MENARCHE, PUBERTY AND VITAMIN D

INTRODUCTION

Recent findings, a number of epidemiologic studies and clinical trials claim that for normal growth and puberty sufficient levels of vitamin D₃ are important. Various studies investigate the role of vitamin D₃ and its metabolites in specific reproductive disorders of women and men. It is known, that vitamin D₃ modulates reproductive function in both women and men.

Vitamin D deficiency has been associated with chronic diseases, such as diabetes mellitus, certain types of cancer, neurologic disorders, cardiovascular risk, obesity and autoimmune diseases [1]. Nevertheless, data on the vitamin D status and its association with puberty and its disorders in girls are constrained. This paper is aimed to investigate the link between vitamin D₃ and puberty transition in girls. Vitamin D plays a key role in bone metabolism, maintaining of calcium homeostasis by intestinal and renal calcium absorption [1]. Majority of the effects of vitamin D are mediated by the vitamin D receptor (VDR), which is the only protein that binds 1,25(OH)₂D₃ [1]. The VDR is expressed in almost all body cells, such as immune cells, as well as ovary, testis, mammary gland, uterus, central nervous system cells and others [1]. All these data lead to extensive research on vitamin D₃ and its receptor as a potential influencing factor in the pathogenesis of a large number diseases, including infectious and autoimmune diseases, obesity, cancer, puberty disorders and infertility, connected with nonclassical function of this vitamin [1]. In the last few years, the prevalence of vitamin D₃ deficiency has increased in many parts of the world, what has caused an increasing number of medical research on the subject. Recent studies suggest that vitamin D₃ may be an important factor which triggers normal reproductive physiology. Unfortunately, the mechanisms by which vitamin D₃ deficiency affect female fertility and reproductive physiology are not yet well investigated properly.

There are few studies presenting the association of vitamin D₃ status and sexual maturation.

VITAMIN D AND HYPOTHALAMIC-PITUITARY – GONADAL AXIS

Puberty is the development process – the result of a complex series of molecular and physiological that culminates in reproductive capability. Puberty generally begins between the ages of 10 and 14 among girls. Boys undergo this period later, usually between 12 to 16 years of age. Gonadotropin-releasing hormone (GnRH) actively released from specialized neurons of the hypothalamus initiates the hormonal cascade, which causes activation of gonads and in that way physical changes of puberty. Puberty depends upon well coordinated interactions among all components of the hypothalamic-pituitary-gonadal axis. There are several factors which have an influence on the activation of the hypothalamus to trigger puberty transition [2]. Dynamic changes in glial-neuron interactions, and trans-synaptic changes in afferent glutamatergic, kisspeptinergic and GABA-ergic neurons have influence on GnRH neurons [3]. These changes may induce sustained GnRh peptide release and activation of the pituitary-gonadal axis [4]. Cyp27b1 and VDR are highly expressed in the hypothalamus [5]. Except this, Cyp27b1 and VDR are found in the pituitary and gonads that suggests, that 1,25(OH)₂D₃ may regulate the reproductive axis by its paracrine and/or autocrine activities on it [5]. Walker’s and others research shows that vitamin D₃ receptor expression peaks in the hypothalamus during the peripubertal period in male rats, suggesting that central vitamin D₃ signaling may be important for pubertal transition [6]. Prepubertal vitamin D₃ deficiency, in part, disrupts hypothalamic-pituitary function. Gezen-Ak and others suggested that vitamin D₃ regulates expression of L-type voltage-sensitive calcium channels and nerve growth factor release in the brain [7]. It is possible that vitamin D₃ deficiency
disrupts L-type voltage-sensitive calcium channel expression systems critical for peripubertal GnRH neuronal activation [8]. Studies in VDR null female mice suggest that vitamin D₃ deficiency induces gonadotropin-resistant atrophic ovaries [9].

There are several studies which show that girls with precocious puberty had insufficient levels of vitamin D₃. Precocious puberty is diagnosed in girls when sexual development begins before the age of 8, in boys, it is diagnosed when these changes occur before the age of 9. Dicken and others in their study demonstrated another finding, which demonstrates that peripubertal vitamin D₃ deficiency delays puberty and causes prolonged estrous cycles in mice, which were characterized by extended periods of diestrus and reduced frequency of proestrus and estrus. Moreover, these estrous cycles could be normalized in young adults by correcting the vitamin D₃ deficiency. According to these data Dicken and others suggested that peripubertal vitamin D₃ deficiency delays pubertal transition and disrupts estrous cyclicity by disrupting hypothalamic-pituitary axis physiology [4]. Therefore it is possible that vitamin D₃ directly regulates synthesis or release of gonadotropins and consequently regulates estrous cyclicity in mice. Even though, the relationship between vitamin D₃ deficiency and early puberty remains unclear.

AGE OF MENARCHE AND VITAMIN D

The first menstrual period, menarche, is one of the most significant milestones in a woman’s life. The age at menarche is an important anthropological variant which may influence the overall duration of tissue oestrogen exposure and then affect women’s health in later life [10].

Age at menarche is known to be regulated by genetic and environmental factors [11]. The timing of menarche is genetically determined [12]. Early menarche is related to increased risk of adverse health outcomes during adulthood including obesity, type 2 diabetes, cardiovascular disease and breast and endometrial cancers [13, 14]. In addition, early menarche has been associated with behavioral and psychosocial risk factors during adolescence, such as alcohol consumption and smoking, early sexual debut, and teenage pregnancy [15]. Modification of these factors might contribute to decreased risk of adverse health outcomes related to early menarche [16]. Grivas investigated that girls who lived at higher latitudes appeared to have earlier initiations of menses than girls who live closer to the equator [17]. Although it might be explained by differences in temperature, light-darkness rhythms, and socioeconomic conditions, it also corresponds with a geographic gradient in sun exposure that, in some regions, coincided with vitamin D status [17]. Vitamin D₃ deficiency is associated with the development of adiposity in children and childhood obesity could be a risk factor for early puberty, thus, vitamin D might play a role in the timing of puberty [18]. Childhood obesity could lead to accelerated sexual maturation [19]. The association between vitamin D status and age at menarche could have been confounded by the age or adiposity level, because vitamin D could have been redistributed from blood into adipose tissue as a hydrophobic compound that’s why and adiposity may have an independent risk factor for early menarche [20, 21]. So this way, vitamin D₃ status could indirectly affect the age at menarche by its effect on obesity [22]. In cohort study of school-age girls, vitamin D deficiency was associated with the early onset of menses. The difference in the estimated mean age at menarche between vitamin D-sufficient and vitamin D-deficient girls in the research was almost 1 year [16]. Some studies in mice and humans indicated that increases in leptin resulted in early puberty [23]. 25(OH)D₃ is inversely correlated with leptin concentrations. It is unknown that the expression of leptin or other hormones from adipose tissue would change in response to vitamin D₃ supplementation [16]. The other possible mechanism was that vitamin D had inverse correlation with insulin-like growth factor-1 (IGF-1) [1]. IGF-1 modulates the onset of puberty and pubertal progression by stimulating the GnRH [1]. So, it is conceivable that vitamin D-mediated effects may influence IGF-1 levels and pubertal onset through an effect on gonadotropin and sex hormone [1]. Villamor and others followed a cohort of 242 healthy girls (age 5–12 years) for a median of 30 months and found that vitamin D deficient girls have an earlier initiation of menstruation than girls with sufficient vitamin D₃ [16]. There could be other biological mechanisms involved in the association of vitamin D deficiency with early menarche that are independent of obesity. Early menarche and vitamin D deficiency are both associated with poor health outcomes, and further exploration of their association is important for women’s health [2].

CONCLUSION

In conclusion, this paper was written to show different studies on vitamin D₃ and its influence on puberty. Consequently, vitamin D₃ deficiency was more common in girls with central precocious puberty than girls with normal sexual maturation. Although the mechanism of vitamin D deficiency’s effect on pubertal progression is unclear and not yet well understood. We suggest that vitamin D₃ may regulate sexual maturation in girls. In the recent years emerging data have suggested that vitamin D₃ is not only important for the maintenance of bone health and for calcium and phosphate homeostasis, but also has an influence on neurohormonal regulatory multisystem effects, that can modulate health outcomes in women. Nevertheless, a lot of investigations suggest that an individual’s vitamin D₃ status may adversely impact reproductive functions. A key to the normal physiological initiation of puberty process is a proper administration of vitamin D₃ supplementation which could be an effective strategy to improve reproductive health in the group of adolescent girls.

REFERENCES


