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Neonatology

Evaluation of Clinical features and treatment Outcome of Rickets Cases-Benghazi

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Abstract **Original Research Article**

Rickets occurs when growing bones fail to mineralize. In most cases, the diagnosis is done basing on clinical examination, laboratory testing and radiological imaging. ***Aims:*** this study aimed to investigate demographic and clinical profile of children diagnosed with Rickets and to assess the treatment outcome. ***Subjects and method:*** a comparative follow-up observational survey was conducted by collecting the data from a sample at two points of time, prior to treatment and 6 months after treatment, the sample was purposive, contact details of mothers of the children were kept to assure the 2nd meeting of data collection. ***Results:*** a sample of 153 child was studied, more than 97% of them aged between 1-2 years with mean age of 13.6 months (± 5.99), 53% of them males, 94.8 from Benghazi.62% were early weaned and 58.8 % eat family diet. At presentation the children were found to have delayed walking (17%), failure to thrive (15.7%), lethargy (13.7%), delayed teething (10.5%), rachitic rosary were present in more than 94%. Radiological signs were Osteopenia and cupping in 44.4 % and 18.3 % respectively. Calcium level was ranging between 8-11mg/dl in 99.3% of the cases, alkaline phosphatase is elevated in 43.8%, about 80% have variable degree of vitamin D deficiency, mothers of about 44% of the study sample have vitamin D deficiency, and about 21% reported past history of vitamin D deficiency. Vitamin D supplement was given either orally in 66%, or via parenteral route in 34% both of them produced very significant improvement (t-test= -11.635, P <0.01). ***Conclusion:*** The vast majority of the studied children aged one to two years, a large part of them were subjected to inappropriate early weaning, in addition to that a great portion is consuming family diet which does not contain the recommended requirement of calcium and vitamin D of a growing child, the dramatic improvement in the symptoms post treatment, and presence of maternal history of vitamin D deficiency support the possibility of nutritional insufficiency of calcium and vitamin D, which can be controlled and prevented with minimum efforts and cost.

Keywords: Rickets, Vitamin D deficiency, exclusive breast feeding.

INTRODUCTION

Rickets is a skeletal disorder caused by failure of osteoid tissue to calcify bones in children, usually because of an extreme and prolonged deficiency of vitamin D, calcium, or phosphate. These elements are important for the development of strong and healthy bones. People with Rickets have weak and soft bones, stunted growth, and, in severe cases, skeletal deformities [1].

Vitamin D is extremely important for normal skeletal development and proper cellular function because of its effect on calcium homeostasis as it promotes intestinal calcium absorption [2]. Vitamin D is metabolized in the liver to 25(OH)D and then in the kidneys to $1,25(OH)_2D$. It is also recognized that many other tissues in the body, including macrophages, brain, colon, prostate, breast, and others can locally produce $1,25(OH)_2D$ since all have the enzymatic machinery able to do that. $1,25(OH)_2D$ produced by the kidneys enters the circulation and travels to its major target tissues namely the intestine and bone, where it interacts with vitamin D receptors to enhance intestinal calcium absorption and mobilize osteoclastic activity [3]. For more details, active form of vitamin D is formed in different tissues under different situations as demonstrated in figure (1), starting by Cholecalciferol (i.e., vitamin D3) which is hydroxylated at position 25 in the liver, producing calcidiol (25-hydroxycholecalciferol), this form circulates in the plasma as the most abundant metabolite of vitamin D, and is considered to be a good indicator of overall vitamin D status [1]. The second hydroxylation step takes place in the kidney at position 1, where it is converted to the active metabolite calcitriol (1, 25

dihydroxy cholecalciferol). This cholecalciferol circulates in the bloodstream in minute amounts, technically it is not considered as a vitamin but a hormone [1]. The later active form Calcitriol acts at 3 known sites, as shown in figure 1,to tightly regulate calcium metabolism by the following actions:

- Promotes absorption of calcium and phosphorus from the intestine.
- Increase reabsorption of phosphate in the kidney.
- Acts on bone to release calcium and phosphate.

Furthermore, Calcitriol may also directly facilitate calcification. These actions result in an increase in the concentrations of calcium and phosphorus in extracellular fluid [1]. During infancy and early life, there are three physiological sources of vitamin D which are: (i) maternal reserves built during fetal life, (ii) maternal milk, and (iii) endogenous synthesis from sun exposure. As a matter of fact, vitamin D content of the diet is usually very low almost negligible. The high frequency of vitamin D deficiency among infants is due to the fact that these three potential sources are easily defective [4].

As mentioned previously, cutaneous synthesis after exposure to ultraviolet B rays is the main mechanism of endogenous vitamin D production. If sun exposure is limited because of northern latitude, darker skin, sun block or lifestyle choice of being indoor or other factor, vitamin D levels can be maintained through the intake of supplements and foods that contain vitamin D (either naturally or fortified), to avoid the occurrence of severe vitamin D deficiency which impairs bone mineralization in adult causing osteomalacia, and of growth plates manifesting as Rickets [2].

In a clinical study conducted at paediatricians in the West Midlands in England showed that the overall incidence of Rickets was 7.5 cases per 100,000 children, with significant differences between ethnic groups (South-East Asia: 3.8 x 100,000; Blacks African and Caribbean: 9.5 x 100,000; White 0.4 x 100,000) [5]. Children with vitamin D deficiency may be irritable and reluctant to weight bear, and manifest impaired growth [6], vitamin D deficiency in children from the age of 6 months commonly presented with skeletal (bony) deformity i.e. Rickets typically bowing of the legs (genu varum), nevertheless knock knees (genu valgum) can also occur. Anterior bowing of the femur and internal rotation at the ankle are frequently found, along with swelling at the wrist, prominent costochondral joints, and soft, deformable skull (craniotabes), moreover, severe vitamin D deficiency may cause extra skeletal manifestations such as hypocalcaemic seizures or tetany, particularly in the neonatal period and again during the phase of rapid growth in adolescence [7].

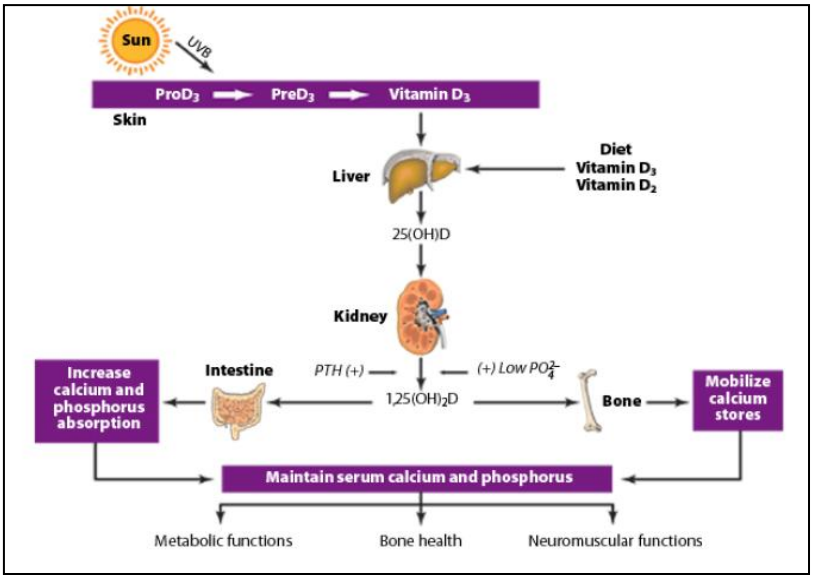

Fig-1: Stages of Vitamin D metabolism (Al Rekhawi, 2017 P. 152)

REVIEW OF LITERATURE

Rickets is metabolic disease of growing bones in infants and children, characterized by impaired mineralization of the osteoid matrix during growth, affecting epiphyseal growth plate and compromising both cortical and trabecular bone, whereas osteomalacia, refers to a deficient mineralization of the osteoid matrix in modelling and remodelling sites [7].

Rickets in the history

Historically Rickets was first recognized in the scientific literature going back to the year 1645 and David Whistler is known as the first physician who published an imposing scientific work on Rickets, it was known as "The English disease", actually it was more than a disease because of its notable impact on social and industrial life [8]. Five years later Dr. Glisson had a scientific participation to the literature of

Rickets. Francis Glisson (1597–1677), born and raised in Rampisham, Dorset, published a book on Rickets, which was particularly appreciated by both the scientific and public communities. His publication was titled "De Rachitide Sive Morbo Puerili, qui Vulgo The Ricketsdicitur, Tractatus" is dated 1650, in this book vitamin D deficiency was first described in association with skeletal deformities by Glisson and colleagues during the mid 17th century in London, England. With the discovery of the therapeutic benefit of cod liver oil, sunshine, vitamin D supplements and fortified dairy products [9]. In the past, Rickets occurred as an epidemic in temperate zone of the world, it was the first childhood diseases caused by environmental pollution, this because air pollutants resulted from factories blocked the ultraviolet rays which are the initiator of active vitamin D form synthesis [10]. The existence of Rickets at that time may be further supported by an autopsy performed on an 18-month-old child in June 1666 by John Locke, he mentioned in his report that the child was harbouring 'rachitic bony changes' [8].

Predisposing factors to Rickets

It is generally agreed that the most important etiological factors of Rickets are the lack of exposure to the sun and belonging to certain ethnic groups (Asian, black.), exclusively breastfed infants who do not receive vitamin D supplementation are most affected, because the concentration of vitamin D in human milk is less than 100 IU/day, but may be even lower if the mother does not have sufficient serum level of it (> 50nmol /l) [11]. Therefore exposure to the sun in early childhood is required to achieve adequate levels of vitamin D in an average duration of 30 minutes per week if the child is naked, clad only in a diaper, and 2 hours per week if the child is fully dressed without a head cover [11].

However, in some geographical areas such as latitude > 40 degrees North or South the globe, "long winters", air polluted geographical areas, and "perennial clouding" geographical areas, there is periodic lack of photosynthesis, [8] therefore vitamin D supplement is strongly recommended as an essential micronutrient, because relying on dietary intake is not enough as only a relatively small number of foods contain substantial amounts of vitamin D, and it is well known that dietary intake covers only 10% of the requirements of vitamin D, [11] the most significant dietary sources being oily fish and cod liver oil. In the UK it is reported that the farmed fish which is commonly consumed in the UK may have less vitamin D content than wild fish. Egg yolk, liver, and wild mushrooms contain small quantities of vitamin D, moreover the amount in most vegetable sources is negligible [12].

Vitamin D deficiency might be complication of some medication, as it is confirmed that all drugs used in seizure control predispose to vitamin D deficiency. The anticonvulsant drugs lead to activation of cytochrome P450 enzymes, this enzyme also metabolises vitamin D. therefore has been recommended that children on anticonvulsants for more than 3 months should be provided supplements of vitamin D in a dosage of three times of that used for normal children[13].

Infant feeding and Rickets

Infants who are breastfed but do not receiving vitamin D supplement or adequate sunlight exposure are at increased risk of developing vitamin D deficiency or Rickets, according to some sources, human milk contains as low vitamin D concentration as 25 IU/L or even less Thus, the recommended adequate intake of vitamin D cannot be met depending on human milk as the only source for the breastfed infant [14]. Although there is evidence that limited sunlight exposure prevents Rickets in many breastfed infants [15].

Regarding formula fed infants, in most developing regions of the world infant formulas are obligatorily supplemented with vitamin D, in the United States, for example, all the sold formula must have a minimum vitamin D concentration of 40 IU/ 100 kcal (258 IU/L of a 20-kcal/oz formula) and a maximum vitamin D concentration of 100 IU/100 kcal (666 IU/L of a 20-kcal/oz formula) [16].

Clinical manifestations of Rickets

Child with Rickets can be presented with pain or tenderness in the bones of the arms, legs, pelvis, or spine, stunted growth and short stature [1]. Untreated long standing Rickets usually results in skeletal deformations. The most typical deformities are seen in the lower limbs after weight bearing with tibial and femoral bowing. However in severe Rickets they may also occur due to muscle pull, in the forearms and the lower limbs before weight bearing. Chest deformity such as pectus carinatum, thoracic asymmetry, and widening of the thoracic base can also occur due to muscle traction on the softened rib cage is also responsible for chest deformation in severe cases [4].

Skull examination will frequently show signs of reduced or failure of mineralization such as unusual softening of the occipital area at thumb pressure in infants older than 3 months (so called "rachitic craniotabes"), enlarged sutures and fontanels, delayed closing of fontanels, and occipital or parietal flattening in the recumbent infant. On the other hand, spine and pelvis deformities are very unusual nowadays, although they were described in severe longstanding Rickets in the past and were responsible for thoracic kyphosis and later dystocia [7]. Additionally, dental development is frequently impaired in vitamin D deficiency with delayed eruption, enamel hypoplasia, and early numerous caries. This mostly concerns deciduous teeth but permanent teeth may also be affected in late or long-standing Rickets [4].

Classification of Rickets

Rickets can be classified according to aetiology in regard to the underlying deficiency of calcium or phosphorus into two main types Calcipenic Rickets and Phosphopenic Rickets as summarized in figure 2 [17].

I. Calcipenic Rickets usually results from inadequate vitamin D, defective utilization of vitamin D or inadequate calcium this type includes [17]:

- Nutritional vitamin D deficiency.
- Calcium deficiency.
- Vitamin D deficiency secondary to:
- Malabsorption.
- Antiepileptic drug therapy.
- Chronic renal failure.
- Liver failure.
- Distal renal tubular acidosis.
- 25 hydroxylase deficiency in liver (rare).

II. Phosphopenic Rickets: known as "vitamin D resistant Rickets" it is not common [1], and occurs in the following situations:

- Low phosphorous intake.
- Prematurity/ Total parenteral nutrition.
- Renal phosphate wasting.
- Proximal renal tubular acidosis.
- Fibrous dysplasia.
- Oncogenic hypophosphataemic Rickets.
- Hereditary hypophosphataemic Rickets.
- X -linked dominant (XLH).
- Autosomal dominant.
- Autosomal recessive.
- Hereditary hypophosphataemia with hypercalciuria (HHRH) [17].

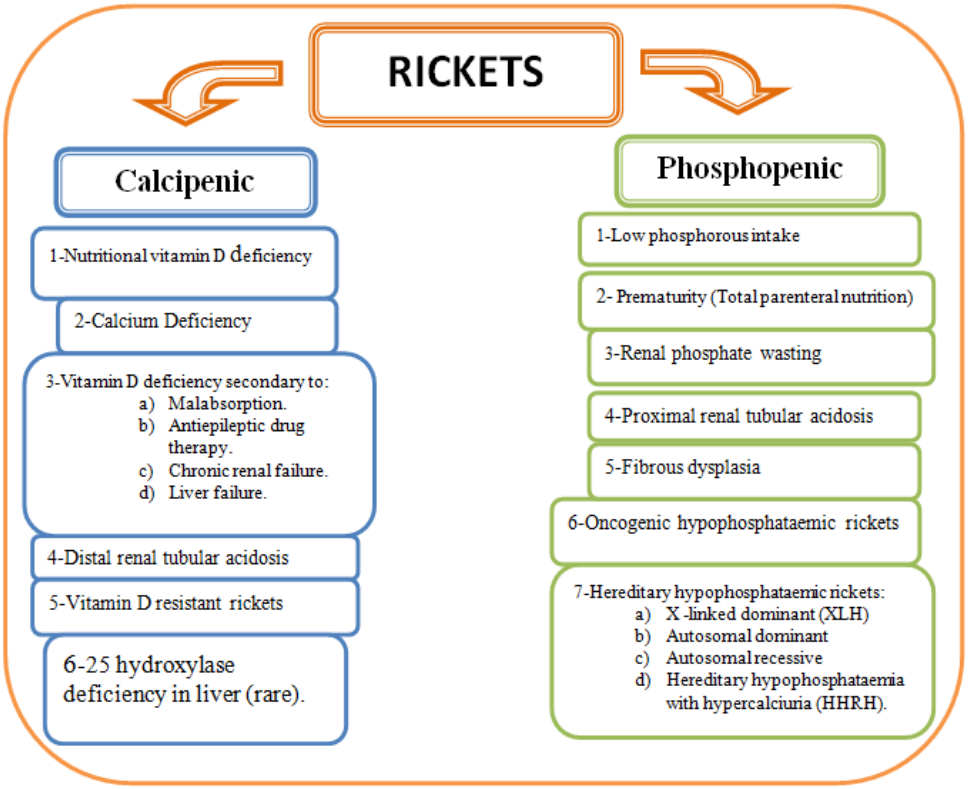

Fig-2: Diagrammatic summary for classification of Rickets.

Radiological features of Rickets

When skeletal radiological signs of Rickets are detected, this reflects the presence of severe mineralization defect, due to extreme vitamin D deficiency, it is reported that a state of deficiency occurs months before Rickets is obvious on radiological and physical examination [16]. Nevertheless radiological signs are very useful for early diagnosis of Rickets, as minor radiological abnormalities occur before any clinical signs can be found at physical examination. In advanced Rickets any part of the skeleton may show radiological abnormalities. However in clinical practice only a limited number of x-ray pictures are conventionally requested for the diagnosis of Rickets, which are films of the wrist in the supine position and a frontal x-ray of the knees are the most useful as they show the most sensitive sites to early rachitic changes. [4] Alterations of the epiphyseal regions of the long bones are most characteristic, in form of widening of the radiolucent space between the bone shafts end (the metaphyseal lines) and the epiphyses which reflects the accumulation of uncalcified cartilage. The metaphyseal lines, normally seen as well defined dense lines, it is distorted and take various aspects, so that it might appear irregular, stippled, fuzzy, frayed, or fringed. They are frequently

hollowed with loss of their flat or convex configuration (so called "cupping") and spread laterally forming "cortical spurs [18]. On thorax the same alterations are observed at the costochondral junctions where "cupping" develops rapidly producing the so-called "champagne cork aspect" which corresponds to the palpable costal rosary [4].

The other skeletal alterations appear more slowly and resulted from insufficient mineralization for example the centres of ossification appear pale and irregular and their appearance may be delayed. The shafts of the long bones usually show diminished density with thinning of the cortices. In severe Rickets in the young infant, this may lead to a shadowy aspect of the shafts and an almost complete disappearance of the cortices. Conversely in older children with long-standing Rickets an apparently paradoxical thickening of the cortex may be observed. This results from the superimposition of layers of partially mineralized osteoid and is mainly seen on the long bones of the lower limbs. It is usually associated with bowing predominantly at the concave aspect of the bone shaft. At the same time, decreased density may also be observed in other parts of the skeleton, particularly ribs, scapula, pelvis, and skull [4].

Only in severe long-standing Rickets small bones and vertebrae are also involved. Besides these signs reflecting defective mineralization, bone x-rays may show deformities, bowing of the tibia and femurs being the most common, but also shipped epiphyses and unrecognized fractures followed by callus formation, particularly in the ribs and fibula [4]. A number of observational studies have shown that even if vitamin D insufficiency is not enough to cause symptomatic bone and muscle disease, it is found to be associated with an increased risk of mortality [19], and increased risk of several common diseases including cardiovascular disease, type 2 diabetes, bowel cancer, breast cancer [15,16], multiple sclerosis [17], and type 1 diabetes [18]. An expert consensus is developing that optimal vitamin D status, reflected by optimal calcium handling and best health, is when serum concentrations of 25-OHD are 75 nmol/l (30 µg/l) or more, Serum 25-OHD has a circulating half life of two to three weeks, but levels are regularly replenished from fat stores, furthermore, it is suggested that Vitamin D deficiency is now known to be linked to infection, inflammation, and carcinogenesis [8].

Health measures to control Rickets

Treatment modality for vitamin D deficiency Rickets is either oral or parenteral, therapeutic dose is indicated if there is clinical evidence of rickets, deformities characteristic of rickets or lab result of vitamin D level of 25 nmol/l or less. The dose of treatment differs according to age of the child, some guidelines suggest giving vitamin D for a duration of one month of a dose of 1000 units daily for infant aged less than 30 days, 3000 units daily for 1-6 months of age and 6000 units for those who are over 6 months [21]. Calcium supplementation is not conventionally considered, it is given if hypocalcaemia exists, otherwise there is little evidence to support the need for it, but calcium intake from food should be assessed and improved if needed [22].

In Canada despite all the measures taken by Health Canada and the Canadian Paediatric Society to reduce vitamin D deficiency, a study published in 2007 in which A total of 2325 Canadian child were surveyed monthly from July 1, 2002, to June 30, 2004 to determine the incidence, geographic distribution and clinical profiles of vitamin D deficiency Rickets cases concluded that, there has been a failure to prevent vitamin D deficiency in Canada, resulting in clinically prominent skeletal and systemic morbidity and an overall annual incidence rate of vitamin D deficiency Rickets of 2.9 per 100 000 children. This condition was most frequently observed among darker-skinned, breast-fed infants and children, with the highest incidence among children from north (Yukon Territory, Northwest Territories and Nunavut). Maternal characteristics in term of skin colour, lack of sun exposure and inadequate vitamin D intake or supplementation found to be the contributing factors [2].

In the UK vitamin D deficiency is considered to be common health problem, therefore it is recommended there to have daily intake of about 400 IU of vitamin D (10 µg) for adults, 280 IU (7 µg) for children aged between 6 months and 3 years, and 340 IU (8.5 µg) per day for infants under 6 months. However, these recommendations only provide sufficient vitamin D to prevent osteomalacia and Rickets, and such an intake alone, in the absence of skin synthesis, will not provide optimal status [2].

AIMS OF THE STUDY

This study collected data of Rickets cases based on symptoms and clinical signs of Rickets and lab finding mainly to address the following aims:

- To investigate the socio-demographic and clinical characteristics and presentation of children with Rickets.
- To assess the effectiveness of therapy on the symptoms, signs and blood vitamin D level.
- To evaluate the risk factors for rickets.

SUBJECTS AND METHODS

Study design a comparative cross sectional study design was adopted to achieve the aims of this study, by collecting the data at two points of time, prior to treatment and after 6 months of treatment. At begging of the study the cases were clinically evaluated and sent for libratory assessment of vitamin D serum level, and then the treatment was prescribed in two

forms, either oral or paraentral vitamin D supplement according to lab result, severity of deficiency and financial capability of the family to buy vitamin D injection form. Then follow up after 6 months of treatment and re-evaluation of the patients using clinical examination and lab assay.

The cases were classified according to vitamin D level as the following
Mild vitamin D deficiency ---------- 20 -30 nmol/l
Moderate vitamin D deficiency ---------- 10 -20 nmol/l
Sever vitamin D deficiency ---------- <10 nmol/l

Treatment regimen

1. Age of less than 1 year with moderate to severe deficiency. Treatment for 6 weeks oral dose of 2000 IU/day, or intramuscular 50000 IU/week, then assessment of blood level of vitamin D, if it reaches 30 nmol/l the patient kept on 400-800 IU/day.
2. Age of 1-18 years oral dose of 2000-3000 IU/day, or intramuscular 50000 IU/week, then assessment of blood level of vitamin D, if it reaches 30 nmol/l the patient kept on 600-1000 IU/day.
3. In case of mild deficiency the patient is given 2000 IU/day for 4 weeks to raise level of vitamin D to 30nmol/l then keep the child on maintenance dose of 400-800 IU/day.

Sampling and settings

The sample of this study was accessed at nongovernmental organization called "Doctors without borders", which provides free paediatric health care services, the participants were selected according to specified inclusion criteria, so the sample is purposive non-random sample, time of data collection extended from October 2016 to December 2017.

Inclusion criteria

- Age limit from 6 months to 3 years.
- Presence of clinical signs or lab result suggesting Vitamin D deficiency.

Data collection tool

The data collection sheet is formed of five parts;

1. The 1st part asks about socio-demographic characteristics of the sample such as age, sex, and address, and birth weight, mode of delivery, gestational age, and maternal history of vitamin D deficiency and family history of atopy.
2. The 2nd part focuses on feeding data of the child such as mode of feeding, age of weaning food allergy, it also asks about drug history, vaccination status, past medical history and hospital admission.
3. The 3rd segment of the questionnaire enquires about developmental data such as age of teething and walking, history of failure to thrive.
4. The 4th part asks about the clinical presentation and finding of the cases such as presence of rachitic rosary, craniotabes, wide anterior fontanel, posing fontanel.
5. The last part includes records of lab investigation of the cases such as levels of vitamin D, calcium and phosphorus, it also records treatment modality if oral or parenteral supplementation of vitamin D, and calcium supplement, and follow up data. (the appendix).

Ethical considerations

The parents of participants were fully informed about the study and its consequences, verbal agreement was guaranteed from the parents of all participants after full explanation of the study scheme, phone number of the parents were recorded to contact them, oral vitamin D supplement was provided to the participants, whereas paraentral supplement when needed was requested to be afforded by the parents.

Statistical analysis

The collected data were entered and processes to Excel for Windows, statistical analysis was done and descriptive results were expressed as percentages, means, standard deviations and range for continuous variables, categorical variables are expressed as count and percentage with plotting of summarizing charts as appropriate. Some inferential statistics were used such as t. test and chi square test ($\chi 2$ test) to find the significance of difference between different groups and categories with considering P value of less than 5% as a cut off level to judge statistical significance.

RESULTS

In this study data of 153 child was collected, 81 of them (53 %) are males compared to 72 (47%) females (table 1, fig 3). Age distribution of the sample is ranging from one month as minimum and 34 months as maximum, with mean age of 13.6 months (± 5.99), age was divided into 4 categories, more than half of the sample (53%) are belonging to the age group of 12 months or less, followed by 44.4 % of the sample belong to age group of 13-24 months, and only 2.6 % of the sample their age is from 25 and 36 months (table 1, fig 4). The vast majority (94.8%) of the sample are from Benghazi, whereas only 8 patients (5.2%) are from outside the city of Benghazi (table 1, figure 5).

Table-1: Demographic characteristics of the sample

Characteristic		Count	Percentage (%)
Sex	Male	81	**53**
	Female	72	**47**
Age* distribution	≤12	81	**53**
	13-24	68	**44.4**
	25 – 36	4	**2.6**
Residence	Benghazi	145	**94.8**
	Outside Benghazi	8	**5.2**

*Mean age =13.6 Months. Std. Deviation =5.99 Months. Median=one year .Minimum age=One month. Maximum =34 months.

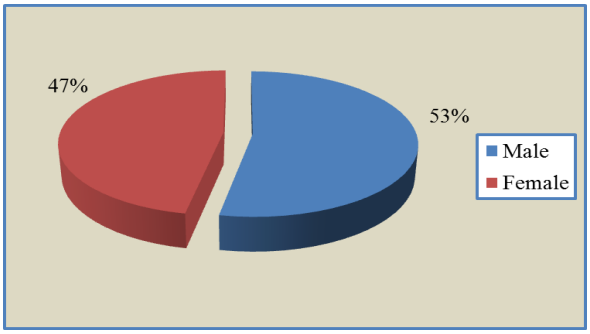

Fig-3: Sex distribution of the sample

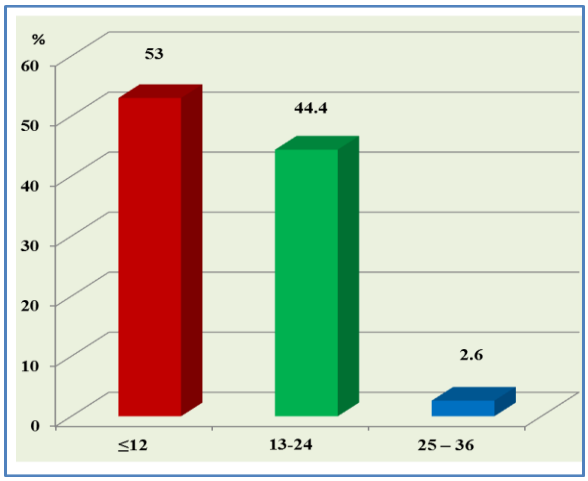

Fig-4: Age distribution of the sample

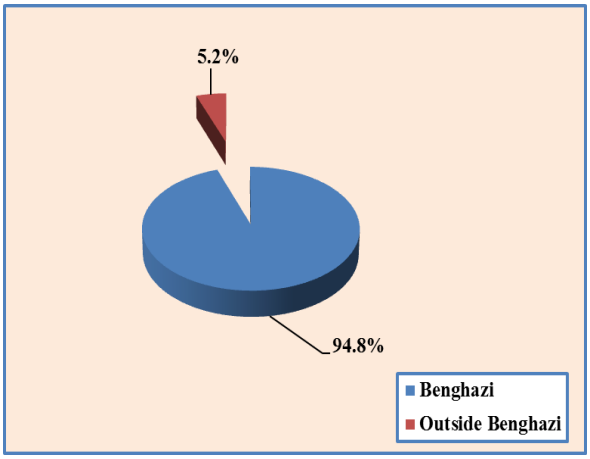

Fig-5: Distribution of the sample according to address

In regard to growth mile stones and vitamin D deficiency (table 2), delayed walking (figure 6) was reported by parents of 26 child (17%), whereas 24 child (15.7 %) have had H/O failure to thrive (figure 7), while the symptoms of vit. D deficiency, as shown in figure 8, 118 child (77%) were asymptomatic at time of data collection, lethargy occurred in 21 child (13.7% of the sample), delayed teething occurred at 16 child (10.5%), skull bossing in 3.9%, irritability in 3.2 %, and very few parents reported bowing of legs in 1.3 % (2 child) limping (0.7%) and constipation (0.7%).

Table-2: clinical presentation of the sample

Clinical feature	Count	Percentage (%)
Failure to thrive	24	**15.7**
Lethargy	21	**13.7**
Delayed walking	26	**17**
Delay teething	16	**10.5**
Bossing skull	**6**	**3.9**
Irritable	5	**3.2**
Bowing lower limps	2	**1.3**
Limping	1	**0.7**
Constipation	1	**0.7**

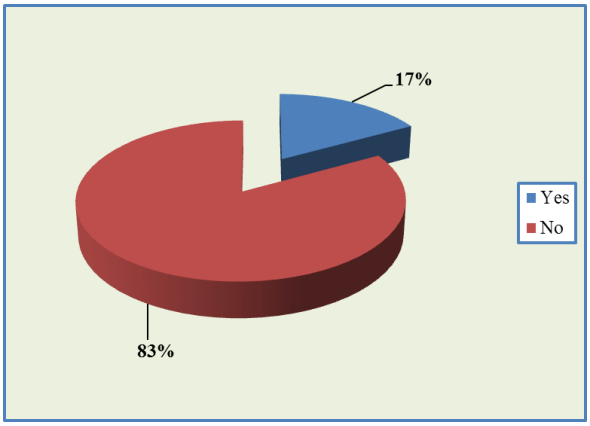

Fig-6: History of delay walking among the sample

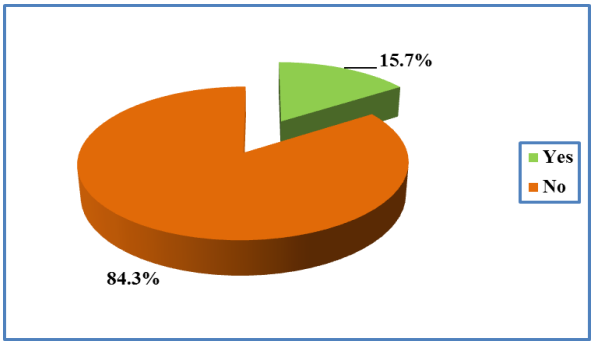

Fig-7: History of failure to thrive among the sample

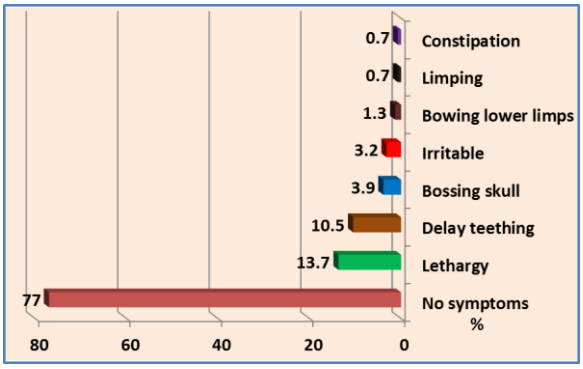

Fig-8: Distribution of patients according to symptoms

By looking at the early life data of the study sample (table 3), starting by the birth weight, most of the children (81.7 %) were born with birth weight ranging from 2.5 to 4 kg, with mean birth weight of 3.22 kg (± 0.67) for the entire sample, and the minimum is 1.3 kg and maximum 5 kg, those whose birth weight less than 2.5 kg represent 11.8% , while children with birth weight greater than 4 forms only 6.5 % of the total sample (figure. 9). Then moving to the gestational age, the vast majority of the studied participants i.e. 92.2% are full term at delivery, while preterm and post term represent 5.2% and 2.6% respectively (figure. 10).

Table-3: Early life data of the study sample

Characteristic		Count	Percentage
Birth weight*	<2.5	18	**11.8**
	2.5 – 4	125	**81.7**
	>4	10	**6.5**
Gestational age	Pre-term	8	**5.2**
	Term	141	**92.2**
	Post term	4	**2.6**

*Mean birth weight =3.22kg. Std. Deviation =0.67kg. Median=3.2kg.Minimum =1.3kg. Maximum =5kg.

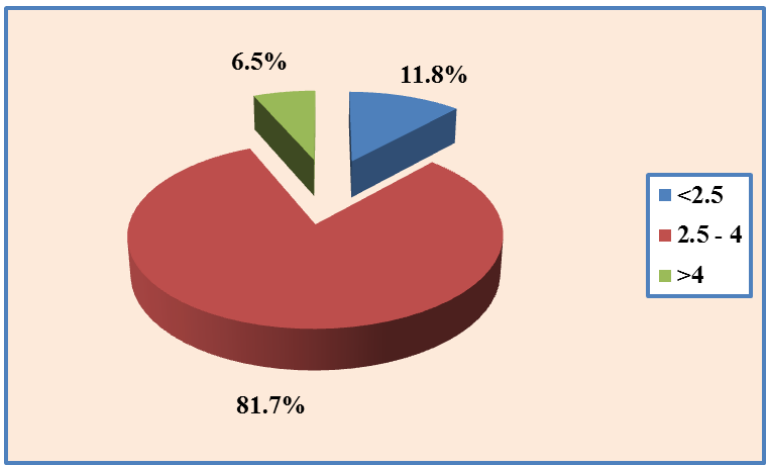

Fig-9: Distribution of patients according to birth weight

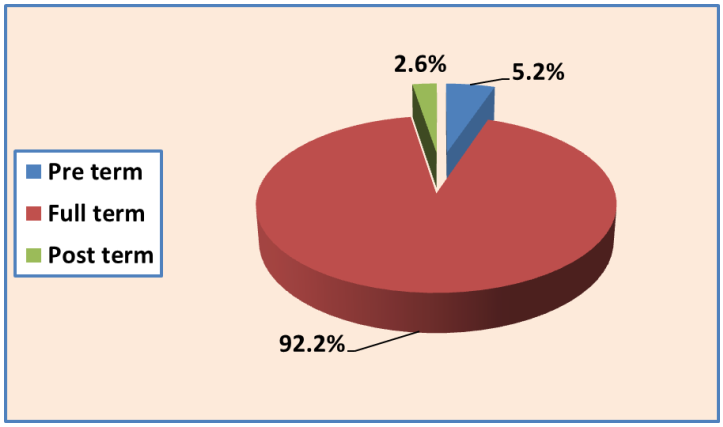

Fig-10: Distribution of patients according to gestational age

Considering the general condition, 119 child (77.8%) are generally well and have no H/O chronic illness. Other children have few health problem such as wheeze chest occurred in 20 participants (13%), FTT reported in 5 participants (3.3%), anaemia in 4 children (2.6), cerebral palsy in 2 cases (1.3), and the same (2 cases, 1.3%) for hypothyroidism, one case suffered from constipation (table 4, figure 11).

Table-4: Distribution of patients according to H/O chronic diseases

Chronic disease in the patients	Count	percentage
No chronic disease	**119**	**77.8**
Wheeze chest	20	**13**
Failure to thrive	**5**	**3.3**
Anaemia	4	**2.6**
Cerebral palsy	**2**	**1.3**
Hypothyroidism	**2**	**1.3**
Constipation	1	**0.7**
Total	153	**100**

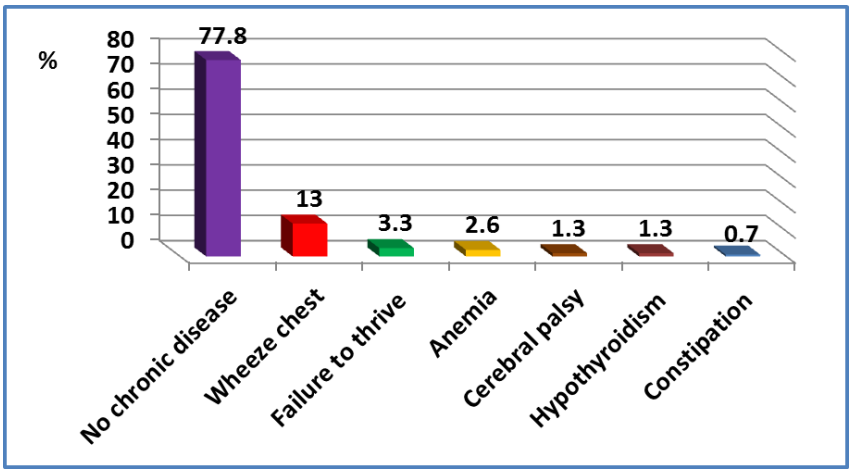

Fig-11: History of chronic disease in the patients

The data about early infant feeding history (table 5) of the study sample showed that; mixed feeding was reported by mothers of 77 child who represent 50.3 % of the whole sample, followed exclusive breastfeeding in 70 child (45.8%), then bottle feeding in 6 cases (3.9%), (figure12).

Table-5: Feeding profile of the study sample

Feeding data		Count	%
Mode of feeding*	Bottle feeding	6	**3.9**
	Exclusive breastfeeding	70	**45.8**
	Mixed feeding	77	**50.3**
Time of weaning**	Normal time of weaning	30	**19.7**
	Delay weaning	28	**18.3**
	Early weaning	95	**62**
Type of food	Family diet	90	**58.8**
	Baby diet	46	**30.1**
	Not recorded	17	**11.1**

*Mean=6.3months, Std. Deviation=4.8months. Median=4months, Minimum = 0, Maximum =18 months.
**Mean =6.1 months. Std. Deviation =1.9 months. Median =6months. Minimum =0. Maximum =12 months.

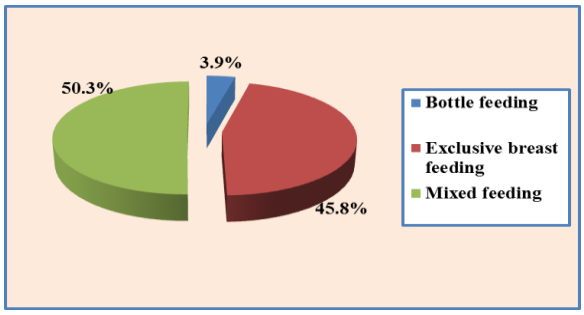

Fig-12: Distribution of patients according to type of feeding

Small part of the sample (19.7% ,30 child) have history of ideal time of weaning whereas about two thirds of the study sample (62% m 95 child) have history of early weaning, and 18.3% (28 child) was reported as case of delayed weaning (table 5, figure13).

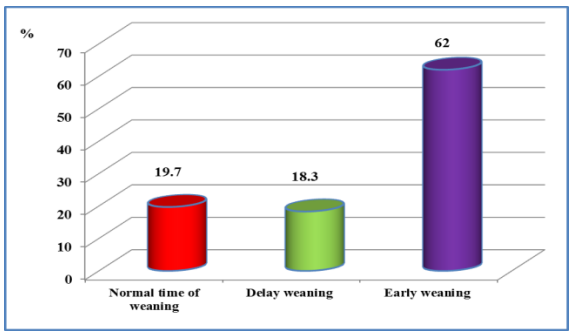

Fig-13: Distribution of patients according to time of weaning

Family diet is eaten by 90 child (58.8%), baby diet is given to 46 child (30.1%), 17 child have no data about their food (table 5, figure 14).

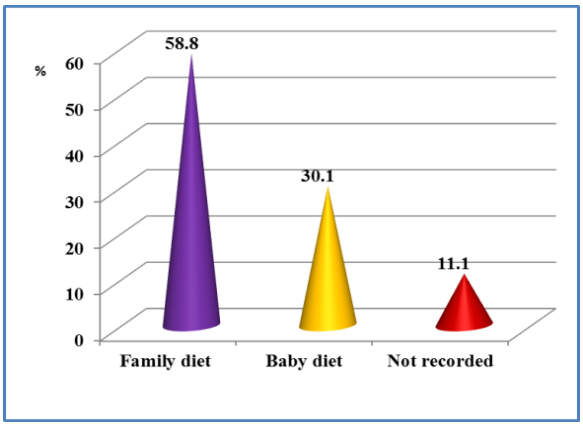

Fig-14: Distribution of patients according to type of food

Some mothers of the study sample have vitamin .D deficiency and they represent 43.8%, and the remaining 56.2 % gave negative history (table 6, figure 15), in addition 20.9% of the mothers have past history of vitamin D deficiency, anaemia is a past health problem of 8.5% of the mothers, diabetes reported by 4% of the mothers, 2% and 1.2 of the mothers have coronary heart diseases and hypothyroidism respectively, on the other hand 63.4% of the mothers are healthy (table 6, figure 16).

Table-6: Maternal current or past illness

Maternal health status		Count	%
Mother having vitamin D deficiency	Yes	67	43.8
	No	86	56.2
Maternal past H/O chronic illness	Healthy	97	63.4
	Vit. D deficiency	32	20.9
	Anaemia	13	8.5
	Diabetes	6	4
	Coronary heart disease	3	2
	Hypothyroidism	2	1.2

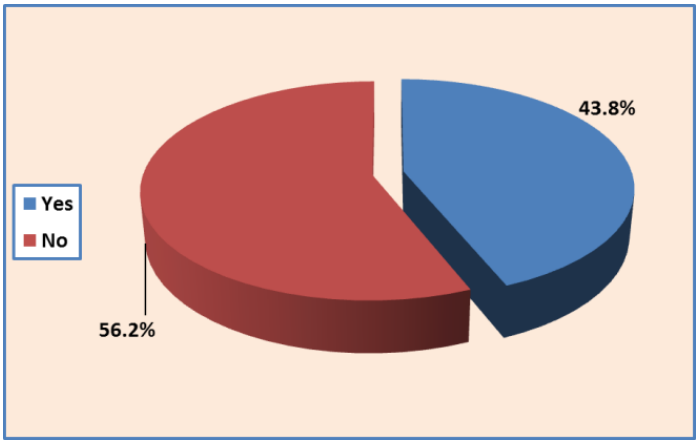

Fig-15: Mothers have vitamin D deficiency

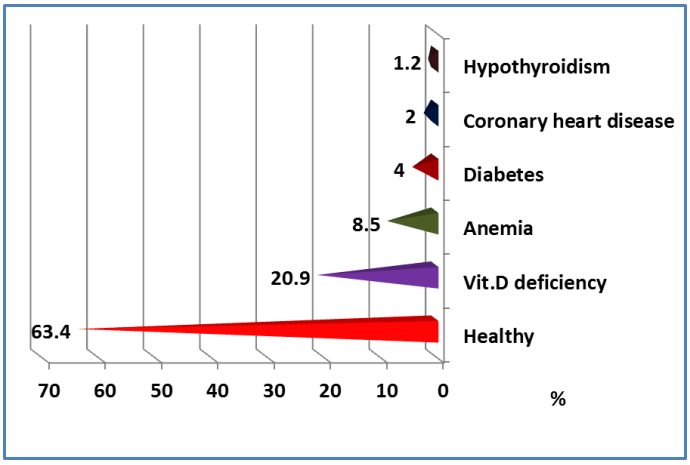

Fig-16: Mothers past history of health problem

By clinical evaluation rachitic rosary is detected in 94.1% of the cases, wide wrist and ankle joint in 64.1%, skull posing in 60.1%, and wide anterior fontanel occurred in 45.8%, bowing lower limbs in 16.3%, Failure to thrive seen in 14.4%, hypotonia in 9.2% and finally craniotabes in 8.5% (table 7, fig 17). Radiological signs showed osteopenia in 44.4%, cupping in 18.3 % whereas 37.3 showed normal x-ray (table 7, fig 18).

Table-7: Clinical and radiological Sign of Rickets

Sign of Rickets		No.	%
Clinical signs	Rachitic rosary	144	94.1
	Craniotabes	13	8.5
	Failure to thrive	22	14.4
	Wide anterior fontanel's	70	45.8
	Posing skull	92	60.1
	Wide wrist and ankle joint	98	64.1
	Bowing lower limbs	25	16.3
	Hypotonia	14	9.2
Radiological signs	Normal	57	37.3
	Osteopenia	68	44.4
	Cupping	28	18.3

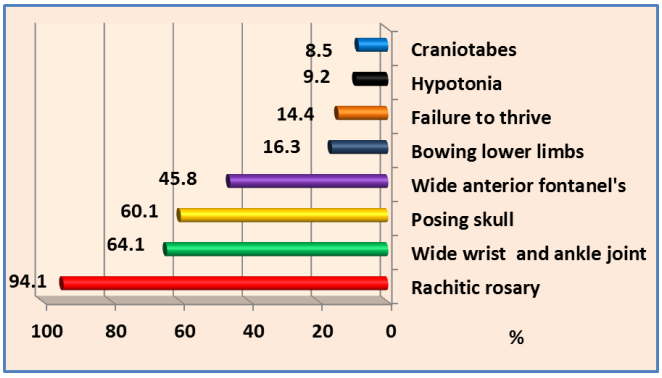

Fig-17: Clinical Signs of Rickets

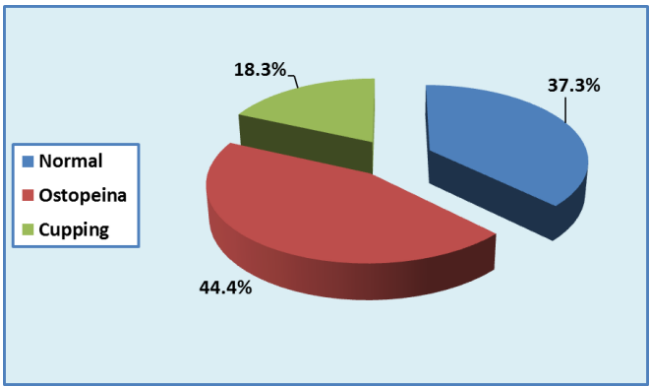

Fig-18: Radiological signs of Rickets

Among the study sample 16.3% (25 cases) have sever vit. D deficiency prior to the intervention (vit.D therapy), which is reduced to 0.7 (one case) post treatment, and 35.9% (55 cases) have moderate deficiency similarly is improved after therapy to be 3.9 (6 cases) , mild deficiency was found in 27.5% of the sample which improved to 10.5 % (16 cases), 20.3 % of the sample (31 child) have normal serum level of vit.D prior to supplementation, which improved to be 33.3% (51 child) post intervention (figure 19), the difference in the counts pre and post vit.D supplementation was tested by chi square and was found to be highly significant $X^2 = 57.521$. df= 3 ; p<0.001 (table 8).

Table-8: Vitamin D level before and after treatment

Level of vit. D/ng/ml	Vit. D before treatment		Vit. D after treatment	
	No.	%	No.	%
Sever(<10)	25	16.3	1	**0.7**
Moderate(10-20)	**55**	35.9	6	**3.9**
Mild (21-30)	42	27.5	16	**10.5**
>30 Normal	31	20.3	51	**33.3**
Not recorded*	0	0	79	**51.6**
Total	153	100	153	**100**

*Excluded from calculation of x^2

Vit. D before treatment: Mean =21.8/ng/ml. Std. Deviation =12.3ng/ml. Median=20/ng/ml. Minimum =0.60ng/ml. Maximum =57ng/ml.

Vit. D after treatment: Mean =45.1ng/ml. Std. Deviation =21.5ng/ml. Median=40ng/ml. Minimum =3.9ngml. Maximum =100ng/ml.

T-test= -11.635 with 304 degrees of freedom; P = 0.0001(Highly significant).

$X^2 = 57.521$. df= 3 ; p=0.0001(Significant).

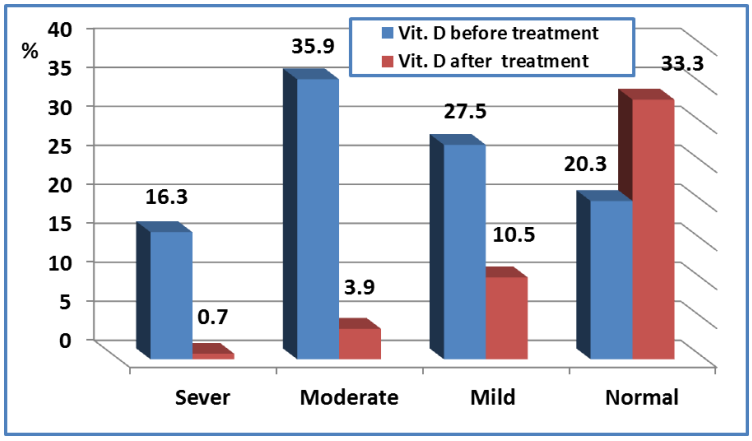

Fig-19: comparison of vitamin D level before and after treatment

The mean serum level of vitamin D before the intervention is significantly lower than that after supplementation (t-test= -11.635 with 304 degrees of freedom; P <0.001) 99.3 % of the sample. Level of serum biomarkers of Rickets before starting treatment are as the following, 99.3% of the cases have calcium level between 8-11 mg/dl, with mean calcium level of 10.2/mg/dl (std. deviation =6.7/mg/dl), 74.5% of the sample with phosphate level of 3.5-6 mg/dl and mean =5.2 mg/dl (std. deviation =1.6 mg/dl), alkaline phosphatise level is normal in 39.9% of the cases, and high in 43.8%, missed in 16.3%, with mean level of 386.5 U/L .std. deviation =399.5 U/L.(table 9).

Table-9: Serum investigation before starting treatment

serum level at starting treatment		No.	%
Calcium * mg/dl	8 - 11	152	99.3
	>11	1	0.7
PO_4 ** mg/dl	<3.5	14	9.2
	3.5 - 6	114	74.5
	>6	25	16.3
Alkaline phosphatase* U/L.**	<250(Normal)	61	39.9
	≥250(High)	67	43.8
	Not recorded	25	16.3

*Mean =10.2/mg/dl Std. Deviation =6.7/mg/dl. Median=9.8.Minimum =8/mg/dl Maximum =12/mg/dl.

Vitamin D supplement was given orally in 66% of the cases the remaining 34% received intramuscular vitamin D supplement (figure 20, table 10), after follow up 64.7 % of the cases showed improvement, while 35.3 did not show detectable improvement (figure 21,table 10).

Table-10: treatment and response to treatment

Treatment and response to treatment		No.	%
Rout of vitamin D therapy	Oral	101	66
	Intramuscular	52	34
Response for treatment	Improved	99	64.7
	Not improved	54	35.3

** Mean =5.2 mg/dl Std. Deviation =1.6 mg/dl. Median=5.5 mg/dl. Minimum =3.2 mg/dl. Maximum =10 mg/dl.
*** Mean =386.5/ /IU.Std.Deviation =399.5/U/I Median=255.Minimum =100/U/I. Maximum =2517/I U.

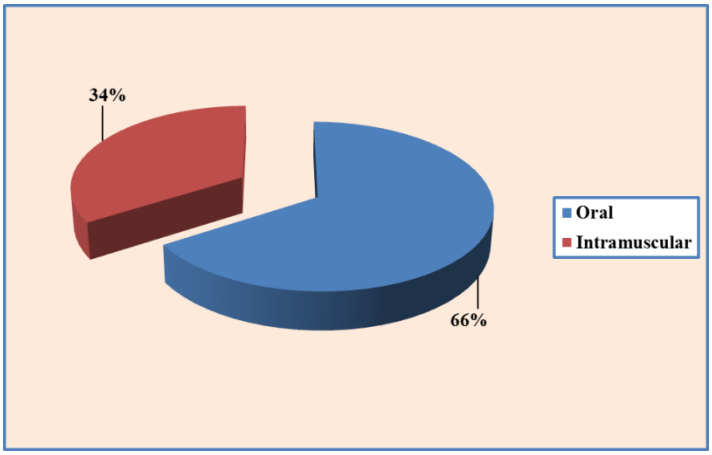

Fig-20: Rout of vitamin D therapy

DISCUSSION

In this study, demographic and clinical characteristics of 153 child was evaluated, number of male children exceeds that of females, this results in agreement with previous study done on Libyan children in 2013, in which male to female ratio was found to be 1.3:1, and stated that there is no apparent explanation for this finding, [(24)]the mean age of the study sample is 13.6 months, more than half of the cases, 53% ,belong to age group of less than one year and 44.4% of the in the 2nd year of their life, so that in total, more than 97% of the disease occurred in age of 1-2 years, in a previous study it was found that, Rickets is very common between age of 6 and 36 months old, because at this age range children experience rapid growth, and their bodies need the most calcium and phosphate to strengthen and develop their bones [1].

The most frequent clinical sign of Rickets among the sample of this study was rachitic rosary, as it occurred in 94.1%, followed by wide wrist and ankle regions, then skull posing and wide anterior fontanel, radiological study was normal in 37.3% of the sample, where as 44.4% have osteopenia and 18.3% showed cupping in their X-ray. It is generally agreed that vitamin D deficiency affects motor activity, teeth formation and causes skeletal deformities of the growing children [25]. In addition these results consistent with other studies with slight difference in the arrangement, so that findings from radiographic investigations include cupping, flaring and fraying of the metaphysis, rachitic rosary and angular deformities of the bones of the arms and legs [18].

Laboratory investigations, calcium level is 11mg /dl in 99 % of the sample, phosphate level 3,5-6in 74.5 % , and alkaline phsphatase level in elevated in 43.8%, these figures are concurrent with previous studies for example that done by Shaw and Kershaw [26], which found that, in vitamin D deficiency Rickets there might be normal or decreased blood levels of calcium; elevated blood levels of alkaline phosphatase or parathyroid hormone; normal, decreased or increased blood levels of phosphate, and decreased blood levels of 25-hyroxy vitamin D [26].

Oral rout of treatment was considered for 66% of the sample compared to34 % have vitamin D therapy intramuscular, consequently vitamin D level before and after treatment showed highly significant difference, in term of marked therapeutic effect of vitamin D supplement which reduced the severe cases from 25 to 1case only, and the mean level was dramatically improved after treatment (t=11.635, P< 0.00), this result signifies the fact that most of cases were having nutritional Rickets, which is due to dietary insufficiency and reduced sun exposure to synthesise the required level of vitamin D.

This result is consistent with most of the available literature, in temperate countries vitamin D deficiency is prevalent to the countries known for lack of sunshine [27], while in Libya, it might be referred to in appropriate prolonged exclusive breastfeeding i.e. delayed weaning which was reported in 18.3 % of the current study sample, Family diet is consumed by 58.8% of the studied sample, which is obviously not fortified diet and does not provide the growing child with his requirement of vitamin D and calcium. Lack of sun exposure is another potential risk factor for vitamin D deficiency among the study sample, despite the prolonged period of sunshine in our country, though this might be justified by social habits of avoidance staying under direct sunshine [24], together with types of dwellings with high walls and small, high windows which do not offer direct access to sunshine [28].

Mothers of about 44% of the study sample have vitamin D deficiency, and about 21% reported past history of vitamin D deficiency, most studies had found that Arab women, lactating mothers and mothers who delivered at term have very low serum 25- OHD concentrations and higher prevalence of hypovitaminosis D compared with white women [29], this another predisposing factor of nutritional Rickets in their siblings as it is generally accepted that the vitamin

D status of the fetus and infant is dependent on the vitamin D status of the mother [30].

CONCLUSION

This study found that the vast majority of the studied children of age one to two years the peak age of growth and bone tissue formation and development, exclusive breastfeeding and delayed weaning were was reported as feeding practice of some of the study sample, and a large part of them were subjected to inappropriate early weaning in addition to a great portion is consuming family diet which does not contain the recommended requirement of calcium and vitamin D of a growing child. The participants clinically presented with delayed walking and teething, failure to thrive and lethargy, on examination the sample clinically showed rachitic rosary, posing skull, wide wrist, knee and anterior fontanel. Radiological signs were quite clear of rachitic changes such as osteopenia and cupping.

Vitamin D supplement was given either orally or via parenteral route, the selection was guided by the severity of deficiency and family capacity of buying injectable form. Moreover, the result of treatment course strongly suggests that the Rickets is nutritional, so that post treatment a significant improvement of the severe and moderate cases was achieved, moreover a greater number of cases were turned to normal serum level of vitamin D. What is more a valuable numbers of the mothers either have vitamin D deficiency currently or in the past? Maternal past or current history of vitamin D deficiency was another clear recorded problem in about two thirds of the sample, which is possible additional risk factor for infant Rickets.

RECOMMENDATIONS

Rickets and vitamin D deficiency is very common health problem that can be controlled by educating society about it to ensure that mothers and infants are sufficiently exposed to sunlight and eat a balanced diet rich in calcium and vitamin D.

However, for growing children it is difficult to ensure adequate sun exposure, therefore it is recommended to provide vitamin D supplement of 200 IU per day for all on breastfeeding and formula feeding, whose formula is not fortified or fortified with inadequate amount of vitamin D. In addition to that, it is recommended that children on anticonvulsants medications for more than 3 months should be provided supplements of vitamin D. Child`s siblings and other family members should also be supplemented.

LIMITATIONS AND WEAKNESSES

The descriptive study design and relatively small sample size are major weaknesses in this study, no data about nationality (racial groups), and type of dwelling or duration sun exposure was collected to find about environmental factors leading to or exacerbate Rickets, hence more specific recommendations might emerge. The generalizability of the results is not practical as no data about the size of whole population of Rickets, and the prevalence of disease among Libyan children, and no consideration of the power of the study.

Strengths

This study to a great extent recorded a reliable data as the informants for all children are their mothers, minimum missing data and the cases were sent to the same lab for serum level of vitamin D and before and after treatment.

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