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Vitamin D - The Essence of Survival

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Abstract

Although there is no evidence of the role of Vitamin D in fertilization, we suggest this area and role of Vitamin D needs to be studied. During the forty weeks, the needs of the fetus to the means of survival through the placenta is maintained. As for calcium, trans-placental pump which is not Vitamin D dependent and is maintaining enough to build the bones and maintain the heart pumping, from the maternal circulating calcium. It is only in situations of severe symptomatic osteomalacia of the mother that cases of congenital rickets were reported. It is true that maternal osteomalacia causes fetal rickets which was reported at the beginning of the twentieth century from China. At birth, maternal Vitamin D deficiency can lead to failure of progress in labor that might increase the rate of Caesarian Section.

When the infant is born with a marginal calcium level that might remain asymptomatic or lead to hypocalcemic convulsions but might present with cardiomyopathy or myelofibrosis. In the first six months of life when no vitamin D supplementation, while breastfeeding from a vitamin D deficient mother, classical features of rickets may remain occult and overlooked, but presenting with hypocalcemic convulsions, respiratory infection, stridor and gastrointestinal symptoms. These are the major infantile killers in the developing world. Later, when started to walk with waddling gait and bowlegs, during the second year of life that features of rickets started to show by delayed dentition and delayed walking, swollen wrist, rachitic rosary and frontal bossing. On reaching adolescence during growth spurt rickets might present as tetany and bone pain with hypocalcemia, the cause in this age might be low calcium diet. Osteomalacia is a common problem in women during childbearing age.

Type of housing being flats or similar houses, with no exposure to the sun being vitamin D deficient men and women are likely to develop many diseases, including cancer breast in women and prostate in men and colon in both. Other diseases associated with vitamin D deficiency include, autism, multiple sclerosis, Diabetes mellitus, rheumatoid arthritis, hypertension, cardiovascular heart disease and many others to the extent of that vitamin D appears to be the essence of survival in all ages from cradle to old age and grave. Even before being born mothers need to expose themselves to the sun regularly in sunny countries, but in cold countries It is essential to supplement main foods including bread with vitamin D, but even in these countries enough exposure to the sun might even cover the dark month's needs. In old age sitting in the sun in a sunny day is necessary and what makes old people sitting in the sun for hours and make them love life to the extent of falling in love, this reminds me of a couple 72 years lady and 69 years man whom were my patients, I attending their wedding in Haverfordwest in 1971, they were my patients who were introduced to each during sitting in sunny days in the open area between the male and female wards at Withibush Hospital in Haverfordwest, Pembrokeshire, Wales UK .

The lady invited me to their wedding which I attended, and both were happy that I attended their wedding. From there, I got a job as assistant professor in pediatrics in the sunniest country in the world, after spending a year in sea croft where I got interested in rickets among Pakistani children from Bradford. In Riyadh I was astonished to see rickets in such a sunny country, when I presented my first thirty cases of rickets, Professor Forfar from Edinburgh who was sharing the session, commenting on my presentation by saying; these are vitamin resistant, but my reply was all responded to a low dose of vitamin D.

Introduction

Over the last decade there have been a plethora of publications on diseases associated with vitamin D deficiency, other than bone related conditions [1]. Sun protection behavior was practiced reducing the risk of skin cancer and can be maintained without affecting vitamin D serum status, although, consistently seeking shade when spending less than 50% of daytime outdoors is associated with lower vitamin D levels [2]. Many new discoveries of metabolites of vitamin D and effects of its deficiency, not only on different organs but on every single cell at different stages of life were reported. I am trying in this communication to sum them up, starting with the forty weeks of intra-uterine life, although a highly secure environment but exceptions may occur. Giving birth itself, although under control in the developed world but a lot of work and facilities are needed in the developing world. Then after birth two years of complete dependence on the mother while breast feeding covers requirement in a kangaroo fashion.

Thirty or forty years ago, we thought we would eradicate rickets in sunny countries, more cases of rickets with their associated new problems, like anemia and myelofibrosis are emerging. It seems, another hurdle comes during adolescence with its growth spurt that a great demand period for calcium, might show as tetany or frank rickets. Menopause and retirement are other periods in which all organs are affected, but bones take the highest burden. These are the periods of ageing I am trying to discuss vitamin D requirements and adverse effects of its deficiency and factors associated with it, namely congenital rickets, hypocalcemia myelofibrosis. Vitamin D, although considered as a vitamin, does not act as a mere vitamin, but it acts as multiple hormones with different offices that have a role on different organs with their specific metabolites.

Vitamin D receptors have been established in various tissues, including the brain, prostate, breast, colon, pancreas, and immune cells. It is not only bone metabolism, but also modulation of the immune response, regulation of cell proliferation and specialization in addition to many others, are all biological functions of vitamin D. Vitamin D might play a substantial role in modifying the risk of Cardio-metabolic outcomes, in many conditions, including diabetes mellitus (DM), hypertension, and cardiovascular diseases. This report explains the origin and the fate, in addition to the outcome of this unique preparation, which plays a fascinating role that might be described as the essence of survival with its role in bone metabolism is the most recognized but least life threatening.

History of Vitamin D and Rickets

The first citation of a case description that simulate rickets was in the book of pediatrics of Rhazes in Arabic (The Practica Puerorum in 900) translated into English and published in 1972 by Radbill [3] who stated: (The finest of his achievements was a monograph on smallpox and measles Practica Puerorum was a unique book of pediatrics. It was republished continuously in Latin through the centuries. It was translated to English in the 18th century and several times, thereafter, considering it as the first ever separate pediatric book. This makes Rhazes deserves to be given, the honorary title of FATHER OF PAEDIATRICS. Radbill stated that: (About a case described he mentioned a child with big head and distended abdomen, he might have been alluding to rickets. [3] It was after more than seven centuries that Glisson in 1650 [4] published (Treaties Rachitide, acknowledging the help of seven of his colleagues. Further editions in English appeared in 1660, 1668, 1671, and 1682. He stated that he studied rickets for five years then wrote about rickets: (It is an absolutely a new disease and never described by any ancient or modern writers in their practical books which are extant at this day of the diseases of children.

On the onset of this disease, he continues: (We affirm that this disease does very rarely invade children presently after their birth or before they are six months old, yeah, perhaps before the ninth month, but after that time it begins by little and little delay to rage more and more to the period of eighteen months then it attained its pitch and exalted and as it were rested in it, till the child be two years and six months old… etc.) He continues to say: (I think one can be pretty sure that the incidence had increased because all these factors which tend to predispose to rickets are such as are daily becoming more pronounced one of these factors inability of women to nurse their own children…. Another is the increase in women's work, a third is crowding in huge towns. In many towns, more than half the children seen in outpatient exhibit the disease to a marked degree. So, the dictum… still holds true, that rickets is the most common and the most fatal of all diseases that affect children).

It seems this is the oldest description of rickets in English literature and most comprehensive and moreover it is not at all different from what is observed today with a difference of being in sunny countries where urbanization and petrol civilization is forming an umbrella depriving the mother and baby off the sun although it is shining all year round [5]. Webster in 1645 in Leyden gave an excellent description of the disease mentioning enlargement of the head and the abdominal cavity, the rachitic rosary, and the whole bony system [4]. Hutchison [6] stressed the importance of diet to treat rickets, particularly milk and cod liver oil. He said: (drugs have no benefit unless to consider cod liver oil as a drug if a child is anemic give iron. Bad diet is a main cause yet other cooperating factors, sunlight I consider one of them. The youngsters should have the benefit of the sun if any. This statement of Hutchison was given before the uncovering of the function of ultraviolet rays let alone its discovery. He is also the first to state an association of anemia with rickets.

In1884 Kassovitz noticed a seasonal variation in incidence of rickets. In 1890 Palm suggested the therapeutic value of sunlight. In 1906 Fredrick Hopkins proposed the concept of essential accessory foods to be known later as vitamins. In 1919 Edward Melanby caused rickets in puppies by giving them a diet lacking a vitamin in cod liver oil. In 1921 McCollum and his fellow workers in Baltimore obtained proof of both the existence and curative value of what they named vitamin D. Meanwhile the value of sunlight was confirmed by Hulchschinsky (1919) and in 1924 Hess demonstrated that it was possible with UV illumination to create anti-rachitic activity in linseed oil. Three years later Windaus showed that the anti- rachitic substance was ergosterol. In 1928 Parsons summed up:(The modern view is that the disease is a general nutritional or metabolic disorder which affects every system of the body, the early symptoms bearing no direct reference to the skeleton.

Thus, rickets may show itself as a respiratory disorder in recurring attacks of bronchitis, as a gastrointestinal affection in recurring diarrhea as a nervous disorder in tetany and convulsions etc. as a muscular disease in severe hypotonia but

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eventually characteristic bone changes always occur [6]. This summing up lasted and holding for nearly ninty years with more features recently, involving the heart as in cardiomyopathy and hypertension; and blood presenting as anemia and myelofibrosis, endocrine with a role in diabetes mellitus and in cell differentiation leading to cancers etc. Later, the eradication of rickets by the economic consumption of cod liver oil and discovery of vitamin D, inherited, types of rickets started to surface as vitamin D resistant rickets appreciated, by failing to respond to cod liver oil and vitamin D. Many of the sub-groups of these were also appreciated, including the end organ defect with alopecia that responded only to very high doses of calcium. Although it is nearly a hundred years, since vitamin D was discovered, its deficiency has reappeared in a sort of an epidemic, but ironically in sunny counties due to the man-made huge umbrella of avoiding the sun and being in an ultraviolet devoid environment and as in temperate countries mainly among immigrants. This occult epidemic needs a panoramic look into factors associated with it (Table 1).

Table 1: Metabolic status in relation to age.

	Calcium level	Vit D status	PTH levels	ALK PH levels	Effects on Bones	Effects on organs other than bones
Intrauterine	Higher	Low	H	H	Normal T1DM in infant	Mother: Triphosphate syndrome Maternal hypertension PE CS Fetus: SGA, T1DM.
Newborn	Higher	Low	H	H	Normal at birth hypocalcemia after first week.	Low birth weight (SGA). Convulsions.
Six months	Low	Low	H	H	Rachitic rosary Swollen wrists HF swollen wrists rickets	Chest infection (4,34) Myelofibrosis (Cardiomyopathy)
One year	Normal	Low	H	H	Rickets	Autism
Adolescence	Low	Low	H	H	Rickets	Carpo-pedal spasm
Adult	Normal	Low	H	H	Osteomalacia	Cancers
Female Pregnancy	Low	Low	H	H	Subclinical osteomalacia	High rate of Cesarean section
Old age	Low	Low	H	H	Osteoporosis	Hypertension

Epidemiology of Vitamin D Insufficiency

It was towards the close of the nineteenth century that most people in rural areas moved to the industrial urban centers to improve their economic status at, in expense of abandoning sunny and healthy housing, for poorly illuminated housing in the slums of the big crowded industrial cities, contributing to many diseases, including vitamin D deficiency rickets that emerged, in a sort of epidemic, among urban cities of Sunny states and among non-Caucasian immigrants in the temperate states [7,8]. This umbrella phenomenon is due to the movement of people from sunny houses in rural areas to cities living in dark flats in multi-story buildings with no sunny courtyards as in rural areas for their children to play in.

In 1980 we reported rickets for the first time among breastfed babies living in flats with inadequate exposure of infants and mothers to the sun in Riyadh the capital of Saudi Arabia in 1980. We postulated that maternal vitamin D inadequacy was a factor in the pathogenesis of rickets in their babies [5,9-12]. To prove this theory, we measured 25OHD levels in the mothers of rachitic infants which was found to be low compared to mothers of non-rachitic infants [11]. Hypocalcemia in infants was more eminent than the maternal level at birth [3]. In this review I am trying to expand on how rickets present, starting in the antenatal period to end in old age and how vitamin D deficiency contributes to different diseases along the life span of a human being. Antenatal needs of cord blood levels and maternal calcium blood levels were evaluated and found to be low correlating with their babies', suggesting an intrauterine origin of rickets in the infants [12]. These findings were confirmed in cord blood samples and followed up after one week in the infants showing a drop.

Vitamin D and effects of its deficiency

Normal antenatal calcium metabolism

Maternal adaptations during pregnancy provide calcium to the fetus without relying on vitamin D. Therefore, the blood calcium, calciotropic hormones, and the skeleton appears normal at birth in the offspring of mothers who are vitamin D deficient or who lack cholesterol or its receptor. In such a situation a vitamin D-deficient neonate is at risk of developing hypocalcemia, which might present as neonatal convulsions, or cardiomyopathy or myelofibrosis later. When breastfed the neonate is at higher risk of vitamin D deficiency which becomes evident because normally little vitamin D or 25-hydroxyvitamin D passes into breast milk

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when the mother is already deficient. Vitamin D supply during pregnancy and lactation should ensure that the baby at birth is vitamin D sufficient and sustained that way during infancy while breastfeeding, [13] but beyond that vitamin D should be supplied through ultraviolet rays or from supplemented diet.

Identification of the current evidence regarding the patho-physiological and clinical facets of vitamin D in the maternal-fetal-neonatal interface is of value because of the significance of the vitamin D endocrine system in human health and high prevalence of vitamin D deficiency in mothers and their infants. Although many questions have still not been resolved by the available literature, there is evidence that:

i. During pregnancy vitamin D participates in fetal skeletal mineralization and growth. Its deficiency leads to birth of an infant with poor mineralization of bones, despite the calcium trans-placental pump. [13].

ii. The neonatal vitamin D level is dependent on the maternal vitamin D status at delivery and pregnancy.

iii. Vitamin D sufficient status at birth may decrease the risk for the development of asthma and type 1 diabetes mellitus in later life.

iv. Recommendations for maintaining serum 25hydroxyvitamin D [25 (OH) D] levels >32 ng/ml to avoid secondary hyperparathyroidism in adults has not been applied to mothers and their babies.

v. American Academy of Pediatrics recommended supplementation of 400 IU of vitamin D per day is sufficient only for infants who are born with normal vitamin D levels.

vi. Supplementation of lactating mothers with high doses of vitamin D (4,000 IU /d) allows the achievement of optimal 25 (OH) D concentrations (>32 ng/ml) in the maternal and infant serum without any risk of hyper-avitaminosis D in the mother.

These researchers suggested that the identification of sufficient levels of vitamin D in mothers and their infants is essential and accordingly advised giving adequate doses of vitamin D supplementation during gestation, lactation, and early childhood [13]. When we first reported rickets in Riyadh, the capital of Saudi Arabia, an all-year sunny city, we proposed a hypothesis that maternal vitamin D was a possible cause of rickets in their babies especially those with their ages were under one year at diagnosis [3]. Almost all the rachitic infants were breastfed, and all were living in an environment with plenty of sunshine but with poor exposure to it as mothers thought that the sun would hurt their baby [5].

Also, their dress does not allow any part of their skin to be exposed to the sun. Their average age at the time of onset of obvious rickets was 10.5 months. 25-Hydroxyvitamin D (25OHD) levels were found to be low in mothers of rachitic infants [10]. This maternal deficiency as an element in the pathogenesis of rickets was confirmed as shown in figure 1 [5]. This has been the first report to document the role of maternal vitamin D deficiency in development of rickets in their breast-fed infants in a sunny country. We further confirmed this impression, in a study to assess the vitamin D nutritional state in 119 pregnant women at term and in their newborns. Concentrations of 25-hydroxy vitamin D 25-(OH) D were below 4 ng/ml in 30 of 119 maternal sera, in 11 of which they were undetectable. The median concentration of 25-(OH) D was 5.7 ng/cc, which is corresponding to that found in Asian vegetarian women at term in London. Fifty of 119 cord samples had undetectable 25-(OH) D, and a total of 81 samples had 25-(OH) D concentrations of less than 4 ng/cc. Despite the low 25-(OH) D concentrations, cord blood samples had calcium concentrations higher than those in maternal blood, while serum albumin concentration was similar in maternal and cord samples.

f1

Higher socioeconomic background of the women, antenatal care, and vitamin D supplementation were associated with significantly higher concentrations of 25-(OH) D. Vitamin D supplementation, however, had no significant effect on 25-(OH)D concentration in cord samples or on the weight of the newborns. This study demonstrated the high prevalence of marginal vitamin D nutrition in adult females in Saudi Arabia, which was considered predisposing their babies to rickets during infancy. In a nation endowed with plentiful sunshine, the exclusion of sunshine by thick dark veils and devoid of sunlight and poorly illuminated housing probably contributes to this low state of vitamin D levels [14]. The great need of calcium by the embryo is achieved by what is called the calcium trans-placental pump which depends on the availability calcium in circulation [13]. It is only in situations of severe maternal osteomalacia where calcium is almost depleted that babies are born with frank congenital rickets as used to seeing China hundred years ago [8].

Effects of vitamin D insufficiency in pregnancy

Prevalence

In a study from Amsterdam, low early-pregnancy vitamin D status was associated with elevated depressive symptoms in pregnancy. Further research, utilizing a randomized controlled design, would be needed to confirm this association and the potential benefits of higher vitamin D intake for psychosocial health [15]. Another study supported previous reports of hypovitaminosis D in anti-phosphates syndrome (APS) patients, making them more like patients with other systemic autoimmune diseases. Hypovitaminosis D may be part of the mosaic of elements that determine autoimmunity, rather than a consequence of chronic disease and its discourse. The observation that patients with thrombotic APS, an aggressive phenotype, may be more deficient than those with exclusive obstetric manifestations, fits well with the beneficial effects of vitamin D on thrombosis

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described both in vitro and in vivo. Consequently, there may be a rationale to assess the efficacy of vitamin D supplementation in APS patients [16].

When specific indications were examined, vitamin D deficiency was linked to a twofold increased risk of caesarean for prolonged labor. Results were similar when prior guidelines for vitamin D deficiency (25 (OH) D < 37.5nmol/L) and insufficiency (37.5-80 nmol/L) were utilized [17]. It was also found that women with low circulating vitamin D concentrations are more probable to experience high blood pressure [18]. Also, since angiogenesis is a crucial characteristic in the pathophysiology of pre-eclampsia these findings could explain the positive influence of vitamin D (3) in reducing pre-eclampsia risk [19]. Maternal circulating 25(OH)D is the most important regulator of neonatal circulating 25(OH)D concentrations, with underlying genetic factors playing a special role [20]. These findings further stress on a positive role of vitamin D in maintaining a normal pregnancy. There is no doubt that enough vitamin D is essential for a healthy start and continuation of pregnancy.

B-Effect of vitamin D deficiency on fetus

There is a great demand for calcium for fetal growth specially heart, brain and bone in which great amounts are needed for bone formation. There is a trans-placental calcium pump [13] which is not dependent on vitamin D level that is why it was observed that the cord blood level of calcium is higher than maternal level at birth [6,7] Also this fact is supported by the rarity of infants being born with clinical florid features of congenital rickets, except in severe maternal osteomalacia as described from China [7] during the first years of the last century.

Second trimester 25(OH) D levels less than 25 nmol/L were associated with higher odds of small for gestational age SGA. This data raises the possibility of vitamin D status that may contribute to racial disparities in SGA [21]. Optimal calcium intake and adequate maternal vitamin D status are both required to maximize fetal bone development. Interactions between these nutrients were evident when either calcium or vitamin D status was determined. Improving maternal calcium intake and/or vitamin D status during pregnancy may induce a positive effect on fetal skeletal growth in pregnant teenagers [22]. P-25OHD concentrations did not affect fertility or pregnancy outcomes, although low P-25OHD may be linked with an increased hazard of late spontaneous abortion [23].

Specker reviewed this subject by expressing that, during pregnancy, maternal and fetal calcium (Ca) demands are taken on through increased intestinal Ca absorption. Increased Ca absorption may be more dependent on estrogen regulation of calcium transport genes than on vitamin D status. Numerous surveys, however, have found that severe vitamin D deficiency with secondary hyperparathyroidism during pregnancy contributes to abnormal Ca homeostasis in the newborn infant. More or less, but not altogether, studies of maternal vitamin D supplementation during pregnancy find a heavier birth weight among babies of mothers with adequate vitamin D status.

Specker stated that observational studies have found a higher incidence of small forgestational age (SGA) infants among mothers who are vitamin D deficient, but this finding might be modified by genetics. The issue of vitamin D status on SGA may not be linear, with increased occurrence of SGA at high maternal 25-hydroxyvitamin D (25-OHD) concentrations. Some studies, but not all, also have found that maternal vitamin D status is linked up with the growth trajectory during the maiden year of life, although the findings are contradictory. There are recent studies that suggest maternal 25-OHD, or surrogates of vitamin D status, are associated with maturation and bone mass later in childhood. They think that these outcomes are not logical and blinded randomized trials of vitamin D supplementation during pregnancy with long-term follow-up are needed to find out the benefits, and possible risks, of maternal vitamin D status on offspring development and bone maturation. The possibility of adverse events with higher maternal 25-OHD concentrations should be taken and investigated in all on-going and future works [24].

The effects of vitamin D deficiency on Labor

Three cases of contracted pelvis in Bedouin women appearing, after two and three previous normal vaginal deliveries, were reported [25]. In these three cases, a Caesarean section had to be done to save the babies. A Roentgen ray screening revealed a pelvis with osteomalacia in all events with typical pseudo fractures (Milkman) and looser zones. Sabol et al. [26] found that 44% of pregnant mothers were not supplemented with vitamin D and 20·3% patients in the supplemented group developed preterm labor, pre-eclampsia and gestational diabetes. Newborns of mothers in the first group had lower cord blood levels of 25(OH)D- D as compared to the second (mean 43·11 ± 81·32 nmol/l vs 56·8 ± 47·52 nmol/l). They also had lower birth weight of 2·4 ± 0·38 kg as compared to the supplemented of 2·6 ± 0·33 kg. They concluded that vitamin D supplementation reduces risk of maternal comorbidities and helps improve neonatal outcomes [26]. Another study did not find any evidence of an association between vitamin D status in pregnancy and GDM, preterm delivery, FGR, SGA and anthropometric birth outcomes. Other results suggest that sufficient circulating vitamin D concentration [25(OH) D 3 ≥ 30 ng/ml] in pregnancy may reduce the risk of caesarean section by obstructed labor [27].

In China, the prevalence of low level of vitamin D (serum 25OHD ⩽20 ng/ml) was 18.9% among pregnant women in the South. They reported that there were no significant differences in most adverse pregnancy outcomes among pregnant women with different levels of vitamin D at 16-20-week gestation except for higher prevalence of gestational diabetes and preterm delivery in women with high level of vitamin D, possibly related to the older

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age and higher body mass index of this group [28]. In another study, -risk for cesarean delivery was increased significantly for vitamin D deficient women; there was no increased risk for gravidae at risk of insufficiency. When specific indications were examined, vitamin D deficiency was linked to at wo fold increased risk of cesarean for prolonged labor [29] Although there is no agreement in these studies, yet it is essential to maintain normal vitamin D levels during pregnancy as many other benefits of normal vitamin D status is appreciated.

Vitamin D deficiency in Newborn babies

Lately it was reported that, despite supplementation with 400 IU of vitamin D daily, the rate of vitamin D deficiency was worryingly high in 4-month-old exclusively breastfed babies living in Izmir, Turkey, warranting the need for extra studies to elucidate the optimal quantity of vitamin D supplementation to the infants, especially during winter. The American academy has recommended dose for vitamin D sufficient babies at birth, so we recommend double that dose in our community [30]. In China, a study suggested that pregnant women and neonates residing in Beijing were at high risk of vitamin D insufficiency. Neonatal 25 (OH) D concentrations were dependently related to maternal 25 (OH) D levels. Maternal and neonatal vitamin D status influenced newborn size [31].

In a review from Australia, there is considerable evidence that low maternal levels of 25 hydroxyvitamin D are associated with adverse outcomes for both mother and fetus in pregnancy as well as the neonate and child. Vitamin D insufficiency during gestation has been associated with several maternal problems including infertility, preeclampsia, gestational diabetes, and an increased rate of cesarean section. Likewise, for the child, there is an association with small size, impaired growth and skeletal problems in infancy, neonatal hypocalcemia and seizures, and an increased risk of HIV transmission. Other childhood disease associations include type1 diabetes and effects on immune tolerance [32]. Hypocalcemia in the neonatal period among full term and premature infants is increasing and, in our cases, it is caused by maternal vitamin D deficiency [10,14]. In situations of severe maternal osteomalacia although the calcium trans placental transfer is not vitamin dependent, as there is not enough calcium in maternal blood the infant might be born with full blown biochemical and clinical rickets to bear the title of florid congenital rickets.

Vitamin D deficiency in the first Six months of the life of infants

An infant born to a vitamin D deficient mother will have a poor vitamin D status, but in most cases with marginally adequate calcium by the natural process of trans-placental calcium pump which, is not dependent on vitamin D status. If the mother is vitamin D deficient, obviously her milk will not contain enough vitamin D, leading to her breastfed infant not able to absorb enough calcium leading to developing hypocalcemia, which might be symptomatic or asymptomatic. This hypo-calcemic phase of rickets is a critical period, as it might present with convulsions when the ionized calcium drastically drops, a situation that always warrants seeking medical advice. Hypocalcemia will stimulate the parathyroid glands leading to hyperparathyroidism, that provokes mobilization of calcium from bone in a trial of correcting the hypocalcemia, but at the cost softening of the bones and enlargement of the growing ends of the long bones giving the features of rickets.

These features are craniotabes in the first two months, rachitic rosary in the next months as the chest bones are fastest in growth in the first six months of life. Other than these bony problems there is evidence that vitamin D insufficiency is linked with increased risk of RSV LRTI in this period of life, suggesting routine vitamin D supplementation during pregnancy, may be a useful strategy to prevent RSV LRTI during infancy [33]. Another study from the USA have indicated that, vitamin D is lower among patients with small for gestational age (SGAO) in early onset preeclampsia (EOSPE) than those without. They suspect that vitamin D may have an impact on fetal growth through placental mechanisms. Cardiomyopathy and myelofibrosis are also serious complications in this period and later.

Vitamin D Deficiency In the second six months of life

In the second six months of life, infants usually present with hypo-calcemic convulsions, chest infection and gastroenteritis, [34] Rarely it might present as heart failure due to cardiomyopathy, which is a serious life-threatening complication that might be missed as respiratory infection. Anemia due to iron deficiency is common in this period [35], but interestingly that in this period rickets is likely to be missed as that its characteristic clinical features are not yet apparent and as the respiratory and gastrointestinal features might dominate and acquire the upper hand in diagnosis. Although very rarely the anemia might be due to myelofibrosis [36] most likely precipitated by hyperparathyroidism, calcium might have been adjusted by the its action. In neighborhoods of high environmental and social and housing elements of inadequate exposure to the sun, meticulous looking for subtle features of rickets is necessary and screening by alkaline phosphatase testing is needed in this age.

Vitamin D deficiency in toddlers

In contrast to the previous phase rickets at this stage might present with delayed teething or delayed motor development as sitting and walking. If started to walk they might present as bowlegs with waddling gait that makes a diagnosis of rickets obvious on walking into the clinic. In this phase, increased head circumference, rachitic rosary, Harrison sulcus bowlegs, swollen wrists, and knock knees are presenting features.

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Autism Spectrum Disorders (ASD)

Autism spectrum disorder (ASD) is a complex Neuro-developmental disorder with multiple genetic and environmental risk factors. The interplay between inherited and environmental factors has become the subject of intensified research in the last several years. Vitamin D deficiency has recently been proposed as a potential environmental risk factor for ASD. Vitamin D deficiency either during pregnancy or early childhood, might be an environmental trigger for ASD in individuals genetically predisposed for the broad phenotype of autism. Along the basis of the effects of the present review, we argue for this possibly important role of vitamin D in ASD, and for the need for urgent research in the field [37]. Maternal vitamin D insufficiency during pregnancy is significantly associated with offspring language impairment. Maternal vitamin D supplementation during pregnancy may reduce the risk of developmental language difficulties among their children [38].

Infections and vitamin D

Observational studies suggest that vitamin D deficiency increases the risk of respiratory infections. This increased risk may contribute to incident wheezing illness in children and adults and cause asthma [39] Vitamin D is involved in the production of defensins and cathelicidin - antimicrobial peptides that provide a natural defense against potential microbiological pathogens. Vitamin D supplementation increases cathelicidin production. Low vitamin D levels are associated with an increased incidence of upper respiratory tract infections [45]. The function of vitamin D in the innate immune system and in the epithelial cells of the oral cavity, lung, gastrointestinal system, genitourinary system, skin and surface of the eye was discussed. Clinical conditions are reviewed where vitamin D may play a role in the prevention of infections or where it may be used as primary or adjuvant treatment for viral, bacterial and fungal infections. Several conditions such as tuberculosis, psoriasis, eczema, Crohn's disease, chest infections, wound infections, flu, urinary tract infections, eye infections and wound healing may benefit from adequate circulating 25 (OH) D as substrate [40].

Vitamin D deficiency in Adolescence

Vitamin D deficiency is prevalent among healthy Korean adolescents and the parent-offspring association warrants vitamin D screening for family members of deficient individuals [41]. Vitamin D inadequacy is a common problem among Egyptian adolescent girls. Inadequate sun exposure, possibly linked to cultural/social factors influence vitamin D levels. Insufficient dietary calcium in some other areas is another leading cause [42]. In India adolescents with severe VDD presented with pain on weight bearing joints, back, thighs, knees, and calves. It appears that adolescents adapt better to severe VDD compared to infants, with less severe clinical, biochemical and radiological manifestations. Difficulty in walking and/or climbing stairs and/or running muscle spasms, and/or facial twitches and/or Carpo-pedal spasms and genu-vulgum. Biochemical serum abnormalities included high ALP low phosphate and low Ca. Varying radiological manifestations due to VDD were detected in all children. Two different radiological patterns have been recognized in adolescents. Three months after injecting a mega dose of cholecalciferol all biochemical abnormalities were corrected with significant improvement of symptoms related to VDD that have been reported in all children and in most of adolescents with VDD.3-6 months after the injection, complete healing of the radiological evidence of VDD was achieved in all rachitic children and the legal age of teens.

Abdullah et al. [43] was the first to report adolescence rickets in Saudi Arabia, an all-year sunny country. In their retrospective study they reported their experience with 34 adolescents 20 females, 14 males with rickets. The commonest cause was vitamin D deficiency (58.8%) followed by rickets due to low calcium intake (11.8%) and genetic causes, including possible 25-hydroxylase deficiency (8.8%). The etiology of nutritional rickets in adolescents is multifactorial, including lack of sun exposure and inadequate calcium intake. The clinical symptoms were nonspecific rendering cases under diagnosed or overlooked. Vitamin D deficient patients needed an average of nineteen months of treatment before recovery. High dose vitamin D plus calcium supplementation was recommended for treatment. Further studies on nutrition and inherited forms of rickets were recommended. Vitamin D deficiency is common among Saudi children and adolescents and is influenced by both sun exposure and physical activity. The forwarding of an active outdoor lifestyle among Saudi children in both at home and schools may counteract the vitamin D deficiency epidemic in this vulnerable population.

Vitamin D supplementation is indicated in all groups, including those with the highest sun exposure and physical action [43]. In another study from Saudi Arabia Al-Othman et al. [44] reported that Vitamin D deficiency is common among Saudi children and adolescents and is influenced by both sun exposure and physical activity. Promotion of an active outdoor lifestyle in both homes and schools was suggested to counteract the vitamin D deficiency epidemic in this vulnerable population. Vitamin D supplementation was suggested in all groups, including those with the highest sun exposure and physical activity. Vitamin D deficiency is also prevalent among healthy Korean adolescents and the parent-offspring association suggested vitamin D screening for family members of deficient individuals [45]. The high frequency of vitamin D insufficiency in childhood (particularly among teenage girls) indicates a need for supplementation and nutritional sustenance.

The prevalence of vitamin D inadequacy and insufficiency among children in Hangzhou, Zhejiang province in China is high, particularly among children aged 6-16 years. They indicate that the recommendation for vitamin D supplementation in children

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should be extended to adolescence [46]. Further study results showed that vitamin D inadequacy is a highly prevalent condition in European adolescents and should be a matter of business organization for public health authorities [47]. These reports of the features of rickets among adolescent male and female children is due to the great requirement of calcium for the growth spurt which needs extra calcium as well as increased vitamin D supplies, but outdoor activities are most important.

In my opinion the cause of rickets in this age group is most likely due to low dietary calcium. In these adolescent boys with activity outdoors, there is a need to increase high calcium containing diets namely milk products than promote absorption of calcium by vitamin D unless there is definite evidence of lack of exposure to the sun as in handicapped children. The adolescence rickets in temperate as well as sunny countries are mainly due to low calcium in the diet, especially those children tend to depend on fast food mainly carbohydrate, with poor content of dairy products and low calcium containing food. From these data it can be stated that adolescence rickets are mainly due to hypocalcemia with less role of vitamin D deficiency per say. The calcium deficiency rickets reported in Africa by Thatcher are included in this group of adolescence rickets or calcium deficiency rickets.

Vitamin D deficiency in adult females

This is a special case I am including in this communication as an objective lesson, making a very interesting example in an article with the title of (The vitamin D complex) published in Nature it reads: (COPD-vitamin D link? In Chronic obstructive pulmonary disease, COPD is primarily an inflammatory disease. The predominating hypothesis holds that cigarette smoke damages the lung tissue, sparking an innate immune response. Immune cells, including macrophages and neutrophils, rush into the lungs to protect the cells lining the air passages from the smoke releasing reactive, oxygen-containing molecules along the room.

Antimicrobial peptides, a group of molecules that harm and kill microorganisms, join the fray, as do pro-inflammatory T cells, inducing the production of antibodies of yet unknown specificity. It identifies a case story of a lady suffering from COPD for years and failed to react to normal dose of vitamin D but when put on 10000 units and maintained on 5000 IU, it produced the alteration. What she can practice now is :(Candice can't separate out the benefits of supplementation from those of not smoking, but she attributes her improved health of both. She has little difficulty keeping her four-year-old daughter up the stairs right off – whereas earlier, she says, "I couldn't do that without losing my breath." [48]. I have named this novel example published in nature to give us unique advice to all tobacco users.

Therapeutic effects of calcium & vitamin D supplementation in an infertile woman with polycystic ovary syndrome (PCOS):

In a case control study, it was shown positive effects of calcium & vitamin D supplementation on weight loss, follicle growth, menstrual regularity, and improvement of hyper-2androgenism, in infertile women with polycystic ovary syndrome (PCOS) (55) P-25OHD concentrations did not affect fertility or pregnancy outcomes, although low P-25OHD may be associated with an increased risk of late spontaneous abortion [49]. During pregnancy, P25OHD changed significantly over time, but similar changes occurred within the control group, indicating no effect of pregnancy per se (P=0.59). Overall, P-25OHD did not differ according to length of breastfeeding at 2 weeks, and 4 and 9 months postpartum, although women breastfeeding for more than nine months had lower P-25OHD levels at a previous visit compared with the controls [50]. Plasma-25OHD concentrations did not affect fertility or pregnancy outcomes, although low plasma-25OHD may be associated with an increased risk of late miscarriage.

Vitamin D role in innate immunity

Vitamin D has a key function in innate immunity activation; the production of antimicrobial peptides (cathelicidin and defensins) following Toll-like receptor stimulation by pathogen lipopeptides is dependent on sufficient level of 25-hydroxyvitamin D. Clinically, there is evidence of the association of vitamin D insufficiency and respiratory tract infections. There is also some evidence of the prevention of infections with vitamin D supplementation. Randomized controlled trials are warranted to explore this preventive effect.

Vitamin D insufficiency and Cardio-metabolic Disorders

Parker et al. [51] reviewed the association between Cardio metabolic disorders and vitamin D deficiency stating that it is becoming progressively more prevalent across multiple populations. Different subjects have indicated a possible connection between abnormal vitamin D levels and multiple pathological conditions including cardiovascular diseases and diabetes. They aimed to evaluate the association between vitamin D levels, using 25-hydroxy vitamin D (25OHD) as an indicator of vitamin D status, and the presence of cardio metabolic disorders including cardiovascular disease, diabetes and metabolic syndrome. They performed a systematic review of the current literature on vitamin D and cardio metabolic disorders using the Pub MED and Web of Knowledge databases in September 2009. Studies in adults looking at the effect of vitamin D levels

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on outcomes relating to cardio metabolic disorders were selected. They performed a meta-analysis to assess the risk of developing cardio metabolic disorders, comparing the highest and lowest groups of serum 25OHD.

From 6130 references, they identified 28 studies that met their inclusion criteria, including 99,745 participants. There was moderate variation (X\T? PY4) between the studies in their grouping of 25OHD levels, design and analytical approach. It was found that the highest levels of serum 25OHD were associated with a 43% reduction in cardio metabolic disorders [OR 0.57, 95% (CI 0.48-0.68)]. Similar levels were observed, irrespective of the individual cardio metabolic outcome evaluated or study design. High levels of vitamin D among middle-age and elderly populations were associated with a substantial decrease in cardiovascular disease, type 2 diabetes and metabolic syndrome. They suggested that if the relationship proves to be causal, interventions targeting vitamin D deficiency in adult populations could potentially slow the current epidemics of Cardio metabolic disorders. A study from Italy confirmed that hypovitaminosis D is very common in the elderly population. The study has been performed in an Italian Region where the supplementation of vitamin D in the elderly was not performed, suggesting that an awareness campaign of the doctors could be very useful to prevent bone metabolism abnormalities [52].

Calcium and vitamin D reduced supplies of calcium were associated with a reduced bone mass and osteoporosis, whereas chronic and severe vitamin D leads to osteomalacia, a metabolic bone disease characterized by a decreased mineralization of bone. The preclinical phase of vitamin D deficiency was most found in the elderly. They summed the major causes of vitamin D deficiency and insufficiency decreased renal hydroxylation of vitamin D, poor nutrition, scarce exposure to sunlight and a decline in the synthesis of vitamin D in the skin. A low calcium intake and a suboptimal vitamin D status were very common in the elderly. Evidence supports routine supplementation for these people at risk of osteoporosis, by providing a daily intake of 700-800 mg of calcium and 400-800 IU of vitamin D. This was considered an effective, safe and cheap means of preventing osteoporotic fractures [51].

Fracture Neck of Femur in old age and its relation to Vitamin D deficiency:

In a study from Spain on 324 patients over 65 years of age admitted to hospital with fracture neck of the femur, 67% were found to have vitamin D deficiency [53]. Vitamin D deficiency and low calcium intake were observed in many elderly subjects. The patients with the lowest BMD values had secondary hyperparathyroidism [54] Vitamin D deficiency leads to secondary hyperparathyroidism, increased bone turnover, and bone loss and, when severe, leads to osteomalacia. The international Multiple Outcomes of Raloxifene Evaluation study, a large prospective intervention trial in postmenopausal women with osteoporosis, offered the opportunity to compare vitamin D status and parathyroid function throughout many countries over the world. Low serum 25OHD (<25nmol/L) was observed in 4.1% of all women in the Multiple Outcomes of Raloxifene Evaluation study, ranging from 0% in southeast Asia (very few patients) to 8.3% in southern Europe. Serum 25OHD was between 25-50 nmol/L in 24.3% of the women. Serum 25OHD showed a significant seasonal relationship, with lower values in all regions in winter. Serum PTH correlated negatively with serum 25OHD ($r = -0.25$; $P < 0.001$). This significant negative correlation was observed in all regions. When serum 25OHD was less than 25, 25-50, or more than 50 nmol/L, respectively, mean serum PTH levels were 4.8, 4.1, and 3.5pmol/L, respectively (by ANOVA, $P < 0.001$). Similarly, mean alkaline phosphatase levels were 83.7, 79.1, and 75.7 U/L ($P < 0.001$), respectively, with increasing serum 25OHD this study, baseline data were available from 7564 postmenopausal women from 25 countries on 5 continents.

All women had osteoporosis. Treatment with vitamin D (3) and calcium increased serum 25OHD and decreased serum PTH significantly; the effect was greater for lower baseline serum 25OHD [55]. Vitamin D deficiency is common among elderly women with a high risk of fracture who live in southern New Zealand. This is most marked in the winter months. Vitamin D replacement is cheap and effective and should be considered in patients over 70 years of age who have a high risk of fracture and who live in temperate climates [56].

Also, in sunny countries there are similar low 25OHD levels with recommendations of even higher vitamin D doses [57]. Another study showed that advanced age, hypovitaminosis D and osteoporosis are independent risk factors for asymptomatic vertebral fractures (VF) in Moroccan menopausal women [58]. These studies show that there is a high percentage of old people having vitamin D deficiency with associated fractures due to poor calcification of bones. Vitamin D deficiency is common among elderly women with a high risk of fracture in those who live in southern New Zealand. This is most marked in the winter months. Vitamin D replacement is cheap and effective and should be considered in patients over 70 years of age who have a high risk of fracture in those who live in temperate climates [54].

Vitamin D in obesity and diabetes

Based on several studies described by Mezza et al, vitamin D deficiency is strongly associated with obesity mostly due to the poor storage of 25(OH)D vitamin in adipose tissue because of its lipophilic properties. The decrease in 25(OH) D levels may occur through several mechanisms such as a decrease in the calcium concentration, an increase in PTH, or a direct effect of vitamin D on worsening insulin resistance and secretion, augmenting the risk of developing type2 diabetes. Interventional studies have provided conflicting and inconclusive results due to the

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different populations studied, chemical formulations of vitamin D, doses, and time frame of supplementation. Further studies are required especially in subjects that are affected by a high risk of developing diabetes (impaired fasting glucose and/or glucose tolerance, possibly without obesity, based on the hypothesized mechanism of action of vitamin D, these subjects may be the main beneficiaries [59-66].

Conclusion

In this Communication l tried to highlight the role of Vitamin D in maintenance of normal health and accordingly survival, through trying to report the adverse effects of vitamin D deficiency from conception to old age. These adverse effects might be considered by some as mere associations without casual relations. Anyhow, this makes it a hypophysis for researchers to investigate as a starting point. for needy research, which is the means of acquiring the true facts. Vitamin D was considered as related to bone health and disease only, but recently its associations to many diseases with strong evidence of that the lack of vitamin D is directly related to its etiology. As hyperparathyroidism and hypocalcemia are sequel to lack of vitamin D, I can say after working on clinical vitamin D deficiency in a sunny country I cannot postulate but state that vitamin D is the essence of survival of humans as well as all living creatures.

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