has authorized the research.

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Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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