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Vitamin D deficiency in mothers, neonates and children

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ABSTRACT

Vitamin D is produced in response to the exposure of skin to sunlight through UV-B synthesis. It can also be obtained from diet and dietary supplements. Vitamin D is essential for strong bones as it helps to absorb calcium from diet. Vitamin D deficiency mainly occurs if strict vegetarian diet is followed as mostly the source of vitamin D is animal based; therefore, exposure to sunlight is restricted or having dark skin color. Low vitamin D levels results in increased possibility of gestational diabetes among pregnant women, low birth weight and pre-eclampsia in infants, and mothers may suffer bone impairment, osteoporosis, hypocalcaemia, and hypertension. Vitamin D deficiency is directly linked with severe complication in mothers and neonates, causing rickets, poor fetal growth and infantile eczema in neonates. Higher prevalence rate of vitamin D deficiency has led professionals to emphasize on development of relevant precautionary measures.

1. Introduction

Vitamin D deficiency has been identified as a major public health issue, which is continuously increasing at a constant rate across the globe. Vitamin D is derived through UV-B-induced synthesis in the skin; however, the environmental factors along with the obsolete lifestyles often limit the exposure of sunlight. Limited exposure to the sunlight along with sedentary lifestyle usually results in the increased prevalence of vitamin D deficiency. Moreover, there are a significant number of orthopaedic complications, which usually affects the wellbeing of patients. Vitamin D deficiency has diversified adverse effects in mothers, neonates, and children.

It is a fact that low mineral vitamin D status during pregnancy is directly associated with accumulated adverse effects. It has been identified that lower vitamin D level has been linked to depression [1], breast cancer [2], type 2 diabetes [3,4], type 1 diabetes [5], cardio-vascular diseases [6], auto-immune diseases [7], infections [8] and autism [9]; although, most of these associations are still under active research. Moreover, inadequate vitamin D deficiency among mothers may result in bone impairment, osteoporosis, hypocalcaemia, preeclampsia, preterm birth, and hypertension. Other studies mentioned that pregnant women with low 25(OHD) levels had an increased risk of gestational diabetes, pre-eclampsia, small for gestational age infants and low birth weight infants but no association with delivery by caesarean section [10]. Similarly, neonates are at excessive risk of poor fetal growth, rickets, and infantile eczema due to deficiency of vitamin D. Furthermore, children may also suffer from severe hypocalcaemia, rickets, and other orthopaedic complications. Therefore, it is said that adequate vitamin D status is healthier for mothers, neonates, and children to regulate their body processes effectively. Increased prevalence rate of vitamin D deficiency has led the scientists and other professionals to focus on the development of precautionary measures. Therefore, many studies have been carried out to assure the wellbeing of patients, suffering from inadequate levels of vitamin D. There are several dietary sources to overcome the vitamin D deficiency along with its serving is shown in Table 1.

Specifically, the core focus of the previously published studies has been made on the deficiency and its prevention among general population. Although, the studies have been conducted by considering mothers, neonates, and children; however, no any study has gathered these three population segments for identifying adverse effects of vitamin D deficiency. Thus, this study has aimed to evaluate the adverse effects of vitamin D deficiency among mothers, neonates, and children collectively. Moreover, certain precautionary measures will be also recommended to this population to address their complexities accordingly.

The review has aimed to retrieve necessary data in regards of vitamin D deficiency among mothers, neonates, and children, which is necessary to be evaluated for better precautionary

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Table 1
Dietary sources.

Nutritional Sources of vitamin D		
Food	Serving	Content of Vit D
Cod liver oil	1 tablespoon	360 IU
Salmon, Cooked	100gram	345 (IU)
Mackerel, cooked	100 g	345 (IU)
Sardines, canned in oil	50 g	250 (IU)
Tuna Fish, canned in oil	85 g	200 (IU)
Egg (Vitamin D is in egg yolk)	1 whole	20(IU)
Milk, non-fat, Vitamin D fortified	1 cup	98(IU)

measures. In this review, information about vitamin D sources has been presented along with the definition of vitamin D deficiency/ insufficiency and its epidemiological prevalence focusing on the Gulf region. In addition to that, the importance of vitamin D to the health of pregnant women, their neonates, and their children later in life has been also presented. This review has also focused on two important issues related to vitamin D deficiency, which mainly include prenatal outcome and the metabolic bone disease in preterm infants. Moreover, the review has also utilized compounded interventions for analyzing its significance in reducing the complexities of vitamin D deficiency. Thus, the review has scrutinized enormous resources for presenting valuable information on the basis of deficiency and approaches to improvise levels of vitamin D in body.

2. Methodology

Qualitative research has been employed for carrying out the review on the basis of previously published literature. A systematic approach has been developed for the assessment of data in regards of vitamin D deficiency among mothers, neonates, and children. The review has mainly considered reliable resources for retrieving data for the last 10 years. The analysis of the collected data has been done in accordance with the standardized principles of systematic review. Thematic and content analysis approaches have been also utilized for the review of literature on the basis of identified variables. Therefore, effective methodological aspects have been utilized for assessing and analyzing collected data.

3. Results and discussion

3.1. Vitamin D sources

Sources of vitamin D for human body include dietary intake and sunlight. Regardless of the sources, it is transported to the liver for conversion to 25-hydroxyvitamin D 25(OHD), a main circulating and storage form. 25(OHD) is transported to the kidneys where it is converted to the active form of vitamin D, which is 1, 25-dihydroxyvitamin D (1, $25(OH)_2$ D), a process that is tightly regulated by parathyroid hormone (PTH). The best assessment of vitamin D level in the human body, is estimation of 25(OHD) in the blood [11]. Sunlight exposure often has a major influence on vitamin D level in human body. The effects of exposure to sunlight are profoundly dependent upon skin color, latitudes, seasons, use of sun-block, and cultural practices. While sunlight is a major potential source for vitamin D, the American Academy of Pediatrics (AAP) always advises to keep infants out of direct sunlight and to have them wear protective clothing, which usually leads to lack of sun exposure in this age group and eventually to vitamin D deficiency [12]. Lack of sunlight exposure, knowing that breast milk is relatively a poor source of vitamin D, increases the reliance on dietary sources of vitamin D plus supplementation for infants and children. Maternal 25(OHD) is assumed to freely cross the human placenta [13], maternal vitamin D status during pregnancy is important for vitamin D of the child not only in the neonatal period but also it extends to early infancy [13,14].

3.2. Definition of vitamin D deficiency and insufficiency

Vitamin D deficiency has been defined as a 25(OHD) level less than 20 mg/ml (50 nmol/l) while vitamin D insufficiency is defined as a 25(OHD) level between 21 and 29 ng/ml (52–72 nmol/l). It is a fact that vitamin D deficiency varies by age group; therefore, there are certain controversies in regards of the standardized level for identifying deficiencies. For this purpose, symptomatic approach is widely used for assessing the insufficiency of vitamin D [15,16]. The vitamin D deficiency has been studied and its global prevalence rate is summarized in Table 2.

3.3. Epidemiology of vitamin D deficiency

Globally, it is estimated that a significant number of people may be affected either by vitamin D deficiency or insufficiency [16]. Vitamin D insufficiency is observed in up to 60% of Caucasian women [17] and the rate among women with dark skin is estimated to be higher [18]. Even in areas with abundant sunshine, vitamin D insufficiency or deficiency is extremely common among women. For instance, substantial proportions of pregnant women reportedly were vitamin D deficient in Ethiopia (80%) and India (66%) [19]. It is anticipated that vitamin D deficiency is more common in countries where head covering and spending more time indoor is common like the Gulf region [20]. In Kuwait, 40% of mothers and 60% of their offspring were found vitamin D deficient on the day of delivery [21]; while earlier study from Kuwait reported more than 75% of pregnant women and approximately 90% of their newborn infants had 25(OHD) level less than 20 ng/ml [22]. In Qatar, 48% of pregnant women were reported to have vitamin D deficiency [23]. In UAE, Dawodu et al. [24] demonstrated low serum vitamin D levels among mothers and their breast fed infants. The results provided justification for vitamin D supplementation of breast-feeding infants and mothers in UAE [24].

3.4. Health outcomes in the perinatal and childhood period

In addition to its well-defined classical functions related to calcium homeostasis and bone development, emerging evidence suggested that adequate vitamin D status could play an important role in other aspects of health. Lower vitamin D level has been linked to depression [1], breast cancer [2], type 2 diabetes [3,4],

Table 2
Global prevalence of vitamin D deficiency [45,44].

Country	Age	Sex	Number of Participants	Mean 25(OH) Vitamin D
Sweden	71	Male	1194	68.7
France	35–65	Male + Female	1569	61
Italy	65+	Male + Female	1006	39.9
Switzerland	25–74	Male + Female	3276	50
Saudi Arabia	20–74	Male + Female	510	32.6

type 1 diabetes [5], higher risk of cardiovascular [6] and autoimmune diseases [7], infections [8] and autism[9], although most of these links remain under active debate.

The relationship between vitamin D status and perinatal health outcomes has also attracted enormous attention in the scientific community. Despite its critical importance, it is still unclear whether maternal vitamin D status plays a role in proper fetal and placental development and consequently affects pregnancy outcomes. Three recent literature reviews have attempted to answer this question [9,10,25]. One of these reviews found no clear evidence to suggest that low vitamin D levels in early pregnancy are associated with adverse pregnancy outcomes, mainly included preeclampsia, fetal growth restriction, preterm birth and still births [9]. The second review concluded that pregnant women with low 25(OHD) levels had an increased risk of gestational diabetes, pre-eclampsia, small of gestational age infants and lower birth weight infants but no association with delivery by caesarean section [10].

The last review based on reviewing five small randomized control trials suggested a protective effect of vitamin D supplement during pregnancy on low birth weight (LBW) but no effect on preterm delivery [25]. All reviews highlighted the need for further research to explore the link between maternal vitamin D level and various maternal and child health outcomes. On the other hand, the relationship between maternal vitamin D level and particular child health outcome such as infections has been investigated. There are a number of possible pathways that suggest a relationship between maternal vitamin D level and infant's predisposition to infections. Vitamin D has a direct role in the production of antimicrobial peptides such as cathelicidin which may help prevent infection during pregnancy and/or early childhood [26,27] (Table 3).

One recent published study proved an association between early onset neonatal sepsis and low maternal vitamin D levels in term infants [28]. Studies have also suggested that vitamin D pathways may be involved in the susceptibility to and outcome of Hepatitis B Virus infection acquired early in life [29]. Bacterial vaginosis, a highly prevalent vaginal infection that predisposes to adverse pregnancy outcomes, is also associated with maternal vitamin D deficiency in the first trimester of pregnancy [30]. In New Zealand, significantly greater risk of respiratory infections (colds, cough, whooping cough, chest infection and ear infection) was found by 3 months of age among infants with cord blood levels of 25(OH)D less than 25 nmol/l [31]. In contrast to this aspect, a cohort study followed-up children at age 9 months and found that mothers in the top quartile of 25 (OH) D statuses in late pregnancy were significantly more likely to report their children having been diagnosed with pneumonia or bronchiolitis, compared with those in the bottom quartile [32]. Thus, the epidemiological evidence has never been conclusive despite the biological plausibility of the link between maternal vitamin D level and infections.

3.5. Rickets

Rickets is a major public health condition that affects bone development in children. It indicates defective mineralization or calcification of bones due to deficiency or impaired metabolism of vitamin D, or calcium. Rickets was considered to be a deficiency disease during the early industrial revolution. It has been eliminated both from the developed world as well as from the developing countries. This disappearance in the early 1960s was mainly due to recognition of the role of sunlight in vitamin D homeostasis, fortification of milk and higher prevalence of formula use beside the use of multivitamin preparations.

Recently, this condition has been reappearing in many parts of the world including some industrialized countries [33]. A higher incidence has also been reported in many Arab countries having plenty of sunshine, such as Saudi Arabia, UAE, Kuwait and Egypt [34]. This reappearance is in part due to the following sociocultural factors: lack of exposure to sunlight, prolonged breastfeeding without supplementation, maternal vitamin D deficiency, poor weaning practices and lower maternal education [35].

In UK researchers reported a surge in rickets cases among children of special ethnic groups who do not get enough exposure to the sun due to religious or cultural reasons. Moreover, it has been found that vitamin D deficiency is linked to this surge together with the increased cases of neonatal hypocalcaemia and craniotabes. It has been further indicated that the early reduced bone mass in these children will also increase their risk for osteoporotic fractures in later life [36].

To prevent rickets and vitamin D deficiency in healthy infants, children, and adolescents, AAP launched guidelines for vitamin D intake as the breastfed infants should be given a daily supplement of 400 IU/day of vitamin D from the first few days of life and continue throughout childhood and the Formula fed infants should meet the 400 IU/day requirement through either formula or additional supplementation, also it was recommended to supplement the lactating mothers with >4000 IU/day [37]. Higher doses of vitamin D supplementation may be necessary to achieve normal vitamin D status in children with increased risk of vitamin D deficiency, such as those with chronic fat malabsorption and those chronically taking anti-seizure medications [37].

3.6. Vitamin D supplements during pregnancy

Supplementation of pregnant women improves neonatal calcium handling, muscular status of their children, and maternal vitamin D levels [38]. Maternal doses up to 4000 IU/day are usually tolerated; however, no trials to determine efficacy on fetal/neonatal stores. Wagner, et al. [39] have clearly indicated that the vitamin D supplementation is directly associated with the better fetus development during pregnancy. Moreover, De-Regil, et al. [40] has mentioned that better muscular functioning along with the regulatory processes of body is mainly dependent on the vitamin D supplementations.

3.7. Osteopenia of prematurity

Osteopenia of Prematurity or poor mineralization of the bone is a relatively common complication in extremely preterm infants with those under 1000 g and less than 30 weeks gestation at most risk. Metabolic Bone Disease (MBD) of preterm infants, defined as a

Table 3
Goals to have adequate levels of vitamin D [46].

Development goals	WHY it is important for mothers and children to have adequate levels of Vitamin D?
Eliminate intense poverty and hunger	Well-nourished mothers are able to provide better healthcare to their children and likely to have healthy infants. The infants are less probable to suffer from malnutrition.
Reduce the toll of Child mortality	Well-nourished women are less probable to have babies with low-birth weight and the infants are less likely to die in infancy.
Develop maternal health	Women are less likely to suffer bleeding during and after childbirth and they suffer less fatal infections.

reduction in bone mineral content relative to the expected level of mineralization for an infant of comparable size or gestational age in combination with radiographic and biochemical changes [38]. Prematurity is the greatest risk factor to MBD due to the following:

- Most calcium and phosphorus deposition occurs during the third trimester.
- Human milk has limited concentrations of calcium and phosphorus,
- The digestive system of preterm neonates has poor absorptive properties.

The current rate of MBD in (VLBW) infants is unknown with no universal consensus on its definition. Reported incidence varies between 10–55% in infants <1500 g [41]. A recent study revealed a high incidence of very low 25-OH-D concentrations in the cord blood of Arab preterm infants in the Middle East, likely attributable to very low maternal vitamin D status (Pediatrics, AAP clinical report, 2013). In Kuwait at Maternity hospital, Neonatal unit, the incidence rate was 26% in 2001 (43/168 infants <1500 which dropped to 11.4% in 2009 (28/244 infants <1500) "unpublished data"), Such drop is related to improvements in nutritional practices in the neonatal department with early feeding and adding sufficient supplementation of calcium and phosphorus to the preterm feeding, added to that early adequate supplementation of vitamin D along with the limited use of post natal steroids in the department all contributed to the decline in MBD incidence in this unit.

The etiology of MBD is complex, and related to both nutritional factors (inadequate intake of minerals), hormones (vitamin D) and to mechanical factors (lack of mechanical stress applied to the bones). The accretion of calcium and phosphorous increases exponentially in the fetus during the third trimester, with 80% present at term. To achieve similar rates of accretion for normal growth & bone mineralization, small preterm infants require higher intakes of calcium and phosphorous per kilogram when compared to term infants. The amount recommendations by AAP: 140–160 mg calcium/100 kcal and 95 to 108 mg phosphorous/100 kcal [42].

The clinical onset of MBD is usually between 6 and 12 weeks after birth. MBD carries a significant morbidity and characterized by a sequence of events. First it starts with biochemical evidence of disturbed mineral metabolism (low phosphate and high alkaline phosphatise). Afterwards, it is followed by reduced bone mineralization leading to abnormal bone remodeling and reduced linear growth which may result in impaired respiratory status and fractures in the acute neonatal phase, and this may affect the linear growth later in childhood. MBD in preterm infants has long-term complications that may affect bone health in adulthood [41–43]. Recommendations to prevent MBD include fortification of nutrition, monitoring of the disease, and early supplementation of minerals and vitamin D.

4. Conclusion

Lower serum vitamin D level is prevalent in the Middle Eastern and North African region (MENA). The lack of population based studies in regards of neonates, infants, adolescents and pregnant women constitutes a major obstacle to solve or minimize this chronic ongoing problem. It is a fact that the prevalence rate of vitamin D deficiency is directly associated with the development of acute to severe complications among mothers and neonates. Moreover, the complications related to rickets have been also observed among children, suffering from vitamin D deficiency. Therefore, vitamin D supplements are directly associated with reducing the complications among mothers, neonates, and children.

Conflict of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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