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Vitamin D deficiency rickets in peri-urban Sanaa, Yemen

A thesis submitted in fulfillment for the Degree of MD(Paediatrics and Child Health) by research

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Dedication

To my dear wife and lovely children
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ABSTRACT

This is a prospective community based case control clinical trial conducted in some villages in the surrounding districts of the capital of Yemen, Sana’a. The aims of the study was to study prevalence, risk factor, and clinical features of rickets, and evaluate the impact of health education as a part of treatment in vitamin D deficiency rachitic children residing the peri-urban Sana’a. Two hundred and fifty cases of infants and young children aged 2-35 months were enrolled in the study. They were selected by active surveillance. Fifty children matched for age and sex were randomly, selected as a control. The duration of the study was two and half years. The cases were interrogated, thoroughly examined. The investigation performed included estimation of serum levels of calcium, inorganic phosphate, vitamin D, and alkaline phosphatase. In addition, x-ray of both wrist joints was done. Clinical, biochemical and radiological re-evaluation following management was performed four to eight months later.

The prevalence of vitamin D deficiency rickets in the surrounding villages of capital Sana’a was found to be 18.7 % (n=250 from those 1335 children examined) and two thirds of the cases were in infants below 12
months of age. The associated risk factors included reduced exposure to sunlight (p<0.05), prolonged breast-feeding without supplementations of solids (p<0.05).

The majority of mothers (90.4% n=226) and of fathers (18% n= 45) were illiterate and were not only unaware of the benefits of sunlight to infants but also they had misconceptions. The predominant clinical features observed (in most cases) included; rosary beads in 96.8 % (n=242) broadening of wrist joints in 82 % (n=205) deformity in the chest in 76.4 % (n=191) and potbelly abdomen, Harrison Sulcus (Harrison Groove), kyphosis were seen in less than half of the cases. Estimation of serum calcium, inorganic phosphate, and vitamin D were significantly low in the cases compared to controls (p<0.05). All the cases demonstrated the radiological features of rickets including, widening of joint spaces, broadening, cupping, and fraying of epiphysis of radius and ulna; delayed bone age was observed in some cases.

The intervention concentrated on intensive health education sessions, vitamin D injections and calcium supplementation. Re-evaluation showed clinical, biochemical and radiological improvement as well as improvement in knowledge, attitude and practice of mothers toward sunlight exposure, which revealed the benefit of health education.
Vitamin D deficiency rickets is a preventable disease, and the preventive measures are feasible and cost-effective. The health system in Yemen must realize the magnitude of the problem and implement an intensive health education program. The program should aim at raising the awareness of mothers on the benefits of exposure of infants to sunlight, better breast feeding and infant feeding practices.
 vậnت النص العربي إلى النص العربي.
تقوم بالأنشطة المتنوعة لتحسين الصحة وتعزيز الصحة والصحة العامة. يبرز الاهتمام بkee و_permissions للحفاظ على صحة جيدة. يوفر الاهتمام بالأنشطة وتعزيز الصحة والصحة العامة. يبرز الاهتمام بkee و_permissions للحفاظ على صحة جيدة.
LIST OF ABBREVIATIONS:

1, 25(OH) 2 D3 = 1, 25 dihydroxyvitamin D

25 OH D3 = 25 hydroxyvitamin D

AAP= American Academy of Pediatrics

Alk. p =Alkaline phosphatase

Ca = Calcium

Cal-D-B 12 = calcium, vitamin D, vitamin B12

CAF = closure of anterior fontanelle

cir = circumference

cm = centimeter

/dl = per deciliter

D2 =vitamin D2

D3 = vitamin D3

ELISA= Enzyme Linked Immunosorbant Assay.

FTT = Failure to thrive.

ht= height

IDDM =insulin dependant diabetes mellitus

IM = intramuscular

i PTH = immune reactive parathyroid hormone

IU = international unit
Kg = kilogram
/L = per litter
mcg = microgram
Mg = milligram
mmol = millimol
M.O.P.H. = Ministry of Public Health
MUAC = Mid Upper Arm Circumference
n = number
ng = nanogram
nmol = nanomol
Pg = pico gram
Pi = inorganic phosphate
SD = standard deviation
SPSS = Statistical Package for Social Science
ug = microgram
UK = United Kingdom
USA = United States of America
Vit D = vitamin D
wt = weight
YR = Yemeni Riyal
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CHAPTER ONE

Introduction and Literature review
1.1 Historical review:

In the mid-1600s, most children who lived in the crowded and polluted industrialized cities of northern Europe developed a severe bone-deforming disease that was characterized by growth retardation, enlargement of the epiphyses of the long bones, deformities of the legs, bending of the spine, knobby projections of the ribcage, and weak and toneless muscles (1, 2). In the latter part of the 19th century, autopsy studies done in Boston and Leiden, The Netherlands, showed that 80–90% of children had rickets (3). In 1822, Sniadecki recognized the importance of sun exposure for the prevention and cure of rickets (4). Palm extended these observations in 1890 and promoted systemic use of sunbaths to prevent rickets (5). In 1919 Huldshinsky found that exposing children to radiation from a sun quartz lamp (mercury arc lamp) or carbon arc lamp for one hour 3 times a week was effective in treating rickets, as demonstrated by a marked increase in the mineralization of the skeleton, especially the ends of the long bones, evident in the child’s x-ray. A similar group of children not exposed to UV radiation showed no cure or only a slight improvement. He concluded that exposure to UV radiation was an "infallible remedy" against all forms of rickets in children (6). Two years later, Hess and Unger (7) exposed seven rachitic children in New York City to
varying periods of sunshine and reported marked improvement in the rickets of each child as evidenced by calcification of the epiphyses.

Simultaneously, Mellanby reported that, he could produce rickets in dogs by feeding them oatmeal and could cure the disease by adding cod-liver to their diet (8). Indeed, it was a common folklore practice on the coastlines of British Isles and the Scandinavian countries to use fish liver oil to prevent and cure this bone deforming disease. At first, it thought that the anti-rachitic activity in cod liver oil was due to vitamin A. However when vitamin A activity was destroyed by heat and oxidation, the cod liver oil continued to have anti-rachitic activity. As a result of these observations, it was concluded that there was a new fat soluble vitamin that was called vitamin D (9). That was known as the anti-rachitic factor, and could be generated in the skin after exposure to sunlight or could be obtained from cod liver oil; it became confusing as to whether there was more than one anti-rachitic factor. This issue was resolved when Power reported that radiation from mercury arc lamp had similar if not identical healing effects on rachitic rats when compared with those brought about by cold-liver oil (10). Once it was known that exposure to sunlight could prevent and cure the disease, Steen bock and black, Hess and Weinstocks independently demonstrated that exposure of food and a variety of other substances to the vitamin D producing radiation from mercury arc lamp
could impart anti-rachitic properties to these substances (11,12). With the
discovery of vitamin D and the delineation of the anti-rachitic properties of
cod liver oil by the 1930s, it became possible to not only treat but also
eradicate rickets in the United States (13). This concept was first used to
make milk anti-rachitic by adding the precursor of vitamin D to milk and then
exposing the milk to radiation from a mercury arc lamp. Today vitamin D2 or
vitamin D3 is directly added to milk (400 IU) (10ug) per liter and other foods
resulting in almost complete elimination of rickets in countries that use this
practice (14).

1.2 Types of bone cells:
. Osteogenic cells (primitive cells, which can differentiate to osteoblast).
. Osteoblast responsible for bone matrix synthesis (bone forming cells),
. Osteoclast responsible for bone resorption (bone eating cells), it remove
calcium & phosphorous from the bone, maintaining their levels adequate in
the blood. Osteocyte (actual mature cells); Bone is a dynamic organ capable
of rapid turnover, weight bearing, and withstanding the stresses of a variety of
physical activities. It is constantly being formed (modeling) and reformed
(remodeling). It is the major reservoir for calcium, phosphorous, and
magnesium. Since bone growth and turnover rates are high during childhood,
so manifestations of bone diseases are more prominent in that period.
Many factors are responsible for normal bone growth as calcium, phosphorous, and magnesium, parathyroid hormone, vitamin D, calcitonin, growth hormone and others. Any defect in one or more of the above-mentioned factors will lead to bone formation defect, our subject of study will concentrate in nutritional vitamin D deficiency rickets (15).

1.3 Definitions:

a) Rickets signify failure of mineralization of growing bones, i.e. it is a systemic metabolic disease resulting from disturbance of calcium-phosphorous metabolism, which presents clinically by various skeletal, muscular and neurological manifestations (15).

b) Vitamin D deficiency: most experts define vitamin D deficiency as a 25-hydroxyvitamin D level of less than 20 ng per milliliter (50 nmol per liter), it could be symptomatic or asymptomatic (16).

1.4 Etiology:

i) Lack of exposure to sunlight (17_22, 23_29).

ii) Deficient supplementation of vitamin D (30_37)

iii) Maternal deficiency of vitamin D and calcium (30_32, 33_40, 41_43)

iv) Increased demand of vitamin D (43_46).

v) Deficiency of other elements as calcium (46_49)
1.5 Prevalence and risk factors:

Once foods were fortified with vitamin D and rickets appeared to have been conquered, many health care professionals thought the major health problems resulting from vitamin D deficiency had been resolved. However, rickets can be considered the tip of the vitamin D deficiency iceberg. In fact, vitamin D deficiency remains common in children and adults. In utero and during childhood, vitamin D deficiency can cause growth retardation and skeletal deformities and may increase the risk of hip fracture later in life. Vitamin D deficiency in adults can precipitate osteoporosis, osteomalacia and muscle weakness, and increase the risk of fracture. The discovery that most tissues and cells in the body have a vitamin D receptor and that several possess the enzymatic machinery to convert the primary circulating form of vitamin D 25-hydroxyvitamin D to the active form 1,25-dihydroxyvitamin D has provided new insights into the function of this vitamin. Of great interest is the role it can play in decreasing the risk of many chronic illnesses, including common cancers, autoimmune diseases, infectious diseases, and cardiovascular disease (50). It has been estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency (51–53). According to several studies, 40 to 100% of U.S. and European elderly men and women still living in the community are deficient in vitamin D. More than 50% of
postmenopausal women taking medication for osteoporosis had suboptimal levels of 25-hydroxyvitamin D below 30 ng per milliliter (75nmol per liter) (55,56,57). Children and young adults are also potentially at high risk for vitamin D deficiency, (52%) of Hispanic and black adolescents in a study in Boston (55,56,57) and 48% of white preadolescent girls in a study in Maine had 25-hydroxyvitamin D levels below 20 ng per milliliter (56). In other studies at the end of the winter, (42%) of 15 to 49 year old black girls and women throughout the United States had 25-hydroxyvitamin D levels below 20 ng per milliliter. (32%) of healthy students, physicians, and residents at a Boston Hospital were found to be vitamin D deficient, despite drinking a glass of milk and taking a multivitamin daily and eating salmon at least once a week (57,58,59,60).

Thacher and Coworkers, described nutritional rickets at least 59 countries in the last 20 years, they found that, calcium deficiency is the major cause of rickets in Africa and some parts of tropical Asia. A resurgence of vitamin D deficiency has been observed in North America and Europe. Vitamin D deficiency rickets usually presents in the 1st 18 months of life, whereas calcium deficiency typically presents after weaning and often after the 2nd year. Along the spectrum, it is likely that relative deficiencies of calcium and vitamin D interact with genetic and /or environmental factors to
stimulate the development of rickets (16). In Saudi Arabia, Abdullah concluded that the cause of rickets in that sunny country is multifactorial including lack of sun exposure, inadequate calcium intake, and genetic causes; he also reported prevalence of 58.5% (23, 61). Elidrissi conducted many studies in Saudi Arabia, and he found that rickets is highly prevalent, but there is no recorded prevalence rate (30). Majid from Al Kuwait concluded that the cause of nutritional rickets is a multifactorial condition, lack of exposure to sunlight, prolonged breast-feeding without supplementation and inadequate weaning practice (21). In Jordon a case control study conducted to determine the frequency of nutritional rickets among hospitalized infants and asses the relation to respiratory diseases, they found 10% admitted infants were racketic, 85% of them were admitted due to respiratory diseases (62). Dawodu and his colleagues conducted a study in United Arab Emirates to see the prevalence of vitamin D deficiency in mothers of racketic children, they identified vitamin D deficiency in 92% of racketic children, and 97% of their mothers in comparison to control where it was 22% ,52% respectively (31). Studies in Saudi Arabia, the United Arab Emirates, Turkey, India, and Lebanon, 30 to 50% of children and adults had 25-hydroxyvitamin D levels under 20 ng per milliliter (61__64). McGrath, Ladahani, and Lee recorded 45% in Queensland and UK (64, 65, 66). Other studies conducted in Nigeria
their results were daily dietary calcium intake was low in both rachitic and control children, children with rickets had a greater proportion of first degree relatives with a history of rickets, shorter duration of breast feeding, delayed age of walking, with prevalence rate of 37% (67, 68). Fraser (2004) conducted a study in China and Mongolia; he concluded that the main causes are lack of sun exposure, deficient calcium in the diet and malnutrition and the rachitic cases were 40% - 60% of the population. Nationwide survey was carried out from 1977 to 1983, in china, 184.901 cases was examined and 75259 were diagnosed as rickets with an over all incidence of 40% (69).

Although rickets is common in Arab countries, prevalence figures are scarce, however in Yemen, 27% and 50%, were recorded by Underwood and Banajeh respectively (70,71). Despite abundant sunlight, rickets and osteomalacia are prevalent in South Asian Countries; the cause of this paradox is not clear, (72, 73, 74). Fischer and Coombs concluded that rickets mainly due to calcium deficiency in Bangladesh (75, 76). Hatun from Turkey concluded that nutritional rickets is due to limited sun light exposure of the mothers, low vitamin D intake for mothers and their children and exclusive breast-feeding (20).

Studies in African countries concluded that rickets exist along a spectrum ranging from isolated vitamin D deficiency to isolated calcium
deficiency or both, along with deficiency of vitamin D and calcium interact with genetic and / or environmental factors (67, 68,77,78,79). In Sudan, a study conducted by El Hag & Karrar in 1995 found that serum alkaline phosphatase was elevated in 75%, serum calcium was recorded to be deficient in 54% and serum phosphate was decreased in 68%, and hypochromic anemia in 79% of them (80). In Libya, the prevalence was high, because of the prolonged breast feeding, infants and mother being kept out of sunshine, mother wearing traditional veils; besides that no food items enriched with vitamin D were used except of infant’s formulas (81). Elzouki in 1989 found that the breast fed infants typically present during late winter and early spring by convulsion, due to hypocalcaemia, all other biochemical data of rickets are affected, low level of phosphate, high level of alkaline phosphate low serum of 25(OH) D and 1, 25(OH) 2 D is normal (82). Atypical case history of these with Vit D deficiency, hypocalcaemia is probably precipitated by increase phosphate load and decreased calcium absorption secondary to altered intestinal environment by the introduction of cow’s milk (82, 83, 84). In Ethiopia, a study conducted by Lulseged, reported that protein energy malnutrition was strongly associated with vitamin D deficiency rickets, and a prevalence of 47% was recorded (85). Akpede conducted a study in Nigeria; he found that more than 50% were rachitic, and among them 47% had isolated
hypocalcaemia and/or hypophosphatemia. The results support the hypothesis that deficiency of calcium may be of at least equal importance with vitamin D deficiency in the etiology of nutritional rickets in Nigeria (86). Graff conducted a study in Nigeria also and found that deficiency of calcium is the main cause of nutritional rickets (87). Yeast in Spain, concluded that rickets mainly affected immigrant infants fed with maternal milk without supplementation (88). Hanley recorded 47% in North America (89). In a study conducted by Holick in 2006, he found that vitamin D inadequacy has been reported in approximately 36% of otherwise healthy young adults and up to 57% of general medicine inpatients in the United States (90). Also Nesby in one of his studies reported a prevalence of 40% (59). In Australia and New Zealand, the prevalence of vitamin D deficiency is much higher than previously thought. One study found marginal deficiency in 23% of women, and another frank deficiency in 80% of dark-skinned and veiled women (37).

We could summarize risk factors and/or predisposing factors into:

a) lack of exposure to sunlight (17–21, 22–29).

b) Breast-feeding without supplementation of vitamin D (20, 33, 47, 91). Since breast milk has very little, if any, vitamin D (usually no more than 25 IU/L), it is usually inadequate in satisfying the infant’s requirement especially after the fourth month (34, 35, 36). Thus, if the infant is exclusively breast-feeding and if the
mother is vitamin D deficient, the infant will become vitamin D deficient and will likely develop rickets (37, 38, 91). c) Deficiency of vitamin D in the mothers is one of the major risk factors (20, 29, 33-35, 38, 91–98). d) Deficiency of calcium in the mothers and osteomalacia (23, 46, 47, 48). Pettifor attributed the high prevalence of rickets in some sunny countries, as Yemen, Bangladesh, Ethiopia and Nigeria due to deficiency of calcium in mothers and their infants (77). e) Wrong customs, some wrong traditional beliefs like dressing, wearing clothes as Purdah, diminished sun exposure and wearing veil of the mothers will lead to diminished vitamin D in mothers subsequently hypocalcaemia seizures in their infants (19,20,23,24,28,30,31,40,41,45,38, 62). f) Immigration from rural areas to crowded cities and living in flats may increase the chance of rickets, due to lack of place for sun exposure (24, 25,29, 44, 74, 88).

g) Long term treatment with anti-epileptic drugs it has long been observed that treatment with phenobarbitone and phenytoin can be associated with rickets. More recently, established agents such as Carbamazepine and Valproate have shown to be associated with lowering of bone mineral (99,100). h) Biological features mainly melanin skin pigmentation, the assumption that the darker the skin the more impermeable it is to ultraviolet B photon has been disproved. The increase of plasma calcidiol after standard ultraviolet radiation
of the skin is similar in subjects of different cutaneous melanin concentration (101). But the amount of UV-B required for cholecalciferol synthesis is higher in Blacks (40, 45) and the minimal erythemal dose of ultraviolet radiation is higher in Asians, (102). i) With restriction of the diet in milk and food allergy (103). Soya beans milk instead of cow’s milk-based infant formula, strict dietary restrictions in food allergy and feedings with Soya bean juice and rice food may precipitate the disease (104,105). j) Social deprivation; Akopede in Nigeria, found a good relation between maternal deprivation and vitamin D deficiency rickets (106). k) Geographical location and annual season: During the winter months, and more extreme altitudes, the sun remains low in the sky for fewer hours, the actinic radiation is subjected to greater scattering and to more absorption by the ozone layer of the stratosphere, as a result the amount of UV-B light becomes insufficient for cholecalciferol synthesis (107,108). l) Social and cultural factors, plasma calcidiol levels are higher in outdoor workers than in those working indoors (108). The exclusion of direct sunlight, for example in women who are confined in their homes most of the daytime or women in Saudi Arabia, who wear dark veils, and thick black garments, when outdoors is obviously equivalent to block UV-B radiation to the skin, such blocking is a cause of
cholecalciferol deficiency in high proportion of females and their children (40, 41).

m) Cold climate was reported by some researches to be a risk factor (108). Some religious customs and/or climatic conditions prevent adequate exposure to ultraviolet light (110). n) Air pollution as in India was studied by Agorawal, claimed that, the high prevalence of rickets could be correlated to air pollution (111). o) Premature babies are more likely to develop rickets (109).

1.6 Classification of rickets:

Rickets has been classified in numerous ways. The recent and preferred scheme of classification is that of Harrison and Co-workers, who divide the various forms of rickets into two main types according to their pathogenesis, Type I, and Type II.

Type I rickets: In this type, an abnormality of vitamin D metabolism leads to deficiency of active vitamin D (1,25(OH)2D). The chemical transformation of vitamin D occurs sequentially in a number of sites in the body (skin, liver, kidney), thus interference with the process of any these sites will decrease or inhibit the formation of the final product. Such interference may be due to:

- Inadequate exposure to sunlight (17–21, 22–29)
• Deficient nutritional vitamin D intake (37, 38, 91, 97,98)
• Mal absorption of fat-soluble vitamin
• Liver diseases leading to failure of hydroxylation and/or mal absorption.
• Renal glomerular destruction resulting in depressed vitamin D activation to 1,25 (OH) 2 D.
• Long-term anti-convulsant therapy especially combination of phenobarbitone and dilantoin (99, 100)
• A disorder caused by functional reduction in the kidney 1 alpha hydroxylase enzyme, so called Vitamin D dependant rickets, (pseudo-vitamin D deficiency, increased requirement for vitamin D). This Heterogeneous syndrome, transmitted as an autosomal recessive, is due to incomplete conversion of (25 OH vit.D3) to (1, 25 (OH) 2 D3)

Type II rickets: The second type of rickets, the target cell abnormality group, accompanies a number of renal tubular disorders in which there is decreased reabsorption of phosphate; thereby lowering extra cellular fluid phosphate concentration; failure of demineralization is a consequence of inadequate serum phosphate rather than calcium. The three most common disorders are:
- Primary renal hypophosphataemic rickets (familial vitamin D resistant rickets)
- Renal tubular acidosis
- Fanconi syndrome

1.7 Vitamin D metabolism:

Vitamin D (calciferol) is a collective term for two steroid-related and cholesterol-derived naturally occurring compounds:

A) Plant origin vitamin D2 (ergocalciferol), which is derived from the plant sterol ergo-sterol.

B) Animal origin vitamin D3 (cholecalciferol), which is produced in the skin by the effect of ultraviolet irradiation on (7-dihydrocholesterol) present in Malpghian layer of the epidermis.

Once vitamin D is synthesized in the skin or ingested in the diet, it enters into the circulation and binds to a vitamin D binding protein (Vit D either D2, or D3), which is transported to liver where it is hydroxylated on carbon 25 to generate the major circulation Vit D 25-hydroxyvitamin D (25(OH) D) (1,3,112). Measurement of 25 hydroxyvitamin D3 is most
sensitive index of vitamin D status of population. The half-life of 25(OH) D in human circulation is 2 weeks and concentration ranges from 8-55ng/ml (113); 25(OH) D is biologically inert and require a further hydroxylation in the kidney to 1,25 dihydrxy vitamin D (1,25(OH)2 D) (1,3,112). For human and most mammalian the kidney is the principal site of hydroxylation, however during pregnancy the placenta play the same role as the kidney in formation of 1,25(OH)2 D (113,114). The circulating 1, 25(OH)2 D half-life is approximately 4-6 hours and its concentration in normal condition is 26-65 pg / ml (17).

During the initial exposure to sunlight provitamin D3 is efficiently converted to previtamin D3 during the prolonged exposure to sunlight, however, there is little additional increase in previtamin D3 production, because once formed previtamin D3 is photoisomerized to biologically inert photoproducots, Lumisterol and tachysterol (116). Vitamin D3 is also exquisitely sensitive to sunlight, as a result any vit D3 that is formed in the skin and dose not escape into the circulation when exposed to sunlight is rapidly degraded into 5,6-trans-vitmain D3, suprasterol I and suprasterol II (107,116).

Skin: 7-dehydrocholesterol (provitamin D3)

▼
When radiation between 290 and 315nm (Ultra-Violet-B radiation) strikes the skin, approximately 10% is reflected and the other 90% is absorbed or scattered. The ultraviolet B photons that are transmitted into the epidermis and dermis convert cytoplasmic stores of provitamin D3 to previtamin D3 (120). Once previtamin D is made in the skin, it immediately begins to thermally equilibrate to Vit D3 by a temperature-dependant process. This thermal equilibration takes approximately 1½-2 days to reach completion at body temperature in humans. Studies of vit D metabolism in vivo indicate that the more vitamin D given, the higher concentration of 25(OH) D in plasma (39). In temperate geographical regions, the plasma concentration of
25(OH) D is highest in late summer and lowest in late winter this reflect the seasonal changes in the intensity of solar ultraviolet B- radiation (290-320nm) (47). Even with extensive solar irradiation in tropical regions or with whole body exposure beside the sea in summer the plasma concentration of 25(OH) D rises but not higher than 80ng/ml. Evidently, the greatest rate of formation of vit D in skin cannot maintain 25(OH) D concentrations above that level. Nevertheless, the capacity to synthesize 25(OH) D is considerably greater than the plasma levels produced by ultraviolet irradiation would suggest large doses of vit D, which gives rise to signs of vit D toxicity, could raise plasma level of 25(OH) D to more than 400ng/ml. These observations lead to the conclusion that a key factor determining plasma level of 25 (OH) D is the input of vit D to the site of hydroxylation in liver. The concentration of 1,25 (OH) 2 D in plasma is 30-50pg/ml which is 1000-fold lower than that of 25 (OH) D. Furthermore the 1,25 (OH) 2 D concentration is independent of the supply of 25 (OH) D precursor. A multiple controlling factors have been proclaimed to influence the formation of 1,25 (OH)2 D in proximal convoluted tubules of the kidney (62). The postulated controlling factors are PTH, Calcitonin, prolactin, growth hormone, insulin, glucocorticoids, gonadal steroids, calcium, phosphorous and even 1,25 (OH)2 itself, by regulating 1-hydroxylase. The standard view of the regulated secretion of 1,25 (OH)2 D
is that this active metabolite is produced to maintain calcium homeostasis by stimulating target cells in the intestinal mucosa, in the renal tubules and in bone to increase their transport of calcium. Thus PTH, secreted in response to hypocalcaemia, enhances the activity of renal 1-hydroxylase. The action of 1,25 (OH)2 D in stimulating the target cells increases the extra cellular calcium leading to fall in PTH secretion. This feed back mechanism is typical of the endocrinal loops, which link the secretion and function of peptide hormones.

Holick have estimated that when a young adult is exposed to a whole body of sunlight that causes minimal erythema (1 minimal erythemal dose), the rise in the circulation of vitamin D3 is comparable to an oral dose of 10,000 IU of vitamin D3, therefore the capacity of human skin to produce vitamin D3 is quite large. It has been recommended for the elderly that 10 – 15 minutes of sunlight exposure of hands, face and arms two-three times a week is more than adequate to provide the body with its vitamin D3, requirements (118). An increase in the sun’s zenith angle results in an increased path length for the UVB photons to travel, and this explains why at higher latitudes (above ~35° latitude), very little, if any, vitamin D3 is produced in the skin from November through March (14). It is probable that children and young adults make and store enough vitamin D during the spring
summer, and fall to get them through the winter months without developing vitamin D deficiency. However for the elderly and very young children who may not be exposed to sunlight during the productive time of the year, their vitamin D stores may be low, therefore during the winter time they would benefit from Vit.D supplementation in order to prevent vitamin D deficiency (14). The sun emits a broad spectrum of radiation. The thin layer of ozone that envelops the earth absorbs the high-energy photons that are most damaging to life on the earth (below 290nm) (13,112).

The recommended daily allowance is 400 IU (10 microg), since the year 1941. In the year 1997, the suggestion was 500 IU (12.5 microg) in absence of sun exposure (122). That was recommended by American Academy of Pediatrics. Daily food intake of 100-200 microgram of cholecalciferol (50-100gm cod-liver oil), or weekly exposure to two minimal erythemal doses of ultraviolet radiation (20-40) minutes whole body exposure to midday midsummer sun will give this daily requirement (120,121). In absence of sun exposure 1000 IU of cholecalciferol is required daily for both children and adults (55). Food Safety Irish Authorities recommend vitamin D supplementation for all infants from 0-12 months, 5 ug / daily in Ireland starting on May 2007.

1.8 Calcium homeostasis:
It is the process of effectively maintaining constant extra-cellular calcium concentration, which is normally 9-11mg%. This can be achieved by increasing calcium absorption from intestine and increase calcium resorption from the bone whenever there is tendency to fall in calcium levels. Also, precipitate calcium in the bone, and increased excretion of calcium from the kidney when serum calcium level rises above normal level.

Regarding the action of 1,25(OH)2 D in calcium homeostasis, Costanzo found that 1,25(OH)2D is the primary regulating factor determining changes in intestinal absorption capacity and bone resorption to maintain the calcium serum level within normal limits. In comparison to its action in the intestine and bone, vitamin D appears to have punitively minor influence on calcium transport in the kidney (132).

Vitamin D deficiency prevents the efficient absorption of dietary calcium and phosphorus from the intestine. In a vitamin D–deficient state, only 10–15% of dietary calcium and 50–60% of dietary phosphorus are absorbed. The poor absorption of calcium causes a decrease in serum-ionized calcium levels. This is immediately recognized by the calcium sensor in the parathyroid glands, resulting in an increase in the expression, synthesis, and secretion of parathyroid hormone (PTH). PTH conserves calcium by increasing tubular reabsorption of calcium in both the proximal and distal
convoluted tubules. PTH, like 1,25(OH)2D enhances osteoblast to increase the production of mature osteoclast to mobilize calcium stores from the skeleton. PTH also decreases phosphorus reabsorption in the kidney; causing loss of phosphorus into the urine. The serum calcium level is usually normal in a vitamin D deficient infant or child. However, the serum phosphorus level is low, and thus there is inadequate calcium-phosphorus product, which is necessary to mineralize the osteoid laid down by osteoblast. Thus, typically, infants with vitamin D deficiency rickets have a normal serum calcium level, low normal or low fasting serum phosphorus levels, elevated alkaline phosphatase levels, and low 25(OH) D levels. Only when the calcium stores in the skeleton are totally depleted the infant or child become hypocalcaemia (133). The secondary hyperparathyroidism stimulates the kidneys to produce 1,25(OH)2D, and thus, 1,25(OH)2D levels are normal or often elevated, that is why the measurement of 1,25(OH)2D is of no value in determining a state of vitamin D deficiency.

1.9 Homeostasis of inorganic phosphate:

In most mammals, 80%-90% of body phosphate is present in bone mineral as a major component of hydroxyapatite. The rest is in the soft tissue, blood cell, extra cellular fluid and muscles. In soft tissue phosphorous represent about 0,2%. In the cells it is present in the form of inorganic and
organic phosphate as bound to sugars, lipids, proteins, nucleic acids, and various nucleotides. In the plasma one-fourth of total phosphate is present in the form of inorganic ions, the major fraction being phospholipids. The concentration of inorganic phosphate (Pi) in plasma is not set at a steady level like that of calcium, it varies among animals being highest in some fishes, and it varies with age highest in newborn. Plasma Pi level is influenced by various Pi fluxes entering and leaving extracellular compartment; Pi enter the extracellular compartment from the intestine and various soft tissue and from bone. It leaves extracellular compartment through urine, as the result of difference between glomerular filtration and net tubular reabsorption by back flux into the intestinal lumen and by transfer into the soft tissue and bone for the process of matrix mineralization. Among various Pi transfers, the renal fluxes appear to be important with respect to setting plasma Pi level (129). Indeed the range of re-absorption varies from 0-100%, therefore, because of such enormous flexibility, renal tubules, play the main role in controlling Pi level in plasma. The inorganic phosphate re-absorption mainly occurs in proximal convoluted. However, the distal and terminal parts of the nephron are also the site of Pi absorption. The mechanism of re-absorption of Pi from proximal tubules occurs by transfer of Pi from the lumen to the microvilli that
lines the tubular lumen to the intracellular compartment against an electro-
chemical gradient by sodium countransport (130).

1.10 Role of parathyroid hormone:

Parathyroid hormone is an 84 amino-acid peptide, secreted from parathyroid chief cells. Parathyroid hormone gene is located close to insulin gene on the short arm of chromosome 11 (123). The serum calcium level is the major regulator of parathyroid hormone synthesis and release, the major role of parathyroid hormone is prevention of hypocalcaemia, it does so by three main mechanisms, (i) increase the net release of calcium and phosphorous from bone into extra-cellular fluid (123). (ii) Increase renal calcium re-absorption and phosphorous excretion by inhibiting their re-absorption from renal tubules (124). (iii) and indirectly, increasing intestinal calcium absorption by stimulating renal 1, 25 dihydroxy vit D synthesis (125).

Intact PTH and amino-terminal fragments are cleared rapidly from the circulation (<10min), carboxy-terminal fragments are cleared slowly (2h) this heterogeneity of circulating forms of PTH causes particular problem for its measurement. There is diurnal circadian variation in serum PTH secretion with higher values in the early morning (126). PTH is rapidly released from parathyroid gland in response to fall in plasma ion calcium it acts on the kidney and intestine (indirectly) and bone to restore the concentration of these
cations, to a normal set point, which in turn inhibit PTH secretion. Biologically PTH level is extremely low <50pg/milliliter. There is individual Set- point value for plasma ionic calcium above that set- point glandular secretion decreased, below that set- point glandular secretion of PTH increased (125).

In a study performed by Scriver, the development of rickets passes into three stages. These stages are characterized by unique changes in the serum concentration of calcium, phosphate, Immune reactive PTH (i PTH), 25(OH) D3, and the severity of radio graphically assessed bone lesions (126). In the first stage of rickets: there is mild hypocalcaemia, appropriate increased serum i PTH, normal or decreased serum phosphate, and decreased serum 25(OH) D3. In the second stage: serum 25(OH) D3 decreases slightly or not at all, the serum calcium return to normal level, paradoxically small decrease in serum iPTH, Hypophsphatemia, and bone lesions worsen during this stage. In the third stage, when florid rickets becomes manifested, serum 25 (OH)D3 decreases to an undetectable level, hypocalcaemia again becomes apparent, and is more severe than stage one, hypophsphatemia and PTH increases. The underlying of these biological and osseous changes is the decrease in production of (1,25 (OH)2 D3), which is due to decrease in 25(OH) D3.
A decrease in active vitamin D (1,25 (OH)₂ D₃) results in decreased intestinal absorption of calcium, decreased bone resorption, hypocalcaemia, increased PTH secretion and hypophosphatemia. The resulting decreased calcium and phosphate in serum is insufficient for the normal mineralization of bone. The increased PTH secretion and hypophosphatemia represent a compensatory mechanism designed to correct hypocalcaemia, but it occurs at the expense of osseous demineralization caused by hyperparathyroidism (126).

1.11 Role of Calcitonin Hormone:

Calcitonin is synthesized and secreted by the para-follicular c- cells of thyroid gland. These cells are of neuroectodermal origin and migrate to the thyroid during fetal life. As for insulin and PTH, the gene encoding calcitonin is on the short arm of chromosome 11. It is 32 amino acid peptide. Calcitonin like bioactive material has been identified in thymus, lung, adrenal medulla, brain and parathyroid glands but none of these are major sources of circulating calcitonin (127). The serum calcium concentration is the major regulator of calcitonin secretion (as PTH) but the effect is opposite to that of PTH, hypercalcaemia stimulates while hypocalcaemia suppress calcitonin secretion. As with PTH, calcitonin influences serum calcium levels by action on bone, kidney and bowels. It inhibits bone resorption perhaps by reducing osteoclast
cytoplasmic motility. It binds to specific receptor in the kidney to increase calcium, phosphate, magnesium and sodium excretion and stimulate, hydroxylation in the proximal tubules to produce 1,25 dihydroxyvitamin D. This promotes intestinal calcium absorption indirectly and there have been suggestions that it may in addition have a direct but inhibitory effect. The net effect is delayed calcium absorption and this may be important in preventing postprandial hypercalcaemia and hypercalcinuria (128)

1.12 Pathophysiology

Normally the cartilage cells at epiphyseal line proliferate forming columns extending towards the shaft of the bone. The matrix in-between the cell columns get calcified, next cartilage cells degenerate and their places is invaded by capillary loops and osteoblast deposit the ostoid matrix which immediately get calcified and changed to osseous tissue. In rickets the cells does not degenerate and the capillaries does not invade the cartilage cells area except in a very irregular manner. The proliferating cartilage cells continue to grow causing thickening of the rachitic metaphysis i.e. in spite of growing but also there is no calcification.

Extreme premature infants are at risk of developing multiple deficiencies. Bone formation is a complex process, integrated by hormonal and growth factors and dependant on an adequate supply of calcium,
phosphorus, magnesium and vitamin D. The process of bone matrix formation is as critical as that of subsequent mineralization and deficiency at any stage of bone formation may give rise to a common final presentation of disturbed bone growth. The etiology of rickets of prematurity is multi-factorial but a major component is likely to be a consequence of deficiency of calcium and phosphorus rather than vit D. The vitamin D status of the infant at birth is largely dependant on the maternal vitamin D (109). There is a good evidence that 25 hydroxy cholecalciferol crosses the placenta in human with a close correlation between maternal and cord blood level, both in term and preterm. Term infants approximated maternal values while pre term shows lower level. In contrast to (1,25(OH) 2D) serum level shows no correlation between maternal and cord blood, consistent with the concept that the feta-placental unit has its own source of (1, 25(OH) 2 vit D) in utero (109,114).

At birth, the pre term infant may not have full expression of hepatic 25 hydroxylation of vit D, but the majority of studies would support the concept that this ability appears to be achieved very early in postnatal life. Calcium unlike phosphorous is not well absorbed from formula milk; the higher bioavailability in human milk can result in 70% absorption provided that phosphorous and vit D contents are adequate. In low solute milk, the absorption of calcium is in the range of 30-60% and 80-90% of this absorbed
calcium can be retained; calcium absorption increases with both gestational age and postnatal age. Absolute calcium retention increases with the amount of calcium ingested and with higher calcium intake can be greater in pre term infants than in utero. The concentration of calcium in the formula is therefore important, as is the quantity of milk consumed. Preterm infants absorb phosphorous very efficiently (86-97%), (109,113,114,124,126,129,130).

1.13 Clinical manifestations:

There is a very wide range of clinical manifestations, head sweating, abdominal protuberance (due to hypotonia, concomitant iron deficiency anemia, flaring of ribs, visceroptosis) frequent susceptibility to respiratory infections, delayed dentitions, delayed milestone, apathy, anorexia, loss of appetite, and irritability (1,3,).

Extra skeletal manifestations associated with hypocalcaemia lead to tetany, seizures, laryngospasm, and hypocalcaemic cardiomyopathy (69, 70, 75, 83,139 __142,). Often there is delayed motor development with hypotonia in the absence of hypocalcaemia. In older children and adolescents, symptoms similar to those observed in adult osteomalacia, including bone pain, waddling gait, and fatigue, may be present (7, 36, 69, 70, 90, 133). Hematological disorders are often observed in rickets, including hypochromic anemia and the
rare Von Jacksch–Luzet syndrome. This syndrome is associated with severe anemia and a profile of chronic myeloid leukemia with erythroblastosis, leukocytosis, myelocytosis, and possible myeloblastosis. The spleen and liver can be enlarged as a result of extramedullary hematopoiesis. The bone marrow is hypoplastic. This syndrome is often cured with simple vitamin D therapy (69 143,144,145).

Vitamin D deficiency causes global poor mineralization of the skeleton. Clinical and radiological bone manifestations predominate in areas of rapid bone growth, including the long bone epiphyses and the costochondral junctions (6, 28,135). This is why rickets is mostly observed before 18 months of age, with maximum frequency between the ages of 4 and 12 months. Skeletal deformities are usually a result of long-standing rickets. Hypertrophy of the costochondral junctions leads to beading and the classic rachitic rosary that progress with involution of the ribs and protrusion of the sternum (pigeon chest) and recession of the costochondral junctions and traverse depressions causing Harrison’s groove. Once the child begins to stand, gravity pushing on the lower limbs results in either inward (genu valgum) or outward (genu varum) tibial and femoral bowing. Muscle pull can also cause bone deformities in both upper and lower limbs even before the infant begins to walk. Muscle traction on the softened ribcage is responsible
for the chest deformation, leading to pecuts cranium, thoracic asymmetry, and widening of the thoracic base. Softening of the occipital area (rachitic craniotabes), enlarged sutures and fontanelle, delayed closing of fontanelle, and occipital or parietal flattening can also be observed (1.3, 5, 6, 12, 13, 36, 70). Tooth development is impaired, with delayed eruption, enamel hypoplasia, and early dental caries. The pelvic bone structure is flattened in rachitic children. Because of the high incidence of infant and maternal morbidity and mortality in rachitic women, children were often delivered by caesarian section (1, 55).

1.14 Diagnosis:

1.14.1. Clinical

1.14.2. Biochemical:

- Normal or decreased serum calcium
- Low serum phosphate,
- Low serum vitamin D
- Elevated serum alkaline phosphatase

1.14.3. Radiological: best seen in lower end of radius & ulna
• Rarified bones.

• Widening of joint spaces.

• Broadening of epiphysis

• Cupping of epiphysis.

• Fraying of epiphysis

• Fractures, usually green-stick fracture.

1.15 Prevention:

• Health education as a part of primary health care program, (18, 21, 25-28, 40,136).

• Adequate vitamin D from the fourth month onward, that can be achieved by either exposing the infants to sunlight in the morning or addition of vitamin D drops, 400 IU daily) or both (20,79,87).

• Sufficient diet for the mothers in childbearing period containing adequate amount of calcium and vitamin D (29,30,31, 35,40,42,59,66,93,94,96)

• Addition of solid food as early as possible, that contains vit D & calcium, WHO recommended starting solids at the 6th month.

• Mandatory fortification of milk and Margarine (137).
• Addition of vitamin D and folic acid for epileptic patients under treatment with phenobarbitone and epanutin.

• Addition of vitamin D drops for children of well-known families suffering from rickets. Meat consumption reduces the risk of nutritional rickets and osteomalacia (138).

1.16 Sequalee of vitamin D deficiency:

• Increased frequency of febrile convulsions, and this is exaggerated by hypocalcaemia (38,139,140).

• Tetany and hypocalcaemia convulsions (38,139,140)

• It has been proved that, there is an association between vitamin D deficiency and cardiomyopathy. The most striking biochemical finding in this illness is hypocalcaemia. Reduction in serum calcium level may affect ventricular contraction; later on may lead to ventricular failure, (141,142).

• Rickets should be considered as one the conditions that can lead to severe hematological disorders in infants such as myelofibrosis (80,143,144,145).

• Tubbs found that the volume of the posterior cranial fossa is significantly smaller in children with rickets, and 29% of the study group had an associated Chiari I malformation (146).

• Living above 35-degrees latitude for the first 10 years of life imprints on a child for the rest of his life 100% increased risk of developing multiple
sclerosis if he is vitamin D deficient, no matter where they live thereafter. Living below 35 degrees latitude for the first 10 years of life reduces the risk of multiple sclerosis by approximately 50%. Women who ingested more than 400 IU of vitamin D per day had a 42% reduced risk of developing multiple sclerosis. Similar observations have been made for rheumatoid arthritis and osteoarthritis (90,147,148,149).

- Holick, and Krause, reported that people living at high latitudes in both the United States and Europe were at higher risk of hypertension (90,150).

- Diabetes Mellitus Type I; several studies suggest that vitamin D supplementation in children reduces the risk of type 1 diabetes. Increasing vitamin D intake during pregnancy reduces the development of islet autoantibodies in offspring. For 10,366 children in Finland who were given 2000 IU of vitamin D₃ per day during their first year of life and were followed for 31 years, the risk of type 1 diabetes was reduced by approximately 80%. Among children with vitamin D deficiency, the risk was increased by approximately 200% (151__154).

- Brain, prostate, breast, and colon tissues, among others, as well as immune cells have a vitamin D receptor and respond to 1,25-dihydroxyvitamin D, the active form of vitamin D. In addition, some of these tissues and cells express the enzyme 25-hydroxyvitamin D-1₉-hydroxylase. Directly or
indirectly, 1,25 dihydroxyvitamin D controls more than 200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, apoptosis, and angiogenesis. It decreases cellular proliferation of both normal cells and cancer cells and induces their terminal differentiation. One practical application is the use of 1,25-dihydroxyvitamin D₃ and its active analogues for the treatment of psoriasis (90,149,152,154). An adequate supply of vitamin D seems to reduce the incidence rate or improve the prognosis of several cancer forms included, breast, colon cancer as well as lymphoma. People living at higher latitudes are at increased risk for Hodgkin's lymphoma as well as colon, pancreatic, prostate, ovarian, breast, and other cancers and are more likely to die from these cancers, as compared with people living at lower latitudes. Both prospective and retrospective epidemiologic studies indicate that levels of 25-hydroxyvitamin D below 20 ng per milliliter are associated with a 30 to 50% increased risk of incident colon, prostate, and breast cancer, along with higher mortality from these cancers. (90,98,121,149,152,155).

- Myopathy secondary to vitamin D deficiency is an uncommon in children (145). Studies on some cases of ichthyosis only showed improvement after they had been given vitamin D (81,157).

1.17 Treatment:
Lawrence postulated that adequate ultraviolet light or 10 mcg (400 IU) orally daily of vitamin D preparation and an adequate dietary supply of calcium and phosphorus prevent rickets. As little as 20 min/day of ultraviolet light to the face of a light-skinned baby is sufficient; however, significantly longer periods of exposure are necessary for children with melanotic skin. Human milk contains little vitamin D. Addition of phosphate is needed, vitamin D supplementation is critically important for infants living in an inner-city area and those with increased skin pigmentation. Treatment for rickets may be administered gradually over several months or in a single day dose with 15,000 mcg (600,000 IU) of vitamin D. An alternative and recommended therapy is to administer vitamin D in a single day dose (156).

Holick the leader of vitamin D deficiency and rickets researchers postulated that the best method to effectively treat and cure rickets is to give a total of 5–15 mg (200,000–600,000 IU) of vitamin D$_2$ or vitamin D$_3$ orally with adequate dietary calcium (90). These doses can be given safely either as a single-day therapy or as daily doses of 2,000–4,000 IU/day for 3–6 months (30, 86, 87). Typically there is rapid correction of both serum calcium and phosphorus levels within 6–10 days and normalization of PTH levels within 1–2 months. Alkaline phosphatase decline and healing of radiological signs of rickets are observed within 3–6 months depending on the severity of the
deficiency (30, 86). For those who may not comply with this regime, it is recommended that 5 mg (200,000 IU) of vitamin D be given as a single oral dose, with a follow-up dose of 5 mg 3 months later. It is imperative to initiate therapy with large doses of vitamin D, since giving small daily doses of 200–400 IU/d will not restore adequate stores of vitamin D as rapidly as either a single large dose or daily doses that are 10- to 20-fold higher than the recommended adequate intake (30, 85 86,87).

Nield and his colleagues comparing a single intramuscular dose (600,000 IU) of vitamin D to a lower daily oral dosage (2,000 IU) for four weeks found that patients who received the intramuscular dose responded promptly without hypervitaminosis, whereas 40 percent of infants who received the oral dosages had no or minimal response (158). The physician must determine the best treatment strategy for each patient on a case-by-case basis. For example, if compliance is a major concern, the single intramuscular dose may be more appropriate. The earliest biochemical change after treatment initiation is a rise in the level of phosphorus followed by calcium within the first week. Radiographic changes may be evident within a week, and physical examination findings may normalize within six months. No matter which treatment course is chosen, the physician has to closely monitor the child's progress. With regard to nutritional rickets, the most important role
of the primary care physician is helping parents prevent it. Along with sun protection advice, measures needed to prevent nutritional rickets must be stressed to the child's caregivers. Besides all, exclusively breastfed infants, (and some older children also) may need vitamin D supplementation. Parents should be encouraged to give their children diet that is rich in calcium (158).

Anne concluded that the best line of treatment is to (a) Educating parents to expose their children regularly to sunshine; (b) Periodic dosing (prophylaxis) of young children with vitamin D; and vitamin D fortification of foods, especially milk. Some industrialized countries still carry out the last measure. Periodic dosing and education appear to be the most practical approaches in developing countries (159).

Fraser, one of the pioneers in vitamin D deficiency rickets researches, urges caution concerning oral supplementation, because orally administered vitamin D appears to bypass the protective mechanism that prevent excessive 25 (OH) D 3 formation. The margin of safety with oral vitamin D between the nutrient requirement and toxic intake is narrow. The signs of vitamin D toxicity are usually related to hypercalcaemia, like thirst, anorexia, polyurea and the risk of metastatic calcification (39, 72).
Brody concluded that rickets heals promptly with 4,000 IU of oral vitamin D per day administered for approximately one month. During this treatment, the doctor should monitor the levels of 25-OH-D in the plasma to make certain they are raised to a normal value. The bone abnormalities (visible by X ray) generally disappear gradually over a period of 3-9 months. Parents are instructed to take their infants outdoors for approximately 20 minutes per day with their faces exposed. Children should also be encouraged to play outside. Food items that are good sources of vitamin D include cod liver oil, egg yolks, butter, and oily fish. Some food items, including milk and breakfast cereals, are also fortified with synthetic vitamin D (160).

RajaKumar, also one the big name in this field, concluded that the best line of treatment of vitamin D deficiency rickets is the use of cod-liver oil in the treatment and prevention of rickets. The eventual public health prevention initiative of fortification of milk with vitamin D lead to eradication of rickets in the United States (3).

From the above mentioned protocols of treatment, we will use the next regime, because we think it satisfy all the needed requirements. Vitamin D injection 20,000 IU every four days for ten injections given IM. One ml ampoule contains vitamin D2 (20,000 IU).
1.18 Increased intake:

Most cases of intoxication with Vit D result from excessive treatment of hypoparathyroidism, rickets, and renal osteo-dystrophy, etc, with concentrated preparation, especially ‘Stoss Therapy’ administration of 600,000 unit for prevention of rickets is not now used but was formerly a cause. Persistence of toxicity may last for many weeks, because of storage in adipose tissue. Despite its potency, an advantage of synthetic analogue 1, 25 dihydrxyvitamin D (and 1alpha hydroxy D) is its short half-life and the more rapid return to normocalcaemia after inadvertent over dose. Clinical sings reflect hypercalcaemia, are nausea, vomiting, anorexia, constipation and polyurea, FTT, nephrocalcinosis, ectopic calcifications. Vitamin D intoxication is treated by oral alendronate. Hypercalcaemia caused by Hypervitaminosis D is treated by Pamidronate infusions (161).

1.19 Health Education:

Mother’s health education can be defined as the process of influencing behavior and producing changes in knowledge, attitudes and skills necessary to maintain or improve health of the mothers or the family. Educating the medical community and those families at risk is critical to
eradicate this preventable disease, educating the nurses, medical students, and physicians are an essential step in prevention of diseases. Although it is part of prevention and treatment, it could be considered more important than treatment. Eradication of illiteracy is the responsibility of the government, and health education is the responsibility of government in partnership with Ministry of Public Health. It should be integrated as a part of primary health care programs. Spreading of knowledge on the preventive measures of vitamin D deficiency rickets in mass media is vital item in that matter. In addition to educating mothers on the proper way, procedures, proper time of exposing the children to sunlight, changing knowledge toward the wrong behavior is to be managed and eradication of wrong customs could be solved by health education, teaching the mothers how to deal with sunlight must be clarified; early introduction of the additional nutritious food is described to the mothers; also the ideal weaning practices must be considered in our program of health education. Improving the nutrition of the mothers and advising them in the necessity of good nutritious diet in childbearing period is essential. Improving the attitude of the mothers on regarding sunlight exposure is other entity should be considered while we are teaching them in benefits of sunlight. Physicians and medical assistants in the rural area are uniquely suited to take a leadership role in mothers education. They build long-term, trusting
relationships with families, providing opportunities to encourage and reinforce changes in health behavior. Mother’s education is, therefore, an essential component in the preventive measures to eradicate the diseases including rickets.

Justifications and objectives:

Justifications:
1- Nutritional rickets appears from clinical practice to be highly prevalent among Yemeni children, yet no surveys or studies have been done.

2- It has a high morbidity (and slight mortality) in childhood including susceptibility to infections, delay of growth and development, failure to thrive short stature, pathological fractures, bone deformity, school problems and physical handicap.

3- It can lead to deleterious effects in adulthood including difficult labor, reduced educational chances, high risk of economic dependence, tendency towards segregation and poverty.

4- The available preventive measures are affordable and highly cost effective.

Objectives:

The objective of the research is to:

a) Study the prevalence, risk factors, and clinical features of vitamin D deficiency rickets in Yemeni children.
b) Evaluate the health education as a part of treatment of vitamin D
deficiency rickets

c) Evaluate the efficiency of treatment and prevention with vitamin
     D injections.
CHAPTER TWO

PATIENTS AND METHODS

CHAPTER TWO : Patients and methods:

2.1 Study design:

This is a prospective community based and case control clinical trial.
2.2. Study area:

These are villages in the outskirts of the capital Sana'a. Most of them are semi-urban. The climate is nearly cold all the year the temperature ranges from 5-33°C. It is a mountainous area; its height 3000 meters above sea level. The living facilities are available in most of the villages, including electricity, water supply, paved roads, schools, TV transmission, and health centers. Ten of these villages have been selected for the study because of three reasons: (i) they are within easy reach of Sana'a; the distances range between 30-35 kilometers. (ii) Central electric current is available. (iii) There is a clinical impression that most of the cases of rickets that come from the catchments area of Sana'a, came from these villages. The villages selected include:

1-Massoud: It is the largest village whose residents are nearly 3700. It is surrounded by mountains from the north and south, situated in a valley between them, and most of the agricultural fields lie within this valley. The sunlight shines for several hours during the day. The weather is very cold. In the village, there are three Mosques and two schools; one is basic while the other is a primary and a secondary school. There is a small health center composed of three rooms and two toilets and there is a refrigerator. We used this center for our study. The
examination room and the treatment room was shared with the staff for interviewing parents, clinical examination and blood sampling. We also provided scales for weight and height measurements. One of the rooms was situated peripherally. It has two small iron windows and an iron door. This room was used for taking x-rays. The examination room was big and contains six chairs and was used as waiting room also. Explanation of the study objectives to parents and educational sessions as well as finalization of questionnaire data was done in this room. The educational sessions included nutritional advice, sessions of videos, cinema and illustrations that helped to change mother's knowledge, attitude and practice. During the clinic days, one of the toilets was used as a dark room for processing of x-ray films. We stayed at Massoud the whole period of the study (see Annex Ia, Ib and Ic).

2-Magwalla the second largest village, the distance from Sana'a, is nearly 30-40 kilometers, and lies north of Massoud, and far from it by nearly five kilometers. The total population is nearly 2600. There was no health center, but there were two schools, we used the one which was not functioning. Three of the class rooms were selected as examination and treatment room, interviewing and education room and a peripheral classroom for taking x-rays. The toilet was used as a dark
room. The radiology and laboratory equipments were transferred to this village during the study period. (see Annex II). The staff was accompanying the author in the morning time during the whole period of the study and they were paid daily incentives during the clinic days.

3-Algiraf is a small village with population of 700, and lies on the neighborhood of Massoud and it is embedded within Qat fields. It is very cold it has one private health center, and another private clinic run by a health worker. It has two schools. There is one big hall in the center of the village used for celebration, marriage and ceremony etc. We used this hall as our interviewing, examination and education room. The study cases and controls were asked to go to Massoud clinic for x-ray and blood sampling (see Annex III).

4-Algahshi is more or less in continuation of Algiraf village and lies within the same valley. The residents were 650 people; it has one small health center supervised by a nurse. The center was used for interviewing, data collection and education. Mothers were asked to take their infants to Massoud (about 3-4 kilometers far) for x-ray and laboratory testing (see Annex IV).

5-Dar Amr is a small village in continuity with Algiraf village, its residents may reach up to 430 it has the same characters as seen in
Algiraf and Algaushi. Because there was no school or health center the recruited mothers and children were asked to join the clinic in Algiraf village.

6-Almoaayen village is 15 kilometers east of Massoud and lies on a shadow of a high mountain. The residents are about 660 people; it has one school, which we used for the study. We asked the headmaster to evacuate one room for us for examination and educational sessions that were conducted by the help of school teachers. The parents were also asked to take their children to the near-by Massoud village for x-ray and blood sampling (see Annex V).

7-Alserrien, it is situated five kilometers north of Massoud and its population is about 840. It also lies on the shade of a high mountain, which blocks the sunlight in the morning until midday. There was no health center or school. We asked mothers to take their children to Massoud or Magwalla, whichever is easily accessible to them. Interviewing, examination, education, x-ray and blood sampling were done there.

2.3. Study duration

The data was collected from April 2004-to August 2006.

2.4. Study population:

The total number of population in the area is nearly 35,000; the children aged from 2-35 months, were about 1335. Most of the male residents are farmers as well as soldiers at the same time, while the females are housewives and farmers working in Qat farms.

2.4.1 Sample Size:

There were 250 cases. The size was calculated according to the equation below:

\[ N = \frac{Z^2 \times PQ}{D^2} \]

N Sample size
Z Statistical certainty =1.96
P prevalence = 17% **
Q Probability of failure (95%)
D Desired margin of error (0.05)

\[ N = \frac{(1.96)^2 \times 0.17 \times 0.95}{(0.05)^2} = \frac{0.6531}{0.0025} = 248 \]

2.4.2. Inclusion criteria

Children aged from 2-35 months who show at least two of the
clinical criteria: (see Annex VIa, VIb).

- Broadening of wrist joints
- Rosary beads on the chest
- Pigeon chest
- Delayed closure of anterior fontanel
- Bowing of legs
- Hypotonia

** M.O.P.H. Statistics

These signs are the most commonly seen in practice, easy detection from the first look to the patients, and a number of researchers used those items as a manifestations that can be accepted for diagnosis of rickets (18,94,95).

2.4. 3. Exclusion criteria:

- Age ≥ 36 months.
- Severely ill child suffering from other disease.
- Child with other obvious skeletal deformity.

2.4.4. Selection of controls:

Fifty cases were selected as controls. They were chosen randomly from the same age group (2-35 months). They were children
coming with mild respiratory infections or diarrhea and when examined they were normal without any of the obvious manifestations of rickets mentioned in inclusion criteria of case selection.

2.5. Research tools:

2.5.1. Questionnaires (Annex XI).

2.5.2. Anthropometrics measurements tools, for weight, height, and skull, chest, mid upper arm circumference.

- Weight is taken to the nearest 250 gram by using Seca scale *
- Length, height were measured to the nearest millimeter using inelastic tape measure.
- Skull, chest, MUAC, measured to the nearest millimeter using inelastic tape measure.

2.5.3. Establishment of study clinic:

- One room for interviewing, education, mother advice and children examination.
- One room for laboratory technician.
- One room for taking x-ray.
- One dark room for film processing usually the toilet was
selected.

- Clinic equipments, stethoscope, sphygmomanometer, torch, tongue depressors, inelastic tape measure and weighing scale (see Annex VIIa, VIIb).

*Seca Deutschland, Midizinsche Waagen and Messsyteme Seca GmbH & Co Kg Hammer Steindamm 9-25, 22089 Hamburg

2.5.4. Laboratory equipments:

- Centrifuge, #

- Refrigerator (belong to the health center pharmacy).

- Butterfly needles, disposable syringes, and surgical, spirits, cotton, micropipettes and markers.

- Laboratory kits* for assay of serum, calcium, phosphorous, Alkaline phosphatase and vitamin D

2.5.5. X-ray equipments

- Portable X-ray machine and its accessories (Ap-MaH-1) X-ray tube; grades, cartridges; signs (see Annex VIIIa, VIIIb)

- X-ray films, Agfa*** Manufacturer
• Fixer and developers Agfa Manufacturer
• Three metal tanks for fixer, developer and water
• Protective aprons made of lead used by the x-ray technician and the mothers

# RM. 1805 Jia Yi Ge,JiaZhouHaoYuan,9013  Bin He Da Dao, Futian District, Shenzhen, China.
*.Randox ltd., Ardmore, Diamond Road, Crumlin, Co, Antrim United Kingdom,BT29 4QY.
***Agfa –Gevaert Group, Septestraat, 2640 Mortsel ,Begium.

2.6. Research team:

a) A laboratory technician whose duty is to collect the blood samples from children, centrifuge samples, separates the sera and store in the refrigerator. When samples reach one hundred specimens then transferred to Sana’a, for assays by laboratory specialist, (Prof Saleh Al Salami, Dr Habiba A Saleh and Dr Saeed Al-Shibani) (see Annex IX).

b) An x-ray technician whose function is to prepare everything related to x-ray from construction of x-ray room, fixer and developer preparation, taking x-ray for the babies and film processing.

c) Two collaborators, one of them is taxi driver, as well as soldier, other one is a soldier. They live in Massoud village and
belong to the same tribe as the locals. They are trusted by locals. They help (i) In recruiting and convincing mothers to come to the clinic (ii) Announcing the appointment days and in introducing the team to the residents. (iii) They also fetch mothers and children who failed to come for follow up. They were paid nominal incentives for their contribution.

d) A pharmacist (the health center personnel) whose duty is to issue medications, and injections. He is living in Massoud village.

e) Three schoolteachers and two local collaborators They live in the area and help in dissemination of information between students and residents.

f) The principal investigator is responsible for,

- Planning, implementing and supervising all aspects of study.
- Examination of all the children (active surveillance).
- Selection of the cases and controls.
- Interviewing mothers and completing the questionnaires.
- Thorough Physical Examination and anthropometric measurements of cases and controls.
- Prescribing medications.
• Ensuring blood sampling, storage, transport and analysis.

• Holding explanation and educational sessions for teachers, interviewers, collaborators, residents and mothers.

• Evaluation, follow up and giving mothers assurances and feedback.

• Data analysis and thesis writing.

  g) Statistician: who entered the data, did the preliminary analysis and checked on the tests of significance.

2.7. Study procedure;

  2.7.1. The following consents were obtained:

    1- Written consent from Department of Pediatrics, University of Khartoum

    2- Written consent from Department of Pediatrics, University of Sana'a,

    3- Written consent from Deputy Minister of Public Heath, Yemen

    4- Permission from local leaders

    5- Informed verbal consent from the parents.

  2.7.2. The author holds introductory meeting with village's health workers, interviewers, helpers and collaborators. The study
objectives, methodology, and benefits were explained, any queries were cleared, and misconceptions were removed. After gaining confidence, the clinic is constructed and the clinic days were declared. The interviewers and helpers would go around the village the day before, announce to the mothers the clinic day and convince mothers to bring their children for medical check up. In the morning of the clinic day, announcement of the team arrival was made using the Mosque's Loudspeakers.

2.7.3. All attending children (sometimes-sick adults) are taken care of. Those who were ill (e.g. had gastroenteritis, respiratory, infection were examined and given treatment. From those children examined 1335 (250 of them were fulfill the inclusion criteria were considered as the desired group of study). Controls were randomly selected.

2.7.4. The study objectives and benefits were explained to the mother and informed verbal consent in obtained. The questionnaire (on birth history, nutritional, family, social and medical history) was completed. Thorough physical examination of the child was done and anthropometric measurements were taken as follows:
• Weight in kilogram (Kg) was taken using Seca scale with the baby lying down in light dress.(see Annex Xa, Xb)

• Length was measured in centimeters using inelastic tape measure, we used that tape in recumbent position for infants and children who did not stand yet, by making marks on the table opposite the farthest point in the head and the heel with the neck and legs extended. For older children we measured standing height by using a meter scale fixed to the wall. The child would stand bare footed, straight with neck extended.

• Skull circumference was measured using inelastic tape by placing the tape around the head, at a point just above the eye brows and the ears passing to the most prominent point of the occipital prominence.

• Chest circumference using inelastic tape, by placing the tape around the chest along the nipple line.

• MUAC by using inelastic tape around mid point of upper arm (between tip of acromion and olecranon)

2.7.5. Then the infant is sent for x-ray both wrist, and lastly to the laboratory for blood sampling. Three milliliters of venous blood would be drown from the cubital vein in sterile syringe. This is
centrifuged, and the serum is transferred to a small tube and stored in a refrigerator 0-8 C. When we collected one hundred specimens we transferred them to the laboratory in Sana'a for serum assay of Calcium, Inorganic phosphate, Alkaline phosphatase using Spectrophotometer, Novaspec II*. Determination of 25-hydroxy vitamin D using ELISA technique (vit D kits)** This was done in the National Central Health Laboratory in Sana’a. The entire laboratory tests were under supervision of Professor Saleh Al Salami, Director of Laboratory Department Faculty of Medicine and Health Science, Sana’a University, Dr Habibah A Saleh, laboratory specialist and Dr Said Al-Shibani, laboratory specialist.

2.7.6 While the mothers were waiting for results we asked them to be back for intervention, finalize the questionnaire by the principal investigator (see Annex XIa, XIb, XIc) and start health education sessions. Using coaching technique, the mothers were asked about their knowledge, beliefs and practices towards infant feeding, infant nutrition, and infant exposure to sunlight. Many advices were given to
them regarding the benefits of exposure to sunlight, the way of exposure, best time of exposure and asking them to add food rich in calcium and vitamin D such as eggs, cod liver oil and cheese to their children’s diet. All the team of the clinic is involved in health education. We also asked the school teachers to participate. The Imam, the leader of the mosque, was approached to announce to the people especially on Fridays the benefits of sunlight exposure especially early morning and the nude regime. Continuous education was carried on by the local helpers at home.

The workdays started at 9 am to 1 pm three times to four times /week. The long period of contacts with the residents let, them have more trust on the team considering us as members of that area. We conducted many visits to the other villages other than Massoud for searching for the new cases as well as follow up of the recruited cases that had been given treatment. In the same time the mothers were asked about their knowledge,
beliefs and practices toward infant feeding, encourage them to improve their infant nutrition and infant exposure to sunlight. Regarding Magwalla village visiting, we transferred our portable x-ray and other equipments to the non-functioning school as mentioned before, and stayed there for one month. The examination of children, educational sessions for mothers and teachers, and the selection of the cases and controls as well as blood sampling and x-ray for wrist was conducted in the same manner as what had been done in Massoud. Those villages, which were far from Massoud, we made several visits to them; interviewing, educational sessions and examinations were performed and the recruited cases were transferred to Massoud for x-ray and blood samplings.

2.7.7. The treatment schedule for every case resembles what had been done by Holick, Laurence, Nield, Anne, and Brody (90,161,163,164,166). In this study, we adopted the following regime; a) Messages on the importance of sunlight exposure of young children should be given to mothers and the general community. Health education sessions, were conducted to all recruited mothers, to improve awareness, to change the
knowledge on wrong beliefs, to improve attitude, and to proceed in correct practice regarding sunlight exposure and early introduction of additional nutritious solid food. b) Exposure of the baby to sunlight in the early morning (a weekly exposure to two minimal erythemal doses of ultraviolet radiation 20-40 minutes whole body will be sufficient. Ksiazyk estimated that skin synthesis of vitamin D could obtain the level of 10,000 IU (250ug) when the whole body is exposed to the sun (154). Holick also mentioned the same idea, he even mentioned that, hands and face exposed twice weekly to sunlight is sufficient to provide the baby with the daily requirements (90). Insist upon exposure of the body to sunlight on the morning at least 15 minutes. c) Vitamin D injection 20,000 IU every four days for ten injections given IM. d) We advised the parents to add diet rich in calcium and vitamin D such as cod liver oil, eggs and cheese. e) Calcium syrup

All cases of active rickets were managed as follows:
1- Mothers were subjected to health education on the benefit of exposing infants to sunlight in the early morning, and explaining for them the correct way of exposure to sunlight; i.e. to remove clothes of the babies during the time of exposure. The need of babies to sunlight from the second month onward was also explained. In addition, mothers were advised to add solid food to their breast feeding infants at the age of four month and in the same time to enrich their diet with calcium and vitamin D.

2- Health workers were asked to keep reminding mothers on those advices every now and then, especially during the time of vitamin D injections, and whenever they ask or come for medical help for other medical problems other than rickets.

3- Local village’s leaders (Sheikhs) were also helpful in the educational field, because they were living with them and had easy access to the families in their houses. Due to the familiarity of those people to the residents, the families would accept the advice from Al-Sheikh very easily.

4- Parents were also given nutritional advice regarding addition of food containing calcium, and vitamin D such as cod liver oil, cheese, eggs and meat.
5- Vitamin D injections had been given to all cases in the form of
one ml ampoule containing:

(i) Vitamin D2 ........................20,000 I.U

Vitamin D injections was given by the nurse intramuscular in
the upper quadrant of the buttock every four days

(10 injections) the total vitamin D given was 10 ampoules

X 20,000 IU. =200,000 IU.

6- Calcium syrup each 5 ml contain 750 mg

2.7.8. Fallow up Schedule:

The nurse and health worker in the village were keeping close follow
up of all the cases and monitoring complaints by mothers. Children
who became sick or show adverse effects were notified to the author
next day. Clinical evaluation was conducted from all the cases but
biochemical and radiological was done for 100 of the cases about 4-8
months of the day of starting the treatment.

Regular visits to the area for the purpose of ensuring treatment,
reassurance and enforcing health education. Evaluation of all treated
cases was conducted at four-eight months interval by clinical
examination, anthropometric measurement. However, a second blood
sampling (for calcium, phosphate, vitamin D and alkaline
phosphatase) as well as a follow up x-ray of the wrists could only be
done on 100 cases for logistic reasons.

2.7.9. The controls were managed as follow:

1) History and full clinical examination.

2) Anthropometric measurements.

3) Venous blood sampling for calcium, phosphorous, vitamin D
   and alkaline phosphatase.

4) X-ray of both wrists.

2.8. Data analysis and statistical methods:

The data was analyzed using the computer. The Statistical Package for
Social Sciences, System II (SPSS-11) and Epi Info V6c were used for
simple tabulation and tests of significance. For the categorical
variables, the Chi-Square test to the 0.05 significance level was used.
The 95% confidence level of serum samples means and standard
deviation was calculated. The student t-test was used to determine the
level of significance of paired data.

2.9. Ethical approval:

1) Written approval from Department of Pediatrics, and Faculty
   Research Board, Faculty of Medicine, University of Khartoum

2) Written approval from Post Graduate Medical Studies Board,
University of Khartoum

3) Written approval from Pediatric Department of Pediatrics, Faculty of Medicine and Health Sciences, Sana’a University

4) Written approval from Post Graduate Studies and Scientific Research, Sana’a University

2.10. **Budget item:** (this is all self funded).

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 4 visit for the principal investigator to Sudan</td>
<td>4000 US$</td>
</tr>
<tr>
<td>2. Lab. technician cost for the total period</td>
<td>1000 US$</td>
</tr>
<tr>
<td>3. X-ray technician cost</td>
<td>1000 US$</td>
</tr>
<tr>
<td>4. Other collaborating members</td>
<td>1000 US$</td>
</tr>
<tr>
<td>5. Transport cost</td>
<td>1500 US$</td>
</tr>
<tr>
<td>6. X-ray machine</td>
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<tr>
<td>7. X-ray accessories</td>
<td>300 US$</td>
</tr>
<tr>
<td>8. X-ray films</td>
<td>300 US$</td>
</tr>
<tr>
<td>9. X-ray developers and fixers</td>
<td>300 US$</td>
</tr>
<tr>
<td>10. Centrifuges syringes</td>
<td>400 US$</td>
</tr>
<tr>
<td>11. Lab. analysis for vitamin D</td>
<td>2450 US$</td>
</tr>
<tr>
<td>12. Ca, P, Alkaline phosphatase</td>
<td>1200 US$</td>
</tr>
<tr>
<td>13. Other expenses</td>
<td>1000 US$</td>
</tr>
<tr>
<td>14. Educational fees*</td>
<td>9000 US$</td>
</tr>
</tbody>
</table>
* Educational fees are the only item paid by Sana'a University.

2.11. Constrains:

1. Budget financing.

2. Parents refuse blood sampling. (Five patients).


4. Parents refusing x-ray. (only one patient)

5. Parents refusing cooperation from the beginning. (Two villages)

6. Some villages have no general electric supply.

7. Some villages have only local generators for electricity at night.

8. Parents refusing blood sampling in the evaluation stage. (two)

9. Some villages do not have the proper place for doing the study

10. Vit D kits were not available in Yemen. We imported it from Jordan.
Chapter Three: Results:

A total of ten villages in the surroundings of Sana'a district were selected because (i) they were within the reach of town (ii) cases of rickets from nearby Sana'a come from these villages (clinical observations and personal communication). Three villages were
excluded because of logistic reason (lack of space, lack of electricity).

The population of each village is variable and cases were selected by active surveillance. The total number of children examined (n=1335) and the cases of active rickets (n=250) as well as the controls (n=50) (who were randomly selected) is shown on Table 3.1.

3.1. Child Characteristics;

3.1.1. Age distribution of the study group and controls

In the cases group children aged below 12 months comprised 80.4%, while those aged 12-24 months, formed 16.4% in comparison to control group, where those aged below 12 months were 56% while those aged 12-24 months were 30% (see Table 3.2)

3.1.2. Sex distribution:

Among cases males constituted 46.8%, while female form 54.2% in comparison to 58% males and 42% females in controls (see Fig.3.1).

3.1.3. Duration of breast feeding:
Among cases infants who were still on breast were 85.2 %, followed by those who were breast fed for 7-12 months and they formed 12%, in comparison to controls where 78% were still on breast feeding (see Table 3.3).

3.1.4. Age of introduction of solid foods:

The highest frequency (72%) of introduction of solids among the cases was seen in those aged 3-6 months, followed by those who did not start solid food forming 24.4%, in comparison to 84% in those aged 3-6 months in controls (see Table 3.3).

3.1.5. Vaccination status:

Among cases group 76.4% were fully vaccinated and 15.6% were incompletely vaccinated, in comparison to 94% and 2% in the control group respectively, (see Table 3.3).

3.2. Socio-demographic characters:

3.2.1. Father education:

Among the cases group fathers who finished secondary school education formed the majority (40.8%) followed by those who finished primary school level (24.8%). The illiterate formed 18% and those who received higher education were 16.4% in comparison to controls where the results were 52%, 18% and 14% respectively, (see Table 3.4a).

3.2.2. Mother education:
In the cases group the illiterate mothers comprised 90.4% which is similar to mothers in the control (see Table 3.4a).

3.2.3. Father occupation:

The majority of the fathers of the cases were farmers as well as soldiers in the same time comprising 46%. Those working as employees constituted 22.4%. In comparison to controls 76% were farmers as well as soldiers. Those working as employees formed 14% (see Table 3.4a).

3.2.4. Mother occupation:

The majority (61.2%) of mothers in the cases group were farmers. The housewives comprised 38.8%. In control group, the housewives were 22% while the farmers were 78% (see Table 3.4a).

3.2.5. Family income:

The majority of the families of the cases have an income ranged between 10,000- 45,000 Yemeni Rails/month; they formed 83.2%, followed by those whose income ranged between 46,000-100,000 Yemeni Rails / month they comprised 13.6%. The controls were 92% and 6%, respectively, (see Table 3.4a).

3.2.6. Residence:

Among the cases group those residing the peri-urban area comprised
97.6%. While those living in the rural area constituted 2.4%. The ratio in controls was nearly the same (see Table 3.4b).

3.2.7. Number of rooms:
The highest ratio of the cases (63.6%) was living in houses having 1-3 rooms followed by those who have 4-6 rooms who comprised 33.2%. among the controls the percentages were 56% and 44%, respectively, (see Table 3.4b).

3.2.8. Water supply:
This is categorized according to the availability of water in the house. Those who have water supply inside their houses among the cases group comprised 96.4%. The controls bear a similar ratio (see Table 3.4b).

3.2.9. Toilet facilities:
Those families with satisfactory toilet facilities (pit-latrines) comprised 97.2% in cases group. In controls, those who have pit-latrines were 98% (see Table 3.4b).

3.2.10. Aminities:
Families who have TV in their houses formed 97.2% and 98% in the cases and controls respectively, (see Table 3.4b).
3.3. Family Characteristics:

3.3.1. Number of living siblings:

Those families who have 4-7 children comprised 53.2% in the cases group. Those having 1-3 children formed 39.6%. In controls, those families who have 4-7 children formed 64%, while those families having 1-3 children comprised 32% (see Table 3.5).

3.3.2. Number of dead siblings:

The highest number of deaths was seen in those siblings who died at age below 1st month in both cases and controls. The percentage was 3.6% and 4%, respectively, (see Table 3.5).

3.3.3. Number of children with rickets in the family

Among the cases group 58% gave no history of family members affected with rickets while 25.2% gave positive history of family members affected with rickets. Regarding the controls in 72%, there was no history of family members affected with rickets (see Table 3.5).

3.3.4. Number of handicapped children in the family

In the cases group the handicapped children in the family comprised 5.2%; in comparison to control group where the handicapped children were 2% (see Table 3.5).
3.4. **Family Behavior:**

3.4.1. Was the baby taken out door during daytime?

Mothers who took their children outdoor comprised 75%. While those who were not taking their children outdoor were 24.4%, compared to the control group where 96% of the babies were taken outdoor (see Table 3.6).

3.4.2. Did mother believe that baby needed exposure to sunlight?

Those mothers who agreed with the idea in the cases group comprised 68.4%. While those mothers who did not agree with the idea formed 23.2%. In comparison, 96% of mothers in the control group agreed with the idea (see Table 3.6).

3.4.3. Time of exposure to sunlight:

Among the cases group those mothers who exposed their children to sunlight in early morning comprised 60 %, while those mothers who did not expose their children to sunlight formed 24.4%. In comparison to 90% and 4% of mothers in the control group, respectively, (see Table 3.6).

3.4.4. Regularity of exposure to sunlight:
Mothers who exposed their children daily to sunlight comprised 52.8% of cases group. While those mothers who did not expose their children were 24.4%, in comparison to 86% and 4% in control group, respectively (see Table 3.6).

3.4.5. Dressing of children during sun exposure:

The numbers of children who were dressed during the time of exposure were 88% in cases group. While in controls those who were not dressed during exposure to sunlight comprised 90% (see Table 3.6).

3.4.6. The reason why mothers did not expose their children to sunlight:

In the cases group those mothers who exposed their children to sunlight formed 75.6%, while 15.6% of the mothers did not expose their children to sunlight because they think the children might suffer from fever and catch cold. In comparison to 96% of mothers who exposed their children to sunlight in controls (see Table 3.6.).

3.5. Clinical Features:

3.5.1. Symptoms:

Most of the parents of the cases complained that their infants had delayed sitting, walking or inability to stand, compared to their peers as well as delayed dentition, loss of activity and floppiness in comparison
to their previous siblings. Excessive sweating, mainly of the scalp hairs was also mentioned by some parents.

Convulsions, was seen in 34.8% of the cases, compared to 12% in controls (see Table 3.7).

3.5.3. Anthropometric Measurements:

The overall mean (± SD) weight detected in the cases was 7.12 (1.510) kg; compared to controls, the mean (± SD) weight was 7.65 (1.998) kg.

The overall mean (±SD) height in the cases group was 67.79 (6.978) cm compared to controls mean (±SD) height of 69.92 (9.574) cm.

The overall mean (±SD) skull circumference was 44.31(2.953) cm compared to controls mean (±SD) skull circumference of 45.18 (3.415) cm.

The overall mean (±SD) chest circumference mean (±SD) was 41.91(2.829) cm in cases compared to controls mean (±SD) chest circumference of 44.12 (4.270) cm. The overall mean (±SD) MUAC was 12.18 (1.119) compared to controls mean (±SD) MUAC of 12.88 (1.380) cm (see Table 3.8)

3.5.2. Signs:

The most frequent sign observed in the cases group was rosary beads; it was found in 96.8%, followed by widening of wrist joint that comprised
82%. Those children with deformity in the chest (pigeon chest) were forming 76.4%. The other signs that were frequently noted were potbelly and Harrison groove, which were seen in 47.6% in each; in addition to apparent Kyphosis seen in 42%. Delayed dentition and hypotonia were seen in 33.6% and 25.2%, respectively. The least frequent signs noted were bowing of the legs, knock knees, and delayed closure of anterior fontanelle as well as craniotubes; they were seen in 4%, 4%, 3.6% and 4% of cases respectively. In comparison to controls most of the above signs were absent except for hypotonia, delayed closure of anterior fontanelle, and craniotubes (see Table 3.9) and (Figure 3.2).

3.6. Biochemical characteristics of cases and controls:

3.6.1. Serum calcium level:

Normal range (8.1-10.4mg/dl) of serum calcium was seen in 27.2% of the cases in comparison to 96% in the controls, mild decrease in serum calcium level was detected in 41.2% of cases compared to 4% in controls, the remaining 31.6% of the cases group were lying in moderate to severe category that ranged between 5.8-7.3mg/dl (see Table 3.10).

3.6.2. Serum inorganic phosphate level:
The normal inorganic phosphate level of 2.7-4.5mg/dl was seen in 52% of the cases, in comparison to 88% of the controls. Those with mild decrease in the cases group were 31.6%, compared to 12% in controls; the remaining 16% of the cases were those lying on moderate to severe decrease in phosphate level, which ranged from (see Table 3.10).

3.6.3. Serum vitamin D3 level (25 Hydroxyvitamin D3):

A normal serum vitamin D3 (25OH vit.D3) level ranging between 47.7-144nmol/L was detected in 51.6% of the cases group, compared to 96% of the controls; mild deficiency (37.7-47.7 nmol/L) was seen in 30% of cases. In comparison to 4% in controls; those of moderate to severe deficiency in the cases group comprised 18.4% (see Table 3.10).

3.6.4. Serum alkaline phosphatase level:

A normal level of alkaline phosphatase (40-180 IU/L) was seen in 29.2% of the cases compared to 48% of controls; those cases with moderate elevation were 46.8%, compared to 32% in controls. Those with high level (> 360 IU/L) were 24%, compared to 20% in controls (see Table 3.8).

3.7. Radiological Findings:

Among cases widening of joint spaces and broadening of epiphysis was seen in 98%. Cupping of epiphysis was detected in 74.4% of the cases.
Fraying of epiphysis was seen in (66%) of the cases and delayed bone age was detected in 62.8% (see Table 3.11).

3.8. Diagnosis:

Active rickets was diagnosed

a) clinically

b) biochemically

c) radiologically

3.9. Management:

Discussed in methodolog

3.10. Response to treatment:

3.10.1 Clinical evaluation:

Rosary beads which were initially found in 96.8% of cases dropped to 13.2% after treatment. Broadening of the wrists initially seen in 82% of cases dropped to 12% after treatment. Delayed dentition dropped from 33.6% before treatment to 3.6% after treatment. Pigeon chest was seen initially in 76.4% of cases dropped to 6.4% after treatment. Harrison sulcus and pot belly initially found in 47.6% of cases dropped to 3% after treatment. Kyphosis dropped from 42% to
3.2% after treatment. Hypotonia also showed dramatic response and dropped from 25.2% to 0.4% after treatment.

Bowing of legs and knock-knees did not show any significant improvement, they were 4% and declined to 2.5% (see Table 3.12 and Figure 3.3).

3.10.2. Biochemical improvement (n=100):

The overall mean (±SD) serum calcium of the cases before treatment was 7.69 (0.79) mg/dl raised to 8.14 (0.67) mg/dl after treatment.

The overall mean (±SD) serum inorganic phosphate of the cases before treatment was 2.76 (0.59) mg/dl raised to 3.30 (0.63) mg/dl after treatment.

The overall mean (±SD) serum Vitamin D of the cases before treatment was 50.04 (20.13) nmol/L raised to 68.26 (17.55) nmol/L after treatment.

The overall mean (±SD) serum alkaline phosphatase before treatment was 479.07 (228.38) IU/L declining to 342.25 (163.85) IU/L after treatment (see Table 3.13).

3.10.3. Radiological improvement (n=100):

Widening of joint spaces and Broadening of epiphysis which were detected in 99% of the cases before treatment, dropped to 5% after
treatment. Cupping of epiphysis which was detected in 80% of the cases before treatment dropped to 5% after treatment. Fraying was observed in 76% of the cases before treatment was dropped to 5% after treatment. Delayed bone age, which was observed in 63% of the cases before treatment, dropped to 7% after treatment (see Table 3.14 and Figure 3.4).

These radiological changes are shown in (Figures 3.5 a and b, 3.6a and b, 3.7a and b, 3.8a and b, 3.9a and b, 3.10a and b, 3.11a and b, 3.12a and b, 3.13a and b, 3.14a and b).

Table 3.1, Names of villages visited and number of population, cases and controls.

<table>
<thead>
<tr>
<th>Village name</th>
<th>Number of population</th>
<th>Number of cases*</th>
<th>Number of rachitic cases*</th>
<th>Number of controls*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>Other 1</td>
<td>Other 2</td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
<td>----------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>1- Massaoud</td>
<td>3700</td>
<td>520</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>2- Magwalla</td>
<td>2600</td>
<td>460</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>3- Algyraf</td>
<td>700</td>
<td>80</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>4- Algahshi</td>
<td>650</td>
<td>95</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>5- Dar amer</td>
<td>430</td>
<td>30</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>6- Alsareen</td>
<td>840</td>
<td>70</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>7- Almoaayen</td>
<td>660</td>
<td>80</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>9580</strong></td>
<td><strong>1335</strong></td>
<td><strong>250</strong></td>
<td><strong>50</strong></td>
</tr>
</tbody>
</table>

* All cases and controls were children aged < 36 months.

Table 3.2 Age distribution of cases and controls
<table>
<thead>
<tr>
<th>Age (in months)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>( % )</td>
</tr>
<tr>
<td>&lt; 12</td>
<td>201</td>
<td>(80.4)</td>
</tr>
<tr>
<td>12-24</td>
<td>41</td>
<td>(16.4)</td>
</tr>
<tr>
<td>&gt;24 (14)</td>
<td>08</td>
<td>(03.2)</td>
</tr>
<tr>
<td>Total</td>
<td>250</td>
<td>(100.0)</td>
</tr>
</tbody>
</table>

X² = 17.10          p < 0.05

Table 3.3 Child Characteristics:
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Cases n</th>
<th>Cases (%)</th>
<th>Controls n</th>
<th>Controls (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (in kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average (2.5-3.5)</td>
<td>240</td>
<td>96.0</td>
<td>47</td>
<td>94</td>
<td>0.46047</td>
</tr>
<tr>
<td>Low birth weight&lt;2.5</td>
<td>10</td>
<td>04.0</td>
<td>03</td>
<td>06</td>
<td></td>
</tr>
<tr>
<td>Duration of breast feeding ( in months )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Still on breast feed</td>
<td>213</td>
<td>85.2</td>
<td>38</td>
<td>76</td>
<td>0.07177</td>
</tr>
<tr>
<td>2-6</td>
<td>6</td>
<td>02.4</td>
<td>01</td>
<td>02</td>
<td></td>
</tr>
<tr>
<td>7-12</td>
<td>30</td>
<td>12.0</td>
<td>09</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>≥12</td>
<td>01</td>
<td>00.4</td>
<td>02</td>
<td>04</td>
<td></td>
</tr>
<tr>
<td>Age of introduction of solids (in months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not yet</td>
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<td>06</td>
<td>12</td>
<td>0.01574</td>
</tr>
<tr>
<td>3-6</td>
<td>180</td>
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<td>42</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>&gt; 6</td>
<td>09</td>
<td>03.6</td>
<td>02</td>
<td>04</td>
<td></td>
</tr>
<tr>
<td>Vaccination:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to date</td>
<td>191</td>
<td>76.4</td>
<td>47</td>
<td>94</td>
<td>0.01563</td>
</tr>
<tr>
<td>Incomplete</td>
<td>39</td>
<td>15.6</td>
<td>01</td>
<td>02</td>
<td></td>
</tr>
<tr>
<td>Not vaccinated</td>
<td>20</td>
<td>08.0</td>
<td>02</td>
<td>04</td>
<td></td>
</tr>
<tr>
<td>Number of previous hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>94.0</td>
<td>48</td>
<td>96</td>
<td>0.61523</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>4.80</td>
<td>01</td>
<td>02</td>
<td></td>
</tr>
<tr>
<td>&gt;1</td>
<td>3</td>
<td>1.20</td>
<td>01</td>
<td>02</td>
<td></td>
</tr>
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Table 3.4a Socio-demographic characteristics:
<table>
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<tr>
<th>Criteria</th>
<th>Cases</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
<td>n</td>
</tr>
<tr>
<td><strong>Father Education:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n. of school years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>45</td>
<td>(18.0)</td>
<td>9</td>
</tr>
<tr>
<td>3-6</td>
<td>62</td>
<td>(24.8)</td>
<td>8</td>
</tr>
<tr>
<td>7-12</td>
<td>102</td>
<td>(40.8)</td>
<td>26</td>
</tr>
<tr>
<td>&gt;12</td>
<td>41</td>
<td>(16.4)</td>
<td>7</td>
</tr>
<tr>
<td><strong>Mother Education:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n. of school years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>226</td>
<td>(90.4)</td>
<td>45</td>
</tr>
<tr>
<td>3-6</td>
<td>22</td>
<td>(08.8)</td>
<td>3</td>
</tr>
<tr>
<td>7-12</td>
<td>02</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Father occupation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Businessman</td>
<td>12</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Farmer + Soldier</td>
<td>(04.8)</td>
<td></td>
<td>38</td>
</tr>
<tr>
<td>Employee</td>
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<td></td>
<td>7</td>
</tr>
<tr>
<td>Farmer</td>
<td>(46.0)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Skilled laborer</td>
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<td>(22.4)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Mother Occupation:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>39</td>
<td>(15.6)</td>
<td>11</td>
</tr>
<tr>
<td>Farmer</td>
<td>28</td>
<td>(11.2)</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>97</td>
<td>(38.8)</td>
<td>153</td>
</tr>
<tr>
<td>Family income in YR.*</td>
<td>Cases</td>
<td>Controls</td>
<td>P value</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------</td>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>10.000-45.000</td>
<td>208</td>
<td>46 (92.0)</td>
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</tr>
<tr>
<td>46.000-100.000</td>
<td>(83.2)</td>
<td>3 (06.0)</td>
<td></td>
</tr>
<tr>
<td>&gt; 100.000</td>
<td>34</td>
<td>1 (02.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(13.6)</td>
<td>1 (02.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.28189</td>
<td></td>
</tr>
</tbody>
</table>

* Yemeni Riyal / mon

Table 3.4b Socio-demographic characteristics:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Cases n.</th>
<th>Controls n</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td></td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Periurban</td>
<td>244</td>
<td>49 (98)</td>
<td>0.73229</td>
</tr>
<tr>
<td>Rural</td>
<td>(97.6)</td>
<td>1 (02)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>(02.4)</td>
<td></td>
</tr>
<tr>
<td>Number of Rooms</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1-3</td>
<td>159</td>
<td>28 (56)</td>
<td>0.59831</td>
</tr>
<tr>
<td></td>
<td>(63.6)</td>
<td>20 (40)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>83</td>
<td>2 (04)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(33.2)</td>
<td>2 (04)</td>
<td></td>
</tr>
<tr>
<td>&gt;6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electricity</td>
<td>08</td>
<td>48 (96)</td>
<td>0.58006</td>
</tr>
<tr>
<td>Yes</td>
<td>(03.2)</td>
<td>2 (04)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>246</td>
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<td></td>
</tr>
<tr>
<td>Service</td>
<td>Total</td>
<td>Piped-in</td>
<td>Piped-out</td>
</tr>
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<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Water supply</td>
<td></td>
<td>241</td>
<td>48 (96)</td>
</tr>
<tr>
<td>Toilet</td>
<td></td>
<td>243</td>
<td>49 (98)</td>
</tr>
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<td>Amenities</td>
<td></td>
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<td>7</td>
<td>1 (02)</td>
</tr>
<tr>
<td>T.V.</td>
<td></td>
<td>243</td>
<td>49 (98)</td>
</tr>
<tr>
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</tr>
</tbody>
</table>
Table 3.5 Family characteristics:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Cases n (%)</th>
<th>Controls n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of living siblings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>99 (39.6)</td>
<td>16 (32)</td>
<td>0.34104</td>
</tr>
<tr>
<td>4-7</td>
<td>133 (53.2)</td>
<td>32 (64)</td>
<td></td>
</tr>
<tr>
<td>&gt;7</td>
<td>18 (07.2)</td>
<td>02 (04)</td>
<td></td>
</tr>
<tr>
<td>Number of siblings who died aged</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 month</td>
<td>09 (03.6)</td>
<td>02 (04)</td>
<td>0.70053</td>
</tr>
<tr>
<td>1-11 months</td>
<td>06 (02.4)</td>
<td>02 (04)</td>
<td></td>
</tr>
<tr>
<td>1-5 years</td>
<td>09 (03.6)</td>
<td>01 (02)</td>
<td></td>
</tr>
<tr>
<td>Number of children with rickets in the family.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>145 (58.0)</td>
<td>36 (72)</td>
<td>0.00101</td>
</tr>
<tr>
<td>yes</td>
<td>63 (25.2)</td>
<td>01 (02)</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>42 (16.8)</td>
<td>13 (26)</td>
<td></td>
</tr>
<tr>
<td>Number of handicapped children in the family.</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>222 (88.8)</td>
<td>48 (96)</td>
<td>0.30054</td>
</tr>
<tr>
<td>yes</td>
<td>13 (05.2)</td>
<td>01 (02)</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>15 (06.0)</td>
<td>01 (02)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.6 Characteristics of family behavior:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Cases n</th>
<th>(%)</th>
<th>Controls n</th>
<th>(%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Was the baby taken out door during day time?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>189</td>
<td>(75.6)</td>
<td>48</td>
<td>(96)</td>
<td>0.00272</td>
</tr>
<tr>
<td>No</td>
<td>61</td>
<td>(24.4)</td>
<td>2</td>
<td>(04)</td>
<td></td>
</tr>
<tr>
<td><strong>Did mother believe baby needed exposure to sunlight?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agree</td>
<td>171</td>
<td>(68.4)</td>
<td>48</td>
<td>(96)</td>
<td>0.00012*</td>
</tr>
<tr>
<td>Disagree</td>
<td>58</td>
<td>(23.2)</td>
<td>00</td>
<td>(00)</td>
<td></td>
</tr>
<tr>
<td>Uncertain</td>
<td>21</td>
<td>(08.4)</td>
<td>02</td>
<td>(04)</td>
<td></td>
</tr>
<tr>
<td><strong>Time of exposure to sunlight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early morning</td>
<td>150</td>
<td>(60.0)</td>
<td>45</td>
<td>(90)</td>
<td>0.00066</td>
</tr>
<tr>
<td>Noon</td>
<td>16</td>
<td>(06.4)</td>
<td>2</td>
<td>(04)</td>
<td></td>
</tr>
<tr>
<td>Late afternoon</td>
<td>23</td>
<td>(09.2)</td>
<td>1</td>
<td>(02)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>61</td>
<td>(24.4)</td>
<td>2</td>
<td>(04)</td>
<td></td>
</tr>
<tr>
<td><strong>Regularity of exposure:</strong></td>
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<td></td>
</tr>
<tr>
<td>Daily</td>
<td>132</td>
<td>(52.8)</td>
<td>43</td>
<td>(86)</td>
<td>0.00022</td>
</tr>
<tr>
<td>3-4time/week</td>
<td>44</td>
<td>(17.6)</td>
<td>4</td>
<td>(08)</td>
<td></td>
</tr>
<tr>
<td>1-2time/week</td>
<td>13</td>
<td>(05.2)</td>
<td>1</td>
<td>(02)</td>
<td></td>
</tr>
<tr>
<td>No exposure</td>
<td>61</td>
<td>(24.4)</td>
<td>2</td>
<td>(04)</td>
<td></td>
</tr>
<tr>
<td><strong>Number of children dressed at time of exposure to sunlight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dressed</td>
<td>220</td>
<td>(88.0)</td>
<td>5</td>
<td>(10)</td>
<td>0.00000</td>
</tr>
<tr>
<td>Undressed</td>
<td>30</td>
<td>(12.0)</td>
<td>45</td>
<td>(90)</td>
<td></td>
</tr>
<tr>
<td><strong>Reason why mothers did not expose their children to sunlight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coldness &amp; fever</td>
<td>39</td>
<td>(15.6)</td>
<td>00</td>
<td>(00)</td>
<td>0.00367*</td>
</tr>
<tr>
<td>No need**</td>
<td>13</td>
<td>(05.2)</td>
<td>01</td>
<td>(02)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>(%)</td>
<td>Controls</td>
<td>(%)</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td>-----</td>
<td>-----------</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>163</td>
<td>(65.2)</td>
<td>44</td>
<td>(88)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>87</td>
<td>(34.8)</td>
<td>6</td>
<td>(12)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>250 (100.0)</td>
<td></td>
<td>50 (100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ P < 0.05 \]

* p value is calculated after adding cells with zero value.
** Mothers who said, the baby needed sunlight only on the 1st two months.
Table 3.8 Anthropometric measurements:

<table>
<thead>
<tr>
<th>Anthropometric measurement</th>
<th>Cases</th>
<th>Controls</th>
<th>P. value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight in kg</td>
<td>7.12</td>
<td>7.65</td>
<td>0.154</td>
</tr>
<tr>
<td>Height in cm</td>
<td>67.79</td>
<td>69.92</td>
<td>0.152</td>
</tr>
<tr>
<td>Skull circumference in cm</td>
<td>44.31</td>
<td>45.18</td>
<td>0.115</td>
</tr>
<tr>
<td>Chest circumference in cm</td>
<td>41.91</td>
<td>44.12</td>
<td>0.719</td>
</tr>
<tr>
<td>MUAC in cm</td>
<td>12.18</td>
<td>12.88</td>
<td>0.760</td>
</tr>
</tbody>
</table>

* One standard deviation.
** Using student t test
Table 3.9 Clinical features of cases of rickets compared to controls:

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Delayed Closure of anterior fontanelle</td>
<td>10 (04.0)</td>
<td>01 (02)</td>
</tr>
<tr>
<td>Craniotabes</td>
<td>09 (03.6)</td>
<td>00 (00)</td>
</tr>
<tr>
<td>Delayed Dentition</td>
<td>84 (33.6)</td>
<td>01 (02)</td>
</tr>
<tr>
<td>Rosary Beads</td>
<td>242 (96.8)</td>
<td>00 (00)</td>
</tr>
<tr>
<td>Pigeon Chest</td>
<td>191 (76.4)</td>
<td>00 (00)</td>
</tr>
<tr>
<td>Harrison Sulcus</td>
<td>119 (47.6)</td>
<td>00 (00)</td>
</tr>
<tr>
<td>Kyphosis</td>
<td>105 (42.0)</td>
<td>00 (00)</td>
</tr>
<tr>
<td>Potbelly</td>
<td>119 (47.6)</td>
<td>01 (02)</td>
</tr>
<tr>
<td>Broadening of the wrist</td>
<td>205 (82.0)</td>
<td>00 (00)</td>
</tr>
<tr>
<td>Bow Legs</td>
<td>10 (04.0)</td>
<td>00 (00)</td>
</tr>
<tr>
<td>Knock Knees</td>
<td>10 (04.0)</td>
<td>00 (00)</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>63 (25.2)</td>
<td>01 (02)</td>
</tr>
</tbody>
</table>
Table 3.10. Biochemical features of cases and controls:

<table>
<thead>
<tr>
<th>Character</th>
<th>cases</th>
<th>controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
<td>n</td>
</tr>
<tr>
<td>Serum Calcium (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal 8.1 – 10.4</td>
<td>68</td>
<td>(27.2)</td>
<td>48</td>
</tr>
<tr>
<td>Low - Mild 7.4 – 8.0</td>
<td>103</td>
<td>(41.2)</td>
<td>2</td>
</tr>
<tr>
<td>-Moderate 6.6 – 7.3</td>
<td>66</td>
<td>(26.4)</td>
<td>0</td>
</tr>
<tr>
<td>-Severe 5.8 – 6.5</td>
<td>13</td>
<td>(05.2)</td>
<td>0</td>
</tr>
<tr>
<td>Serum phosphate (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal 2.7 – 4.5</td>
<td>130</td>
<td>(52.0)</td>
<td>44</td>
</tr>
<tr>
<td>Low - Mild 2.2 – 2.6</td>
<td>79</td>
<td>(31.6)</td>
<td>6</td>
</tr>
<tr>
<td>-Moderate 1.7 – 2.1</td>
<td>31</td>
<td>(12.4)</td>
<td>0</td>
</tr>
<tr>
<td>-Severe 1.2 – 1.6</td>
<td>10</td>
<td>(04.0)</td>
<td>0</td>
</tr>
<tr>
<td>Serum Vitamin D (nmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal 47.7 -144</td>
<td>129</td>
<td>(51.6)</td>
<td>48</td>
</tr>
<tr>
<td>Low - Mild 37.7 -47.6</td>
<td>75</td>
<td>(30.0)</td>
<td>2</td>
</tr>
<tr>
<td>-Moderate 27.5 -37.6</td>
<td>37</td>
<td>(14.8)</td>
<td>0</td>
</tr>
<tr>
<td>-Severe &lt; 27.4</td>
<td>09</td>
<td>(03.6)</td>
<td>0</td>
</tr>
<tr>
<td>Serum Alkaline phosphatase(IU/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal 40 – 180</td>
<td>73</td>
<td>(29.2)</td>
<td>24</td>
</tr>
<tr>
<td>Moderate elevation 180- 360</td>
<td>117</td>
<td>(46.8)</td>
<td>16</td>
</tr>
<tr>
<td>High elevation &gt; 360</td>
<td>60</td>
<td>(24.0)</td>
<td>10</td>
</tr>
</tbody>
</table>

* P is calculated after adding cells with zero values.
Table 3.11 Radiological features of cases and controls:

<table>
<thead>
<tr>
<th>Radiological findings</th>
<th>Cases (n = 250)</th>
<th>Controls (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present (%)</td>
<td>Absent (%)</td>
<td></td>
</tr>
<tr>
<td>Widening of joint spaces</td>
<td>246 (98.4)</td>
<td>4 (01.6)</td>
<td>0.00000</td>
</tr>
<tr>
<td>Broadening of epiphysis</td>
<td>245 (98.0)</td>
<td>5 (02.0)</td>
<td>0.00000</td>
</tr>
<tr>
<td>Cupping of epiphysis</td>
<td>186 (74.4)</td>
<td>64 (25.6)</td>
<td>0.00000</td>
</tr>
<tr>
<td>Fraying of epiphysis</td>
<td>165 (66.0)</td>
<td>85 (34.0)</td>
<td>0.00000</td>
</tr>
<tr>
<td>Delayed bone age</td>
<td>157 (62.8)</td>
<td>93 (37.2)</td>
<td>0.00000</td>
</tr>
</tbody>
</table>
3.12. Clinical evaluation before and after treatment of cases of active rickets:

<table>
<thead>
<tr>
<th>Signs</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present n (%)</td>
<td>Absent n (%)</td>
<td>Present n (%)</td>
</tr>
<tr>
<td>Delay C.A.F.*</td>
<td>10 (04.0)</td>
<td>240 (96.0)</td>
<td>03 (01.2)</td>
</tr>
<tr>
<td>Craniotabes</td>
<td>09 (03.6)</td>
<td>241 (96.4)</td>
<td>00 (00.0)</td>
</tr>
<tr>
<td>Delayed Dentition</td>
<td>84 (33.6)</td>
<td>166 (66.4)</td>
<td>09 (03.6)</td>
</tr>
<tr>
<td>Rosary Beads</td>
<td>242 (96.8)</td>
<td>8 (03.2)</td>
<td>33 (13.2)</td>
</tr>
<tr>
<td>Pigeon Chest</td>
<td>191 (76.4)</td>
<td>59 (23.6)</td>
<td>16 (06.4)</td>
</tr>
<tr>
<td>Harrison Sulcus</td>
<td>119 (47.6)</td>
<td>131 (52.4)</td>
<td>7 (02.8)</td>
</tr>
<tr>
<td>Kyphosis</td>
<td>105 (42.0)</td>
<td>145 (58.0)</td>
<td>8 (03.2)</td>
</tr>
<tr>
<td>Potbelly</td>
<td>119 (47.6)</td>
<td>131 (52.4)</td>
<td>9 (03.6)</td>
</tr>
<tr>
<td>Broad of wrist</td>
<td>205 (82.0)</td>
<td>45 (18.0)</td>
<td>30 (12.0)</td>
</tr>
<tr>
<td>Bow Legs</td>
<td>10 (04.0)</td>
<td>240 (96.0)</td>
<td>6 (02.4)</td>
</tr>
<tr>
<td>Knock Knees</td>
<td>10 (04.0)</td>
<td>240 (96.0)</td>
<td>5 (02.0)</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>63 (25.2)</td>
<td>187 (74.8)</td>
<td>1 (00.4)</td>
</tr>
</tbody>
</table>

* C.A.F. = closure of anterior fontanel.
Table 3.13. Biochemical evaluation of cases of active rickets before and after treatment:

<table>
<thead>
<tr>
<th>Biochemical parameters in serum</th>
<th>Before treatment (n = 100)</th>
<th>After treatment (n = 100)</th>
<th>P. value #</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Means</td>
<td>SD</td>
<td>Means</td>
</tr>
<tr>
<td>Calcium*</td>
<td>7.69</td>
<td>(0.78)</td>
<td>8.14</td>
</tr>
<tr>
<td>Phosphorus*</td>
<td>2.76</td>
<td>(0.59)</td>
<td>3.30</td>
</tr>
<tr>
<td>Vitamin D**</td>
<td>50.04</td>
<td>(20.13)</td>
<td>68.26</td>
</tr>
<tr>
<td>Alkaline phosphatase***</td>
<td>479.07</td>
<td>(228.38)</td>
<td>342.25</td>
</tr>
</tbody>
</table>

* In mg/dl  
** In nmol/L  
*** In IU/L  
# Student t-test is used
Table 3.14. Radiological findings of cases of active rickets before and after treatment:

<table>
<thead>
<tr>
<th>Radiological findings</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td></td>
<td>n (% )</td>
<td>n (% )</td>
<td>n (%)</td>
</tr>
<tr>
<td>1-Widening of joint spaces</td>
<td>99 (99)</td>
<td>1 (1.0)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>2-Broadening of epiphysis</td>
<td>99 (99)</td>
<td>1 (1.0)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>3-Cupping of epiphysis</td>
<td>80 (80)</td>
<td>20(20)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>4-Fraying of epiphysis</td>
<td>76 (76)</td>
<td>24(24)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>5-Delayed bone age</td>
<td>63 (63)</td>
<td>37(37)</td>
<td>7 (7)</td>
</tr>
</tbody>
</table>
Figure 3.3 Clinical features of the cases of active rickets before and after treatment (n=100).
Figure 3.2. Clinical features of cases and controls

<table>
<thead>
<tr>
<th>Condition</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosary beads</td>
<td>82</td>
<td>76.4</td>
</tr>
<tr>
<td>Broadening of...</td>
<td>96.8</td>
<td>82</td>
</tr>
<tr>
<td>Pigeon chest</td>
<td>96.8</td>
<td>82</td>
</tr>
<tr>
<td>Harrison sulcus</td>
<td>47.6</td>
<td>42</td>
</tr>
<tr>
<td>Pot belly</td>
<td>47.6</td>
<td>42</td>
</tr>
<tr>
<td>Kyphosis</td>
<td>47.6</td>
<td>42</td>
</tr>
<tr>
<td>Delayed dentition</td>
<td>33.6</td>
<td>25.2</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Bowleg</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Knock knee</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Delayed closure of...</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Craniotabes</td>
<td>3.6</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>46.8</td>
<td>58</td>
</tr>
<tr>
<td>Female</td>
<td>53.2</td>
<td>42</td>
</tr>
</tbody>
</table>
Figure 3.4 Radiological evaluation of active rickets cases before and after treatment (n=100).

Widening of joint spaces: Controls 0%, Cases 99%
Broadening of epiphysis: Controls 0%, Cases 99%
Cupping of epiphysis: Controls 5%, Cases 85%
Fraying of epiphysis: Controls 5%, Cases 74%
Delayed bone age: Controls 7%, Cases 63%
CHAPTER FOUR

DISCUSSION
4. DISCUSSION:

4.1. The prevalence of rickets and associated risk factors:

This is a clinical trial designed to evaluate the impact of health education and vitamin D therapy on the management of vitamin D deficiency rickets in Yemeni children. It is also a community based case-control study of the prevalence, risk factors and clinical features of rickets. In this study it was found that 18.7% of the children aged 2-35 months in the study area were suffering from vitamin D deficiency rickets. They compose 250 cases of active rachitic rickets out of 1335 children in this age group. The study area is a representation of the surroundings of Sana’a district, because all villages and the residents were similar to each other. They all have similar characteristics, like cold weather, the same altitude, and availability of living facilities. Most of the male residents were soldiers and farmers as well. Females were farmers and housewives at the same time. There are only two studies done in rickets in Yemen by Underwood and Banajeh (74, 75). The results of these two studies showed disparity from our study. They reported a prevalence of rickets of 27%, 50% respectively; this could be explained, by the fact that in both of these studies the
diagnosis of rickets is based on clinical ground only without any biochemical or radiological investigations unlike ours. In addition, Underwood conducted his study in a rural health clinic, and his data was collected from ill children who attended the clinic seeking medical advice for illnesses other than rickets. On the other hand, Banajeh conducted his study in Hospitalized patients with severe pneumonia and were found to have concomitant rickets, which may account for the high prevalence rate (74).

Our study showed that two-third of the cases of the rachitic cases was seen on those below 12 months of age. This could be explained by the fact that breast milk is insufficient in providing vitamin D after the fourth month of life especially if their mothers were vitamin D deficient as well (50,161). Our results were similar to Hatun from Turkey and Thomson of Australia (20,101). They reported that the highest prevalence of rickets was observed in the same age group. Similarly, El-Hag and Karrar from Sudan showed that 42% of the cases of rickets were below 12 months of age (80).

This is in contrast to the findings of Al-Mustafa in Saudi Arabia, Belachew and Wandal in Ethiopia, Robinson in Australia and Thacher and Graff in Nigeria (22, 25, 27, 68, 87). These studies
reported that the predominant age of rickets was seen in children above one year. This may be explained by the fact that, all these studies were hospital based which means that the parents usually notice the rachitic process of their children late, only when they observed their children had delayed milestones or delayed dentition compared to their peers (22, 27, 68, 99).

Ideally the age distribution of the controls should match that of the cases, but because samples were randomly taken, some villages brought most of their children of the same age group, which forced us to take from them the controls (i.e. all were of older age). On the other side, some villages only brought to us most the cases those of young age group). In addition to small size specimen of controls. Female to male ratio of the cases was matching that of controls, with no significant difference between them. There was also no significant difference regarding birth weight, duration of breast-feeding and number of previous hospitalization. The study also showed those children who were still on breast-feeding were forming four-fifth of the cases, which means that the children stayed long duration on breast-feeding without supplementation. It may be true that the long period of breast feeding delayed supplementation participate in the
occurrence of the vitamin D deficiency rickets, as reported in similar studies (23,33,35,47-50,60,96,161).

All children in our study group were breast fed, and the rate was higher than the recorded numbers in Al-Mustafa and Najada, who reported 80% and 82.9% respectively (22,71).

According to the American Academy of Pediatrics (AAP) there are no rigid rules on when to start on infants' solid food. This had been mentioned in Holick report 2007 (50). Also we observed that, the age of introduction of solid food was found more common among the age group 3-6 months, it is seen in 72% of the cases compared to 84% in controls with statistical significant, (p <0.05). This means that delay in of introduction of solid food is a risk factor, which is true especially if the mothers were also vitamin D deficient. This was consistent with what have been mentioned in other studies (47__50, 52__54, 61,100,101). Although some mothers introduced solid food early to their babies, still some children suffered from rickets. The explanation for that was; they introduce the common Yemeni food, which is formed of Assida, and potato's soup, which are deficient in vitamin D and other nutritious elements.
Regarding vaccination, four fifth of the cases were completely vaccinated, compared to controls where all of them were completely vaccinated. This is statistically significant (P < 0.05). This reflects the lack of awareness of the mothers in the importance of vaccination. Even EPI program when applying the program of house to house vaccination, still mothers in the area did not realize the need for vaccination. This is supported by the finding that the vast majority (nine out of ten) of the mothers of the study cases were illiterate compared to 70% in controls which is statistically significant (p<0.05). This could be considered one of the most important risk factors. This finding is in agreement with those reported by Hartman, Wandale, and Lulseged (18, 27, 85).

Our findings revealed that both cases and controls were similar in term of paternal education, family income, residence, housing, electricity, water supply, toilet facilities and amenities, family size, number of sibling deaths and number of handicapped children, all have no significant difference between the cases and controls and seem to have no bearing on the development of rickets in this population. The study showed that the occupation of the fathers was statistically significant factor in comparison to controls, with p < 0.05,
also the mothers occupation showed statistically significant difference with (p<0.05). This may be explained by the small size of the controls. The study also showed that the majority of the cases were from low and middle socio-economic classes and there was no significant difference between the cases and controls. And this is true in our situation, because it proved that, it is a matter of deficient exposure to sunlight and lack of awareness rather than money, because sunlight is free. This could also be attributed to illiteracy and lack of awareness and may be considered an important risk factors. These observations were similar to previous reports in the literature (18, 19, 25, 27, 86). Almost all the children in the study cases and controls were residing the peri-urban areas and there was no significant difference between cases and controls. A high percentage of children with nutritional rickets residing the peri-urban area were similarly reported by Thacher and Belachew from Ethiopia and Saddiqi from Pakistan (16, 25, 28). In controversy to Nesby from USA who reported that, all the cases of rickets were residing in the urban area (59).

All families were having amenities in their houses, but most of the mothers were illiterates and were not aware of the disease and
risk factors. That could be explained by the fact that there are few health educations programs on the National TV and radio, which is a shortcoming the duty of the primary health program.

Out of the many other family characteristics asked about in the questionnaire, there is an important one. It was the presence of the other sibling or family member with rickets. This is significantly present among cases compared to controls (p<0.001). Although this would suggest familial or some environmental factors rather than nutritional rickets but in this set up it is more of a reflection of lack of awareness of need of exposure to sunlight. Most of these children had spontaneous recovery once they were able to run around. This phenomena has been observed by Thacher in Nigeria, who also reported that 3.1% of the first-degree relatives were rachitic (67).

4.2. Family behavior and impact of intervention:

The study showed that three quarters of the mothers of the cases took their children outdoor, compared to nearly all the mothers of controls, which is statistically significant (p<0.05). This tallies with similar observations reported in the literatures (55-57, 60, 66, 69, 72). However, in spite of such a high percentage of mothers exposing their children to sunlight, still these children developed rickets. This is
clearly explained by the fact that mothers used to expose their children to sunlight while they were dressed and even completely covered with clothes, for fear of catching cold (p<0.000 when comparing cases to controls). This finding is inconsistent with Al-Mustafa study in Saudi Arabia, where he reported that 90% of his cases were never exposed to sunlight (22). Our study also showed that mothers who believed in the need of babies to sunlight were significantly less among mothers of the cases compared to those of the controls (p<0.05). Also those mothers who used to expose their children to sunlight in the early morning were three fifth of the cases, in comparison to nine tenth of controls, which is also statistically significant (p<0.05). Moreover only half of those mothers of the cases were regularly exposing their children to sunlight compared to four fifth of mothers of controls, with statistically significant value (p<0.05).

These findings indicate that all the parameters of optimum exposure of infants to sunlight are significantly different among cases compared to controls. This included taking the infants outdoor (p<0.002), regularity (p<0.0002), undressed (p<0.000) and during early morning (p<0.0006). Such observations are not surprising and
have been reported in several similar studies (17, 20, 22, 23, 24, 40, 53, 166).

The intense and frequent health education sessions held by the team in this area has changed mother’s traditional beliefs regarding the need for sunlight after the first two months of age. The phobia from fever and caching cold has been almost eliminated by health education sessions by asking mothers to expose only the lower limbs of the baby to sunlight during the cold days (24).

Although the majority of mothers were exposing their children to sunlight, still they were suffering from rickets this could be explained by the fact that (i) mothers used to expose their children dressed, (ii) not in the morning, (iii) not regularly daily. Their knowledge, attitude and practice were changed after health education sessions. Evaluation of the benefit of health education as an integral part of management has been clearly observed by the changing patterns of beliefs, attitude and practice especially with regard to the value of exposing children to sunlight. As the findings of the study revealed that before treatment three quarter of the cases were exposed to sunlight this ratio raised to 99% after treatment and health education sessions, giving statistically significant results (p<0.05).
Similarly, the time of exposure of the cases to sunlight, the regularity and duration of exposure were all statistically significantly different after management. Regarding the time of exposure three fifth of the cases exposed their children to sunlight in the early morning, after health education sessions this percentage raised to 99%. This is due to change in knowledge, improvement in attitude, and adoption of good practice. The study also showed that there had been a dramatic good response regarding the regularity of exposure of the children to sunlight after health education sessions and changing in knowledge and attitude of the mothers. This is clearly demonstrated in the results. The children were divided into three groups; those who were exposed to sunlight regularly were half of the cases. Those children who were exposed to sunlight but irregularly were one fifth, those children who were not exposed to sunlight at all were forming one fifth of the cases. All those groups were raised to nine tenth after treatment with (p<0.000). Moreover those children who were exposed to sunlight and were dressed before health education sessions were 88%, which dropped to 10% after management with p <0.000 indicating improved awareness of the mothers, better knowledge, attitude, and practice in the proper way of exposing their children to sunlight. In response to
the enquiry why some mothers did not expose their children to sunlight, their replies were that the baby needed the sunlight only in the first two months of life. Their percentage was one fifth of the cases. This wrong belief had been eliminated and clarified after health education sessions to all of them, and their percentage dropped to zero and was statistically significant (p<0.003). To avoid apprehension and fear of catching cold during cold weather we advised the mothers to expose only the lower limbs to sunlight, which is sufficient to satisfy the daily requirements as described by many researchers (24, 50, 56).

The health education sessions had changed the thinking and the behavior of the mothers, changed the mood, improved their knowledge, attitude and practice on the issue of the benefit of sunlight exposure of infant. Such a positive change was reported by Mayako from Japan. He concluded that vitamin D deficiency is best managed by education and disease prevention (141). Moreover many other reports in the literature were sharing these educational benefit of sunlight (45, 46, 55, 56, 57, 60, 66, 71, 72,).

4.3. Clinical features and evaluation of clinical response:
Most of the mothers enrolled in the study complained of delayed milestones, and floppiness of their children in comparison to their peers; convulsions were also encountered in one third of the cases. Other workers reported similar observations (63, 99, 105, 139, 144, 145, 160). Interestingly Hatun, from Turkey reported 78.8% of his study cases were presented with convulsions (20).

The anthropometric measurement (mean ±SD) namely weight, height, skull circumference, chest circumference, and MUAC) were evaluated and there was no significant difference between cases and controls. This was similar to reported figures by Al- Mustafa (22).

Assessment of clinical findings in cases and controls showed that, more than four fifth of the cases had rosary beads, and broadening of wrist joints. Those who had pigeon chest were three fourth; while those had Harrison, sulcus and potbelly were each seen in half of the cases. Kyphosis was seen in three fifth and hypotonia was observed one fifth of the cases. All these features were not detected in the controls except for delayed dentition, potbelly, and hypotonia, and they were observed in a small proportion. Similar to our observations, Ladahani from UK, Saddiqi from Pakistan, and Wandel from Ethiopia detected 73%, 66%, 40% respectively, of their
study, cases were showing clinical signs of rickets, (65, 28, 27). Thatcher from Nigeria, in one of his numerous studies reported that, broadening of the wrists and costochondral junction swellings were detected in 72%, 76% respectively (67). In controversy to our study the most surprising data was reported from Turkey by Hatun, where he did not detect any clinical sign in study cases (20). Also Goel from UK, Akopede from Nigeria, detected only 1% and 4% respectively, of their study cases were showing clinical signs of rickets, (44,86). In controversy to our study, Oginin reported the other surprising figures from Nigeria where he recorded high figures of knock-knees and cubitus vulgus and varus in Nigeria, and attributed them to calcium deficiency, (159). Bonnet from Spain also reported knock-knees in most of his study cases (45). Also Robinson from Australia reported bowing of the legs in 22 % in his study cases (63).

Clinical re-evaluation of the cases, after treatment, revealed dramatic improvement in most of the clinical signs; rosary beads in the chest were seen in almost all the cases before treatment, dropped to 13.2% after treatment, which is statistically significant (p < 0.05). Broadening of wrist joints was observed in four fifth dropped to one tenth (p<0.05) Pigeon chest was observed in three fourth of cases,
dropped to < one tenth (p<0.05). Harrison Sulcus was seen in half of the cases dropped to 2.8% (p<0.05). Potbelly abdomen also observed in half of the cases declined to 3.6%, (p<0.05). Kyphosis also was observed in three fifth of the cases, declined to 3.2%, (p<0.05). Hypotonia seen in one fifth of the cases dropped significantly to 0.4% after treatment (p <0.05). However, the results did not revealed significant drop regarding bowing of the legs, knock-knees and delayed closure of anterior fontanelle. All the above-mentioned signs, which showed significant improvement, were coinciding the observations of Kutluk from Turkey, Bonnet from Spain and Ladahani from England where they reported complete improvement in signs of rickets after treatment,(26,45, 65).

4.4. Biochemical evaluations of active rickets:

The base line serum assay of calcium, inorganic phosphate, and vitamin D has been empirically categorized to, normal, and mild, moderate or severe deficiency. In each of these serum levels in all categories, among the cases documented highly significantly lower levels compared to those of controls (p<0.05). A normal serum level in one quarter of the cases is not surprising and similar observations were reported in the literature (22, 23, 39, 46, 60, 62, 87). The study
also showed that half of the cases had normal serum inorganic phosphate; this is in agreement with others (20,166). Not surprisingly, serum vitamin D was also found to be normal in half of the cases, and this is in agreement with other studies (20, 22, 23, 26, 59,69). Serum alkaline phosphatase is usually raised anyway in the growing child because of the increased metabolic rate, this may be the reason why, still statistically significant (p<0.05).this finding has previously been reported in literatures(26,45,80).

Response to treatment is not only due to vitamin D injections, but also equally due to other lines of management including frequent and regular exposure to sunlight, dietary readjustment and adjuvant therapy in addition to health education.

In the re-evaluation (which was performed four – eight months later), determination of the serum levels of calcium, inorganic phosphate, vitamin D, and alkaline phosphatase, the paired t-test demonstrated a highly significant mean levels of all of these parameters among the cases after treatment compared to before treatment (p<0.05). The significant rise in serum calcium has also been demonstrated by others (23, 26, 28, 45, 46, 65, 71, 86). Similarly, the significant rise in inorganic phosphate serum level and
vitamin D level were also reported in several studies (20, 26, 45, 59, 65, 71, 89, 96). Also a significant decline in serum alkaline phosphatase in response to treatment was previously reported in the literature (22, 80).

4.5. Radiological features and response to treatment:

Radiology is the easiest, simplest and the most cost-effective investigation in active rickets. The best site for radiology in young children is the wrist joints. The most noticeable findings were widening of joint spaces, and broadening of epiphyseal line of the distal ends of radius and ulna was seen in almost all the cases. Cupping and fraying of the epiphysis of the distal ends of the radius and ulna were seen in three quarter and two thirds of the cases, respectively. Delayed bone age was also observed in nearly two thirds of the cases. None of these radiological findings could be detected in any of the fifty control subjects.

Re-evaluation of the cases after management showed significant improvement of all the above-mentioned findings compared to those before treatment (p<0.05). Such improvement in radiological changes following treatment had previously been observed by many workers (26,50).
Although this clinical trial has been very tiring and time consuming and has faced many difficult situations and logistics; yet it was an enjoyable educating exercise that had improved our research experience. It has certainly attained the triple benefit of training of the author and staff, producing a positive impact in the community in both advocacy and therapy as well as testing the validity, of the method of active surveillance in the community to pick up common but hidden nutritional deficiencies.

However, the main message of this exercise is the gratification gained from low cost but effective method of combating diseases in the community by raising the awareness and health education.

Further large-scale clinical trial is needed to investigate the role of the associated risk factors such as maternal nutritional deficiencies (in calcium and vitamin D) in the etiology of infantile rickets.
Conclusions

This community-based, prospective clinical trial showed that:

1. The prevalence rate of vitamin D deficiency rickets in the children of Peri-urban community of Sana’a was 18.7%.

2. The predominant age group affected was infants under one year.

3. The most important possible risk factors include lack of exposure to sunlight, prolonged breast feeding and delay supplementation, illiteracy of the mothers and lack of knowledge, on the benefits of sunlight as well wrong beliefs, attitude and practices.

4. The underlying background factor for these practices is illiteracy, lack of awareness and lack of health education.

5. The intensive health education sessions gave a very good response.

6. This improvement in mother’s knowledge, attitude, and practice is so promising to be utilized for planning futures health education programs to prevent diseases including rickets.

7. Most of the cases showed the clinical, biochemical, and radiological findings of vitamin D deficiency rickets that responded significantly to the lines of management. These lines included; Health education sessions,
vitamin D injections 20.000IU IM given every four days for ten injections, and advising mothers to added nutritious solid food from the fourth month.
Recommendations

1. Prevention of vitamin D deficiency rickets feasible and cost-effective. Health education for the mothers using mass media should be an integral part of Primary Health Care Program.

2. Early introduction of solid foods, enriched with essential elements as calcium, iron, and vitamins, as mixed grains.

3. Pulse high-dose vitamin D therapy has the potential for overcoming problems of compliance with supplementation. Pulse therapy with high dose, 100,000 IU vitamin D, may be appropriate where the prevalence of rickets is high and compliance to vitamin D prophylaxis is low.

4. Those mothers living in villages should be back to old dress, and encouraging them to sunlight exposure especially during pregnancy and nursing.

5. The M.O.H. should consider giving vitamin D drops during immunization sessions for the group at risk.

6. Further researches are needed to clarify many aspects of vitamin D deficiency rickets in Yemen especially rural and suburban communities (e.g. Kawlan, and Al-Hadaa).
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Annex Ia  Massoud village

Annex VII The classroom that was modified to be an examination and educational sessions room.
Annex VIIIa  The portable x-ray machine.

Annex VIIIb  The portable x-ray machine, table and x-ray technician
Annex IX. Laboratory room with equipments and the team work.

Annex Ic. Massoud village and big water tank that supply most of the village houses
Annex II. The vacant school at Magwalla village which used as our study center

Annex Ia. Massoud village
Annex IV. Algahshi village with its valley, showing also Qat farms

Annex V. Almoaayen village.
Annex VIIIa. Shows x-ray portable machine.

Annex VIIIb. The portable x-ray machine, table and x-ray technician
Annex Xa. A child lying on the weighing scale, held by his father.

Annex Xb. A child lying on the weighing scale, held by his mother.
Figure 3.5 Wrist radiograph of the infant M. A. aged four months. (A): shows widening of joint space, broadening, cupping and fraying of distal radial and ulnar epiphysial ends. Note fracture at the epiphysial end of ulna, and green stick fracture at the upper end of radius.

(B): Four months after treatment widening of joint space and healed epiphysial line

Annex VIb. A child with mild broadening of the wrist joint.
Annex VIa. A child with pot belly abdomen and prominent rosary
VIT D DEFICIENCY  RICKETS  IN  YEMENI CHILDREN

A-CHILD IDENTIFICATION:

1-Child record no…………………………………………………………
2-Date of interview…………………………………………………………
3-Child name ……………………………………………………………
4-Birth date ……………………………………………………………
5-Age in months…………………………………………………………
6- sex ………(1) Male ………(2) Female……………………………………
7-Residence ….(1) urban …(2) peri-urban….(3) rural……………………

B-Social History:

8-Father Occupation
   (1) Professional ……(2) Solder + farmer……(3).employee
   (4)farmer ……..(5) Skilled labor ……….(6) unemployed/dead ………

9-Mother Occupation …(1) House wife ….. (2) others………………

10-Father Education. no. of school years……………………………………

11-Mother Education no. of school years …………………………………

12-Total No of living children………………………………………………

13-Income per month YR…………………………………………………

14-No of rooms in the house………………………………………………

15-Electercity ………….(0) No………..(1)…Yes…………………………

16-Water supply:
   (1) piped-in….(2).piped outside…. (3) others …………………

17-Toilet Facilities…(1) Siphon…..(2).Pit-latrine ………(3) others……….…

18-No. of children with rickets in the family:
   (0) none…..(1) one sibling…(2) more than one sibling…(3) cousins…
   (4) far relatives………(9) do not know……………………………………

19-No of handicapped children in the family
   (0) none…..(1) one sibling …(2) more than one sibling…(3) cousins
   (4) far relatives…..(9) do not know……………………………………

20-No of infant deaths in first month……………………………………

21-No of infant deaths between 2\textsuperscript{nd} month till one year 

22-No of infant deaths from above one year to 5\textsuperscript{th} year …………………
C-Medical History:
23-Birth weight..(1) average…(2) below average…………………………   
24-Gestitional age…(1) v. pre-term….(2).pre-term…(3) term…………..   
25-Duration of breast feeding (months) : (88) still on breast .............
26-Age of introduction of solid foods in months……………………….
27-N. of previous hospitalization:
   (0)none…..(1) once ………(2) more than one ...........................
28-Vaccination received:
   (0)none….1 incomplete….2 complete … (9) do not know……….
29-Has the baby taken outdoor during the day time:
   (0)no…(1) yes ......................................................................
If no why………………………………………………………………
If yes ,how many minutes per day………………………………………
30-Does mother believes ,it is wise to expose the baby to sun light?
   (0) no …. (1) uncertain ….(2) yes…. (9) do not know…………..
   If yes:
31- At what time…(1) early morning..(2)noon..(3) late afternoon……   
32-Regularity.(0) no.(1) daily…(2) 3-4/week..(3).<2/week..(4) rarely…   
33-Dressing …. (0) no …(1) dressed……………………………………   
34- Is the child receiving vitamins?..(0).no…..(1) yes……………………
35-Does the mother believe in extension of breast feeding beyond the 1st year?
   (0) no……(1) yes....................................................................... 
36-Convulsion….0) no….1) yes....................................................
37-Other Symptoms ( delay walking, inability to stand, floppiness, sweating...) 
38-**Anthropometric measurement:**
   ..Weight…..(kg).………………………………………………….....
   ..Height…..(cm).………………………………………………...   
   ..Skull cir. (cm).……………………………………………………
   ..Chest cir. (cm).………………………………………………..    
   ..MUAC …. (cm)…………………………………………........
39-CLINICAL SIGNS:
present. = 0 … absent. = 1 ……………………………………………………
Delayed closure of anterior fontanel……………………………………
Craniotabes………………………………………………………………
Delayed dentition…………………………………………………………
Rosary beads………………………………………………………………
Pigeon chest………………………………………………………………
Harrison sulcus……………………………………………………………
Kyphosis……………………………………………………………………
Potbelly……………………………………………………………………
Broad epiphysis……………………………………………………………
Bow legs……………………………………………………………………
Knock knee………………………………………………………………
Hypotonia…………………………………………………………………
Signs of pneumonia(chest infection)………………………………………
Signs of malnutrition……………………………………………………
Signs of vitamin deficiency………………………………………………
Signs of anaemia…………………………………………………………

40-BIOCHEMICAL RESULTS:
Serum vitamin D……………………………………………………………
Serum calcium………………………………………………………………
Serum phosphate…………………………………………………………
Serum alkaline phosphatase……………………………………………

41-RADIOLOGICAL FINDINGS:
Absent = 0 … present = 1 … uncertain = 2……………………………
Widening of joint spaces………………………………………………
Broadening of epiphysis………………………………………………
Cupping of epiphysis…………………………………………………
Fraying of epiphysis…………………………………………………
Delayed bone age……………………………………………………

42-DIAGNOSIS:
Active rickets
43-TREATMENT: 1-A: Vit.D........2- B: sunlight........3-diet........

44-Follow up
46-Outcome:
1- Improved completely
2- Partial improvement
3- No significant improvement
4- Others- died, lost, refuse

Annex XII; Follow up records:

VITAMIN D DEFICIENCY RICKETS IN YEMENI

A- Child identification:

1- Child record no....................................................
2- Date of interview.............................................
3- Child name ......................................................
4- Birth date ......................................................
5- Age in months...................................................
6- Duration of breast feeding (months) : (88) still on breast ...
7- Age of introduction of solid foods in months.................
8- Vaccination received
   (0) none....(1) incomplete....(2) complete .................
9- Has the baby taken outdoor during the day time...
   (0) no....(1) yes
10- At what time...(1) early morning..(2)noon..(3) late afternoon...
11- Regularity...(0) no....(1) daily...
12- Dressing ....(0) no ....(1) dressed......

B- Anthropometric measurement:

Weight.... (kg)........................................
Height.... (cm)........................................
Skull cir. (cm)........................................
Chest cir. (cm)........................................
MUC.... (cm)........................................
C-Clinical signs:

- present. = 0……absent. = 1
- Delayed closure of anterior fontanel
- Craniotabes
- Delayed dentition
- Rosary beads
- Pigeon chest
- Harrison sulcus
- Kyphosis
- Potbelly
- Broad epiphysis
- Bow legs
- Knock knee
- Hypotonia

D-Biochemical findings:

- Serum vitamin D
- Serum calcium
- Serum phosphate
- Serum alkaline phosphatase

E-Radiological findings:

- Absent =0….present =1 …uncertain = 2
- Widening of joint spaces
- Broadening of epiphysis
- Cupping of epiphysis
- Fraying of epiphysis
- Delayed bone age

F-Outcome:

1- improved completely
2- Partial improvement
3- No significant improvement
4- Others- died,lost,refuse