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Original Article

Serum 25-Hydroxyvitamin-D Level in Full-term Neonates with Indirect Hyperbilirubinemia at a Level Requiring Phototherapy

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Abstract

Background: Low antioxidant system may contribute to the severity of neonatal hyperbilirubinemia.

Objectives: This study was performed to clarify the relationship between serum 25-hydroxyvitamin-D (25[OH] D) and the hyperbilirubinemia in full-term neonates.

Study design: This is a cross sectional case control study performed with the aim of determining whether there is an association between serum indirect bilirubin and serum vitamin D levels in newborns with jaundice at a level necessitating phototherapy. The study was carried on 60 full term newborns admitted to the Neonatal Intensive Care Unit of Minia University Hospital, from April 2017 to December 2017. They were classified into 2 groups, Group I: (cases): Newborns with postnatal ages of 3-10 days and gestational ages of 37-40 weeks, with a bilirubin level above the pre-set threshold for phototherapy as recommended by the American Academy of Pediatrics (AAP). Group II :(controls) 30 matched apparently normal healthy newborns were enrolled in the study as a control group. The study included the mothers of case group. All laboratory investigations were done in clinical pathology department, Minia University hospital.

Results: Serum Vitamin D levels were significantly lower in patients than controls ($p<0.01$). There was a strong negative correlation between neonatal total serum bilirubin level and neonatal serum vitamin D in cases group. In addition, we observed that there was a highly statistically significant positive correlation between serum vitamin D level of neonates and their maternal serum level was present.

Conclusions: Indirect hyperbilirubinemia in full-term neonates is associated with decreased serum levels of (25[OH] D)

Key words: Hyperbilirubinemia; neonate; serum 25-hydroxyvitamin D

Introduction

Hyperbilirubinemia is one among the foremost prevalent clinical diseases confronting neonatologists daily. It approximately occurs in 60% of term and 80% of pre- term neonates and develops 2-4 days after birth then spontaneously recovered within 1-3 weeks. [1, 2] In Egypt, about 20.4% of full-term newborns develop jaundice yearly. Incidence of jaundice was found to be higher in low-birth-weight neonates (35.6%) compared with normal birth weight infants (16.9%). [3] Total serum or plasma bilirubin (TB) levels >1 mg/dL (17 micromole/L) occur in the majority term and near-term newborn infants. Infants with severe hyperbilirubinemia (TB >25 mg/dL [428 micromoles/L]) are at risk for developing bilirubin-induced neurologic dysfunction (BIND), presenting acutely as acute bilirubin encephalopathy (ABE) and, if not treated appropriately or in a very timely manner, resulting in long-term neurologic sequelae of chronic bilirubin encephalopathy (CBE, previously stated as kernicterus) [8-12]. Benign hyperbilirubinemia of the newborn, previously stated as "physiologic jaundice," could be a normal transitional phenomenon caused by the turnover of fetal red blood cells, immaturity of the newborn's liver to efficiently metabolize bilirubin, and sterile newborn gut, leading to decreased bilirubin clearance and increased enterohepatic circulation. It typically presents as mild unconjugated (indirect-reacting) hyperbilirubinemia. Mean TB levels normally peak at 7 to 9 mg/dL (120 - 154 micromole/L) [4]. Hyperbilirubinemia is because of increased bilirubin load either because of a rise in bilirubin production or decrease in clearance, or both [5]. For infants with severe and extreme hyperbilirubinemia, identification of the explanation for their hyperbilirubinemia is beneficial in determining whether therapeutic interventions are needed and their timing [6, 7] Vitamin D is a fat-soluble vitamin. Only a few foods naturally

contain vitamin D (fatty fish livers are the exception), so dermal synthesis is the major natural source of that vitamin. Vitamin D from either diet or dermal synthesis is biologically inactive and requires enzymatic conversion to active metabolites. Vitamin D and its metabolites have a major clinical role attributable to their interrelationship with calcium homeostasis and bone metabolism [13]. Vitamin D, or calciferol, is a generic term and refers to a group of lipid soluble compounds with a four-ringed cholesterol backbone. 25-hydroxyvitamin D (25[OH]D) is that the major circulating sort of vitamin D. Vitamin D3 (cholecalciferol) is synthesized no enzymatically in skin from 7-dehydrocholesterol during exposure to the ultraviolet (UV) rays in sunlight. Vitamin D3 from the skin or diet must be 25-hydroxylated within the liver, then 1-hydroxylated within the kidneys to the active form, 1, 25-dihydroxycholecalciferol (calcitriol) [14,15]. In addition to its role in calcium and bone homeostasis, vitamin D potentially regulates many other cellular functions. The vitamin D receptor (VDR) is almost universally expressed in nucleated cells. Approximately 3 percent of the human/mouse genome is under the control of 1,25-dihydroxyvitamin D, the active form of vitamin D. Furthermore, a minimum of 10 tissues outside the kidney express 1-alpha-hydroxylase (CYP27B1), the enzyme responsible for converting vitamin D to its active form, and thus, the active hormone will be generated in an auto- or paracrine way. Thus, the spectrum of activity of the vitamin D endocrine system is much broader than calcium/bone homeostasis, and during this regard, the vitamin D-VDR system resembles that of other ligands of nuclear receptors, like thyroid hormone [16-21]. However, there are not any convincing randomized trial data that vitamin D supplements can decrease cancer risk or prognosis, decrease the risk or severity

of infections or autoimmune diseases, or decrease cardiovascular risks or metabolic diseases additionally; Vitamin D deficiency has also been reported to have a relationship with the maternal, fetal, and placental health. [22-23].

Aim of the work

The aim was to determine whether there is an association between indirect bilirubin and serum (25[OH]D level in term newborns with indirect hyperbilirubinemia at a level requiring phototherapy according to American Academy of Pediatrics (2004).

Methods

This is a cross-sectional case control study carried on 60 full term newborns who were admitted to our nursery, in the period from April 2017 to December 2017. They were classified into two groups: Group I (cases): thirty newborns with postnatal ages of 3-10 days and gestational ages of 37-40 weeks, with a bilirubin level above the pre-set threshold for phototherapy as recommended by the American Academy of Pediatrics (2004) as well as their mothers for vitamin D measurement. Group II (controls): thirty matched apparently normal healthy newborns were enrolled within the study as control group. All laboratory investigations were done the clinical pathology department in Minia University hospital.

Inclusion Criteria of Group I: Any newborns with postnatal ages of 3-10 days and gestational ages of 37-40 weeks, both genders, of any mode of delivery with an indirect Hyperbilirubinemia at level above the pre-set threshold for phototherapy as recommended by the American Academy of Pediatrics was eligible to be included in our study.

Exclusion criteria of Group I: Newborns with pathology that accounts for hyperbilirubinemia like iso-immunisation, infection, polycythemia, cephalic hematoma or a history of asphyxia were excluded from the study. Babies whose mothers had a history of chronic liver disease, renal disorder or on

regular anti-epileptic drug were excluded.

Inclusion Criteria of Group II (Control): Any normal healthy newborn with postnatal ages of 3-10 days and gestational ages of 37-40 weeks, both genders, of any mode of delivery who attended the hospital with absence of jaundice. Exclusion criteria of Group II (Control): Fulfilling the criteria of jaundice and requiring phototherapy, conjugated hyperbilirubinemia, birth asphyxia, septicemia, renal failure, abnormal electrolyte status or any other medical illnesses were excluded.

All cases and controls were subjected to: Full history of mother and baby which included (name, Sex. gestational age, mode of delivery. birth weight, postnatal age, detailed prenatal and natal history, consanguinity, type of feeding, family history of neonatal jaundice). In addition, the mothers of all the newborns were asked about their age, geographical region they lived in, vitamin D use during pregnancy and any disease or drug use which may affect the vitamin D levels. Full Clinical examination was done for all newborn included in studied groups. Laboratory investigations included total and Direct serum bilirubin (TSB & DSB), serum 25 (OH)vitamin D level, complete blood count (CBC), blood group and Rh determination for mother and infant, direct anti-globulin test (DAT) in the infant (direct Coombs test), peripheral blood film for erythrocyte morphology, reticulocyte count, liver function tests and Thyroid function tests.

The screening for neonatal unconjugated hyperbilirubinemia and identifying at-risk infants for hyperbilirubinemia are done for all neonates who born in our hospital. Clinical assessment of all infants for the physical presence of jaundice and additional hyperbilirubinemia risk factors. We used universal measurement of bilirubin consistent with American Academy of Pediatrics (AAP) guidelines because the physical presence of jaundice alone could

also be a suboptimal screening tool [33]. In our center, screening is completed by measuring total serum or plasma bilirubin (TB) levels. Appropriate follow-up based upon risk assessment and thus the infant's age at the time of discharge.

The sample size: was estimated using the Everald's equation for power calculation in diagnostics tests [34]. Assuming the expected lowest sensitivity (SN) to be 95%, the lowest expected specificity (SP) to be 80%, confidence interval (W) for both sensitivity and specificity to be 5% and prevalence of neonatal jaundice to be 15% was done. The remaining samples without significant indirect hyperbilirubinemia of the newborn were considered controls. We used uncorrected chi-squared statistics to judge this null hypothesis with the setting type I error probability to 0.05. Calculations were done using Flahault equation [35]

Methods: Skin was rubbed with antiseptic and 4 ml of blood was taken by a lancet to puncture the skin, and make it bleed, 1ml was collected in a test tube containing 20 µl of EDTA and analyzed as soon as possible for CBC with reticulocytes count, blood group, and RH and 3 mm of blood was collected in a plain test tube, left to clot, then centrifuged for 10 minutes at 1500 rpm, serum was separated and stored at -80oc for quantitative measurement of CRP, vitamin D, TSB, direct bilirubin. From the mothers of cases 2 samples were taken for blood group and serum 25 (OH) vitamin D level measurements of serum total bilirubin and direct bilirubin [36]

Measurement of serum (25[OH]D) [37]

Principle of the test: The determination is predicated on a competitive enzyme linked immunosorbent assay (ELISA). This ELISA assay is suitable for use on open automated ELISA processors. Each assay has to be validated on the respective automated system.

Ranges for serum levels of 25-Hydroxy vitamin D: [30, 31]

Given the controversy surrounding

optimal serum 25(OH)D concentrations, the definitions of vitamin D sufficiency, insufficiency, and deficiency are only approximate. The majority of groups currently use the following values to categorize the vitamin D status, vitamin D sufficiency is defined as a 25(OH)D concentration greater than 20 ng/mL (50 nmol/L), Vitamin D insufficiency is defined as a 25(OH)D concentration of 12 to 20 ng/mL (30 to 50 nmol/L), vitamin D deficiency is defined as a 25(OH)D level less than 12 ng/mL (30 nmol/L), while a "risk" of vitamin D toxicity is defined as a 25(OH)D level >100 ng/mL (>250 nmol/mL).

Ethical consideration

This study was approved by ethical committee, Faculty of Medicine, Minia University. A written consent was obtained from each parent to comply with participate in the study. Protection of the participant's anonymity and confidentiality and avoiding using deceptive practices and giving participants the right to withdraw from our research were done.

Statistical analysis

It was done using standard computer program. The clinical data were recorded on a report form. These data were tabulated and analyzed using the computer program SPSS (Statistical package for social science) version 21 to obtain: descriptive data which were calculated for the data in the form of, mean & standard deviation (SD) for quantitative data and Frequency & distribution for qualitative data. We used analytical statistics (Stewart, 2002) in the statistical comparison between the different groups. Significance of difference was tested using Student's t-test and Mann-Whitney U test: Used to compare mean of two groups of quantitative data of parametric and non-parametric respectively, Inter-group comparison of categorical data was performed by using chi- square test (X2-value) and fisher exact test (FET) and correlation coefficient: to find

relationships between variables. A P value <0.05 was considered statistically significant (S) while >0.05 statistically non-significant (NS). P value <0.01 was considered highly significant (HS) in all analysis (Lind et al., 2005)

Results

In the present study, we found that, there was no significant difference between the control and cases regarding age, gestational age, sex, and mode of delivery, weight and consanguinity as shown in (Table 1).

In the present study, we observed that there was statistical highly significant difference (P < 0.01) between patients and controls as regard total serum bilirubin level (Table 2 & Figure 1). We observed in our study that, serum Vitamin D levels were significantly lower in patients than controls (p<0.01) (Table 2). Also we found that there is a strong negative correlation between neonatal total serum bilirubin level and neonatal serum vitamin D in the cases group (Table 3). In addition, we observed that there was highly statistically significant difference (P=0.00) between patients and controls as regard neonatal 25 (OH) Vitamin D levels , 76.6% (n=23) of patients had deficiency level of neonatal 25 (OH) Vitamin D , while 13.3% (n=4) of patients had insufficiency and 12% (n=3) had normal level of neonatal vitamin D, regarding control group, results showed that 16.6% (n=5), 30% (n=9) and 53.4% (n=16) of the control group had deficiency, insufficiency and normal level of neonatal 25 (OH) Vitamin D respectively, while there were no subjects (patients or controls) had severe deficiency < 5 in the current study (Table 4). In our study, we found that 65% (n=15) deficient Vitamin D jaundiced babies (n=23) their mothers had vitamin d deficiency which is statistically significant (p<0.03) (Table 5). We found also a week positive significant Correlation between serum level of 25 Vitamin D level of the mothers of the studied group and serum level of 25

Vitamin D of their babies with p value (<0.05) (Table 6).

Discussion

Hyperbilirubinemia is one among the foremost prevalent clinical diseases confronting neonatologists daily. It approximately occurs in 60% of term and 80% of pre-term neonates and develops 2-4 days after birth then spontaneously recovered within 1-3 weeks. [1,2]. High bilirubin level could also be toxic to the developing central nervous system and may cause neurological impairment and serious illness [25]. Vitamin D may be a vitamin that plays a crucial role in bone metabolism, it's also considered a steroid with multi system effects and has important roles within the optimal functioning of the many organ systems [26, 27].

In the present study, we found that, there was no significant difference between the control and cases regarding age, gestational age, sex, mode of delivery, weight and consanguinity as shown in (Table1). The non-significant differences between cases and control group is important to confirm the homogenization of the studied groups to induce accurate results as much as possible when comparing between groups and to refer any differences to the studied factors. In agreement of our results, study done by Mutlu et al., (2013) [28] who compared serum vitamin D level in term neonates with hyperbilirubinemia at a level requiring phototherapy and non-jaundiced control neonates, His study was done on neonates who were all breastfed. Our study disagreed with Gartener (2001) [29] who stated that late-onset, prolonged neonatal jaundice was more frequent in breast-fed infants than in artificially-fed, and therefore the association of breast-feeding with prolonged and exaggerated physiological jaundice of the newborn has been considered a frequently and regularly occurring phenomenon with an incidence over two-thirds of all breastfed infants. In the present study, we observed that there was significantly low serum bilirubin

level of normal controls in comparison with jaundiced cases ($p<0.01$) (Table 2).

In the present study, there was highly statistically low level of vitamin D in jaundiced cases compared with control with p value ($p<0.05$). Our results were in agreement with Aletayeb et al., (2016) [24] who compared serum vitamin D level in healthy term jaundiced and non-jaundiced controls. He observed that there was a highly significant difference between patients and controls as regard neonatal Serum Vitamin D levels with ($p <0.001$).

From table (4) we found a week significant correlation between maternal their jaundiced. This can be explained by the fact that the vitamin D stores of the newborn depend entirely on the vitamin D stores of their mother.

In 2009 a study done by Lee et al., [32] who found a well correlation between Vitamin D serum concentration in mothers and their newborns. In contrary to us Mutlu al., (2013) [28] found that there was no difference in serum vitamin D levels between mothers and their neonates.

Conclusions

Vitamin D serum levels were significantly lower in neonates with indirect hyperbilirubinemia than controls. A Highly significant negative correlation between its level and indirect bilirubin levels was present while positive correlation between serum vitamin D level of neonates and their maternal serum level was present.

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Author's contributions

SZ, NS and HM equally contributed in the study concept, design, supervision, methodology, statistical analysis and data collection. ES performed the investigations and laboratory workup. NS wrote the first draft of the manuscript and made a critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript

Conflict of interest

Authors declare they have no conflict of interest

Fund

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Table (1): Comparison between cases and control groups regarding the demographic data

Parameter		Groups (n= 60)		P. value
		Group (I) Cases (n=30)	**Group (II) Control (n=30)**	
Age (days)		6.9 ± 1.8	6.6 ± 2.1	0.60
Gestational age (wks.)		38.2 ± 1.0	38.1 ± 1.1	0.71
Weight (kg)		3.29 ± 0.37	3.54 ± 0.61	0.25
Sex	**Males**	17 (56.7%)	22 (73.3%)	0.17
	Females	13 (43.3%)	8 (26.7%)	
Mode of delivery	**NVD**	16 (53.3%)	14 (46.7%)	0.61
	CS	14 (46.7%)	16 (53.3%)	
Consanguinity	**Negative**	15 (50.0%)	12 (40.0%)	0.43
	Positive	15 (50.0%)	18 (60.0%)	
Type of feeding	**BF**	20 (66.7%)	19 (63.3%)	0.78
	AF	10 (33.3%)	11 (36.7%)	

BF: Breast feeding; AF: Artificial feeding; NVD: normal vaginal delivery; CS: caesarean section

Table (2) Comparison between groups regarding total serum bilirubin and Vitamin D level .

Parameter	Groups		P. value
	Group (I) Cases (n=30)	**Group (II) Control (n=30)**	
Total serum bilirubin (mg/dL)	18.75 ± 2.24	5.89 ± 1.52	0.01**
25 (OH) Vitamin D (ng/ml)	15.45 ± 4.51	26.36 ± 12.62	0.01**

$P < 0.05$ is significant; $P < 0.001$ is highly significant**

Table (3): Correlations between total serum bilirubin and 25 (OH) Vitamin D in cases and control groups.

Correlation	Cases group		Control group	
	(r)	P	(r)	P
Total serum bilirubin and 25 (OH) Vitamin D	-0.82	0.01**	-0.26	0.34

P < 0.05 is significant; P < 0.001 is highly significant**

Table (4): Different ranges of Serum 25 (OH) Vitamin D levels in cases and control groups

Serum 25 (OH) Vitamin D levels (ng/ml)		Patients (N=30)	Controls (N=30)
Severe deficiency < 5	**No. (%)**	0 (0%)	0 (0%)
Deficiency (5 - 14.9)	**No. (%)**	23 (76.6%)	5 (16.6%)
Insufficiency (15 – 20)	**No. (%)**	4 (13.3%)	9 (30%)
Normal (> 20)	**No. (%)**	3 (12%)	16 (53.4%)
P value		0.000**	

P < 0.05 is significant; P < 0.001 is highly significant**

Table (5): Correlation between different ranges of serum levels of Vitamin D in neonates and their mothers in group I.

Serum Vitamin D levels (ng/ml)		Groups		
		Patients (N=30)	**Mothers of cases (N=30)**	**P value**
Sever deficiency <5	**NO**	**0**	**0**	0
	%	**0.0%**	**0.0%**	**0.0%**
Deficiency (5 - 14.9)	**No.**	23	15	0.03 *
	%	76.6%	50%	
Insufficiency (15 – 20)	**No.**	4	8	0.2
	%	13.3%	26.6%	
Normal (> 20)	**No.**	3	7	0.16
	%	12%	23.3%	

P < 0.05 is significant; P < 0.001 is highly significant**

Table (6): Correlation between maternal and neonatal serum 25 (OH) Vitamin D levels in cases group.

Correlation	Cases group	
	(r)	P value
Maternal and neonatal serum 25 (OH) Vitamin D levels	0.17	0.05

P < 0.05 is significant; P < 0.001 is highly significant**

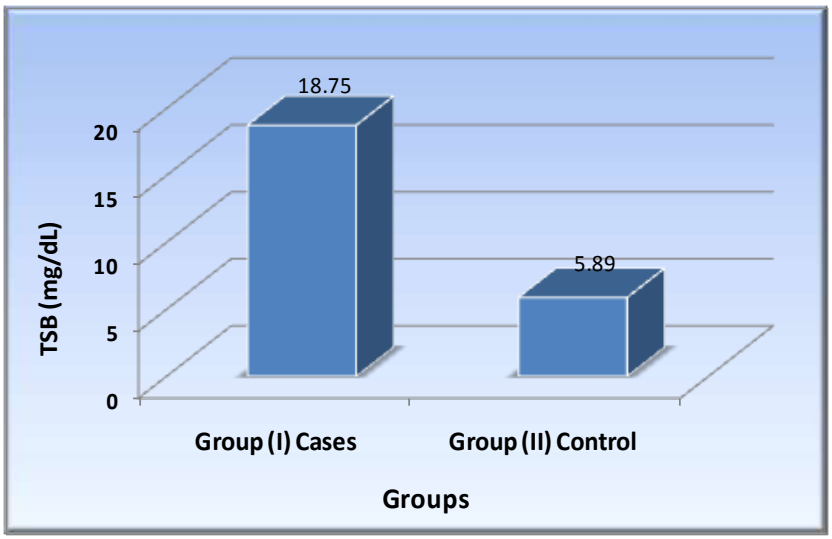

Figure (1): Comparison between cases and control groups regarding Total serum bilirubin.

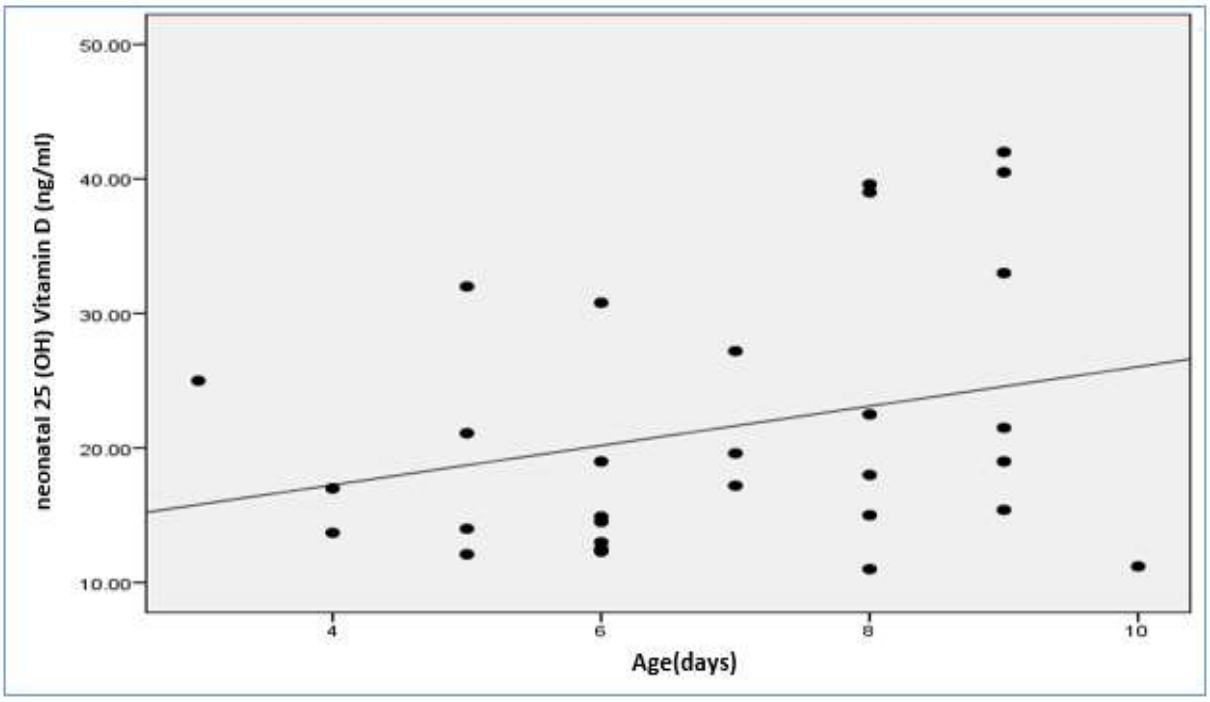

Figure (2): Correlation between neonatal 25 (OH) Vitamin D and age in cases group.

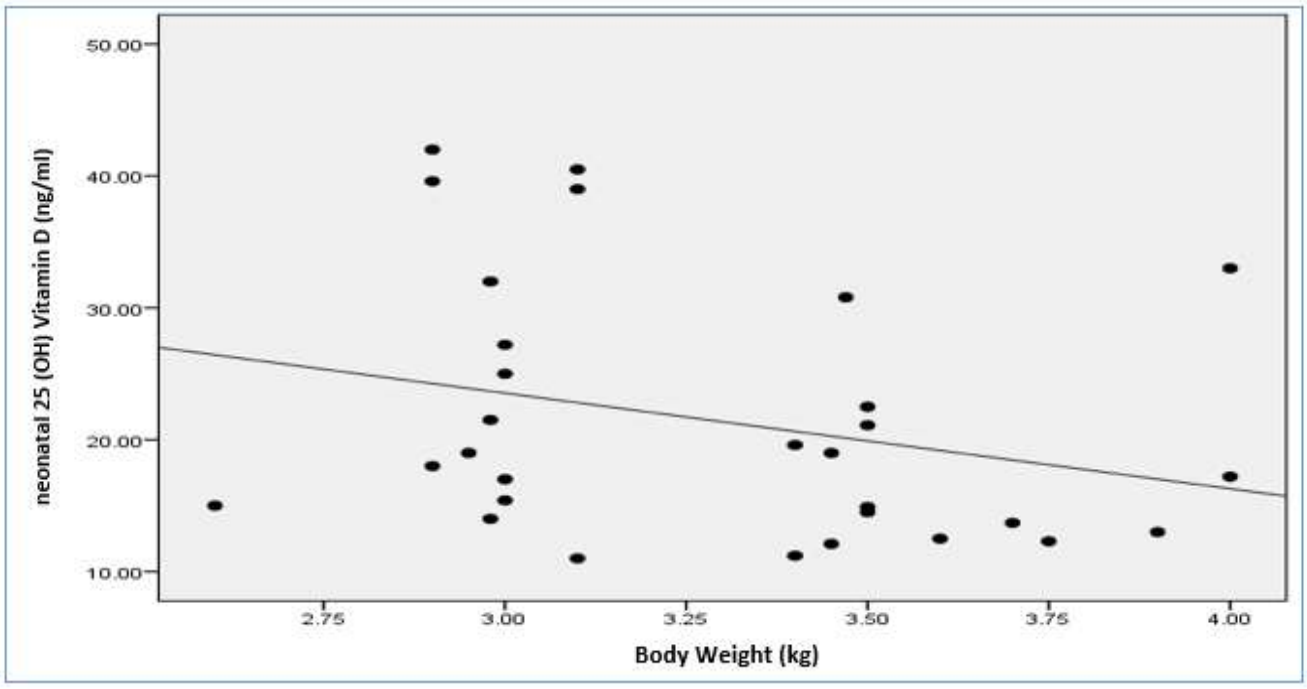

Figure (3): Correlation between neonatal serum level of 25 (OH) Vitamin D and weight in case group.

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