Peak Bone Mass and Prevention of Osteoporosis in Adolescence: Role of Vitamin D and Calcium

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Abstract: Peak bone mass (PBM) reaching 80-90 percent in late adolescence, it is a major determinant of bone mass later in life. Prevention of osteoporosis should start early in life, before PBM is reached. Puberty has varying effects on skeletal mineralization depending on the skeletal site and changes in hormone concentration of different bones. Vitamin D and calcium have been recognized as potential contributors to bone development and bone strength. In Saudi Arabia, vitamin D deficiency is common among youth. Many factors can influence to achieve peak bone mass. Some of these factors can’t be change such as race, gender, however, the ones that can be changed are physical activity and nutrition. Targeting this age group may help generate a better understanding of bone health and reduce the risk of osteoporosis in later life, which is a very costly disease. Therefore, it should be educate school adolescents by developing a program for public health recommendations to improve their knowledge in health and lifestyle and increase their poor information about the nutrient intake, sunlight and bone health, which will be vital for the future of Saudi Arabia.

Key words: Peak bone mass • Adolescence • Vitamin D • Calcium • Osteoporosis • Saudi Arabia

INTRODUCTION

Peak bone mass (PBM) can be defined as maximal bone mineral density which increases dramatically reaching 80-90 percent in late adolescence that is a major determinant of bone mass later in life. The importance of peak bone mass is determined by resistance or susceptibility of fracture [1]. Prevention of osteoporosis should start early in life, before PBM is reached [2]. Bone mass accretion during adolescence appears to be an important development for PBM [3], both females and males between the ages of 12 and 16 years gain the majority of their skeletal bone mass, which is about 40% of their adult bone mass due to an increase in bone size as shown in cross-sectional and some longitudinal studies [4-9]. Epidemiological studies indicate that a 10% increase in PBM, can help to decrease the risk of osteoporosis by 50% in the future [10]. Puberty has varying effects on skeletal mineralization depending on the skeletal site and changes in hormone concentration of different bones [11]. The age by which PBM is achieved in the hip is younger than in the spine and body mineral content (BMC) of the spine continues to increase in the early thirties in females [12]. Bone mineral density (BMD) and BMC may have a large variance at mid-puberty to menarche in both healthy females and males, which is assessed by Dual-energy X-ray absorptiometry (DXA) [13]. Although the bone mass can be influenced genetically by up to 70-80 percent [14], the remainder can be affected by environmental factors such as physical activity and nutrition which can modulate bone mass accretion during growth [13]. Vitamin D and calcium have been recognized as potential contributors to bone development and bone strength [1, 5]. Vitamin D deficiency occurs commonly in many parts of the world [15], because vitamin D synthesis in the skin may be lower during the winter, at the same time the bioavailable sources of vitamin D are limited. In fact vitamin D deficiency can affect the bone mineral acquisition; and can lead to increases of altered bones remodeling in adolescent [16]. Previous studies indicated that there is some interaction between calcium and vitamin D in bone metabolism [17]. Intervention trials in adolescents have shown that calcium intake plays an important role in bone mineral accrual [18, 19]. However, in the past decades calcium intake has declined in adolescents and inadequate vitamin D intake has been exhibited in up to 54% of teens [20]. In adolescents calcium supplementation has shown a positive effect on
BMD based on intervention studies [21, 22]. Sun exposure also has a positive effect on the bone mineralization by increasing the level of vitamin D [23].

In Saudi Arabia, vitamin D deficiency is common among youth [24]. There have been many studies focused on osteomalacia and rickets in both sexes [25, 26]. Other studies indicated that Saudi Arabian females have a low serum of 25(OH)2 D3 value due to inadequate dietary intake of vitamin D and avoidance of sun exposure due to their lifestyle or clothing habits [27-29]. On the other hand, there is not enough data showing the effects of vitamin D deficiency or low calcium intake on bone metabolism and BMD in Saudi adolescents [30, 31]. Vitamin D, calcium and sun exposure or malnutrition can have a suboptimal effect in adolescent bone health; however, this effect has not been given enough attention in intervention trials. From ages 10-19 years there is a significant increase in BMD and BMC at both lumbar spine and the proximal femur, although values for bone mineral density at the femur are greater than those at the spine; however, boys achieve higher bone mass than girls [32-34]. On the other hand, the PBM increased more at 16 yr old in girls than boys [35]. By the time an individual is in their twenties PBM can increase, as well as shown in cross-sectional and longitudinal studies [36]. In pubertal time the gender differences can influence the skeleton growth by changing the sex hormone that governs the sexual maturity, however, that difference is due to the estrogens in females [37], testosterone may not directly influence the skeleton growth at this time [38]. However, the bone mineralization accelerates at puberty more than those who are per-pubertal [11].

Factors Influenced on PBM: Peak bone mass has many factors that can influenced to achieve peak bone mass. Some of these factors can’t be change such as race, gender; however, the ones that can be changed are physical activity and nutrition.

Gender: Man has a higher bone mass than women; however, before puberty boys and girls have similar rates in gaining bone mass. After puberty, boys develop a greater bone mass than girls [11, 39].

Hormonal Factors: Sex hormones are essential for developing bone mass including estrogen and testosterone. When bone mass is related to the pubertal development stages it accumulates more than 37% in bone mass during tanner stage, which is a scale of physical development in adolescent [40]. Girls who have regular menstrual periods have a higher bone density, also the girls who start to menstruate have greater bone density [41].

Race: Some studies showed that, African American girls achieve higher peak bone mass and lower risk for osteoporosis later in their life than Caucasian girls [42].

Genetic: Bone mass is influence by genetic and modified by the environment [43]. Peak bone mass to a great extent is genetically determined from both parents. Also, the similarity between parents and their kids in BMD is present during the early adolescence, however, this increase during the growth suggesting a powerful influence on the rate of the mineralization and skeletal development during puberty [44].

Physical Activity: Healthy bone has shown to be associated with physical activity. Different types of physical activities can provide a great peak bone mass and decrease the age related bone loss [45].

Calcium and Vitamin D Status during Growth: A well balance diet has a great impact in bone health. The National Academy of Sciences (NAS), support that a healthy diet during the adolescence will achieve optimal bone mass accretion and reduce the degree of osteoporosis in later life [46]. Calcium is very essential for bone health as well as vitamin D and other vitamins and minerals such as magnesium and zinc. The deficiency of these nutrients especially calcium and vitamin D in early life has a negative impact for 5 to 10 percent of the population with lower peak bone mass and may increase bone fracture in later life [47]. The highest requirement of calcium is during the adolescence because of the high velocity of growth during puberty. To meet this high requirement of the calcium, thus adolescents have higher calcium absorption than children and adults and a higher level of the active form of vitamin D [48]. Research claims that the optimal vitamin D with calcium supplementation and enough exposure to sunlight through the life span may be important not only to maintain bone health, but also in protecting against many chronic conditions, including cancer, cardiovascular and autoimmune diseases[49]. Calcium supplementation trial indicates the positive relationship in bone mineral accretion [50]. Insufficient calcium intake can impair the lumbar spine [51]. There is an association between insufficient calcium intake and low serum of vitamin D [52]. Vitamin D deficiency is more than double in females than males, for
instance, there is study done in the US showed that adolescent males were consume the adequate intake of vitamin D, whereas the adolescent females were most likely to consume about half as likely as males of corresponding age to meet their dietary reference intakes[53, 54].

Metabolism and Biological Function of Vitamin D on Calcium Absorption: Vitamin D is essential to increase the serum of calcium and phosphorus, which required for the skeletal mineralization. It does not directly affect bone mineralization, however, it increase calcium absorption [55]. Whether, vitamin D3 derives from endogenous or exogenous sources, vitamin D3 will then converted to pro-vitamin D3, which is rapidly converted to vitamin D3, then is transported to the blood by vitamin D binding protein (DBP). Because vitamin D3 is fat-soluble vitamin it needs specific binding to be transported to the liver. At this time, vitamin D is being circulated by mitochondria to the liver in the form of vitamin D calcidiol (25(OH)2D3) and then converted to the active form in the kidney by mitochondria tocalcetiol (1α, 25(OH)2D3). The active form of vitamin D 1α, 25(OH)2D3 due to a tight regulation by parathyroid hormone (PTH), serum calcium and phosphorus and 1α, 25(OH)2D3 itself, as well as a relatively short half-life (4-6 hours), which is not a good indicator of vitamin D status. Once 1α, 25(OH)2D3 is formed then it binds to (DBP) and then travels to its principal calcium regulation target tissue such as intestine and bone. In the small intestine, 1,25(OH)2D3 binds to its receptor, vitamin D receptor (VDR), which binds to retinoid X receptor (RXR) to form a heterodimeric complex with VDR (VDR-RXR). The activated complex (VDR-RXR) binds to specific DNA sequence element (vitamin D responsive element (VDRRE)), which then influences the RNA polymerase. As a result the (VDR-RXR) complex now acts as a transcriptional enhancer in vitamin D activated transcription. After the gene has been activated in the intestine it is enhancing intestinal calcium absorption. Calcium absorption can occur via an active transport process (transcellular) that requires 1α, 25(OH)2D3, or by passive diffusion (paracellular), a vitamin D-independent process [56]. The vast majority of calcium absorption (77-92%) relies upon the transcellular pathway and thus upon the activity of 1, 25-(OH)2D3 [57]. The effect of vitamin D in calcium absorption can be determined by studying knockout mice, which are deficient in key member of vitamin D such as 1α-hydroxyls, encoded by Cyp27b1, which generates 1α, 25(OH) 2 D3 (the active form of vitamin D), the result shows decreased serum calcium and phosphorus, rickets, secondary hyperthyroidism, disorganized growth plate structure and osteomalacia [58]. In support of this, other studies indicated that vitamin D receptor (VDR) plays an important role in calcium metabolism by using KO mice [59].

Vitamin D and Bone Growth: Vitamin D3 is obtained when the skin is exposed to the sun, from cholesterol, or consumed in the diet including fatty fish such as salmon, sardines and mackerel, or from cod liver oil and form fortified food such as milk and orange juice as well as vitamin supplements [58]. However, vitamin D synthesis can be affected by latitude, time of the day, sunscreen, aging, protective cloth, glass and skin pigmentation, as well as the air ozone pollution [60, 61, 62]. Vitamin D deficiency could cause osteomalacia and secondary hyperparathyroidism and high bone turnover [62]. Additionally, other studies showed that vitamin D insufficiency has a detrimental effect in bone remodeling and bone mineral acquisition in adolescence [63-66]. Other studies, demonstrated that inadequate level of vitamin D may have a negative effect on peak bone mass [67]. Previous studies support a positive correlation between serum 25(OH)2D3 and BMD, which can indicate that vitamin D is essential in protecting bones [68]. Another study indicated that when serum 25(OH)2D3 is below < 40 nmol/L, in adolescent, they had a lower mean forearm BMD at both the radial and lunar sites than those with serum 25(OH) D levels ≥ 40 nmol/L (P=0.04) [69]. Moreover, the girls who have vitamin D deficiency had significantly lower cortical volumetric BMD at the distal radius (P<0.001) than girls with adequate vitamin D levels, using peripheral quantitative computed tomography (pQCT) which is used to measure (BMD) [70].

Vitamin D deficiency can be considered in adolescents as a serum 25(OH)2D3 concentration < 27.5 nmol/L (11ng/ml) which leads to bone abnormalities [20]. People who have vitamin D deficiency will only be able to absorb 1/3 to 1/5 as much calcium as they need [71]. Some studies determined that when the serum 25(OH) D is below < 36ng/ml, the PTH, serum alkaline phosphates are increased and lower serum calcium, which can increased risk of bone abnormalities, thus, compromising bone development in the adolescent [72, 73]. Several studies investigated the inverse relationship between PHT and vitamin D in adolescents [74, 75]. Skin pigmentation has a major impact on vitamin D synthesis, reported in levels of vitamin D in Asian people who live in the United Kingdom. It was found that the Asian population has an
extremely high prevalence of vitamin D deficiency [43]. In Western Saudi Arabia, vitamin D deficiency has been widely spread in both genders especially females [76]. The dietary intake of vitamin D in Saudi adolescents is below the recommended (10µg daily) [77]. Data obtained from the National Diet and Nutrition Survey suggested that vitamin D intake is worse in females more than males [78, 79].

**Vitamin D Recommendation in the Adolescent:** The American Academy of Pediatrics (AAP) in 2003 established the recommendation of vitamin D supplementation in adolescent to receive (200 IU/d or 5µg/d) of vitamin D daily. The current recommendation of AAP in all children age is (400 IU/d) of vitamin D indicative that it might be not enough for other children [46, 80]. A study was conducted in 2006 on 212 adolescent for 12 months with two different doses of vitamin D (the old recommendation and the new recommendation of vitamin D) 5µg/d, 10µg/d compared with the placebo to determine the effect of these different doses in bone mineral augmentation. This study showed that the femoral BMC augmentation was higher in both groups more that the placebo, however, the group who received 10µg/d was high than the group who received 5µg/d 17.2%, 14.3%, respectively [80]. Another study was conducted on Danish girls for one-year, randomized, placebo-controlled trial found that there is no significant effect of vitamin D, in both groups (low doses of 200 IU/d and 400 IU/d), on lumbar spine BMC and whole-body [81]. It will be difficult to make a universal recommendation in vitamin D supplementation to find the most effective dosing to achieve the optimal bone health status in school adolescents especially in country such as Saudi Arabia with a lot of sun exposure; there is still a high percentage of low vitamin D in adolescent [31]. Arguments that support vitamin D deficiency in Saudi Arabia: Religious beliefs. Women are veiled at the start of the menarchal age. Men traditionally wear long sleeves. The availability of vitamin D fortified foods. Foods fortified with vitamin D are hard to find. There are other factors which arguably account for more, based on these factors considerations for increasing dosage recommendations for individual person might be based on the baseline vitamin D level, season and their skin pigmentation. The key point to note is that, the old recommendation (200 IU/d or 5µg/d) [82] will not be adequate enough for Saudi adolescents. Thus, the new recommendation (400 IU/d or 10µg/d) [79] will might be adequate recommendation for Saudi adolescents.

**The Cut-Off points of vitamin D in Adolescent:** There is no standard agreement on the level serum of vitamin D. However, there are some suggestions for the cut-off point has been studied (Table 1).

**Calcium and Bone Growth:** Calcium is essential for bone growth and development; 99% of body calcium is in the skeleton. The calcium is also bound to protein, particularly plasma albumin. The dynamic equilibrium with protein-bound calcium and surface layers of calcium fixed in the skeleton is hydroxypatite [90, 91]. In the adolescent period the optimal dietary calcium intake is associated with enhanced peak bone mass at this age [92]. Dietary calcium intake has a threshold effect, the major source of the calcium is found in dairy products, additional sources such as canned fish and calcium fortified food [93]. Some evidence has shown that there is a positive correlation between adequate intake of milk consumption and BMD in adolescent (P< 0.05) [94, 95]. However, calcium absorption can be reduced by oxalates in leaf vegetables and by phytates in whole meal flours. Calcium secretion into the urine is increased by sodium in the diet and reduced by potassium [96]. A higher calcium intake will not cause an increase bone mass because it is tightly regulated by PTH, calcitonin and 1α, 25(OH) 2D3. If the calcium levels drop, PTH will cause resorption of the calcium from the bone, which then causes the reduction of the calcium in the bone [91].

Cross-sectional data indicated that adequate calcium intake has beneficial effects on peak bone mass [97]. Thus, any reduction in this intake can reduce the bone mineralization [98]. Long and short studies revealed that

<table>
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<th>ng/ml</th>
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<th>Bone Health Status</th>
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<tr>
<td>&lt;20</td>
<td>&lt;25-30</td>
<td>Vitamin D deficiency, which lead to rickets [82-86]</td>
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<tr>
<td>21-29</td>
<td>&lt;30-50</td>
<td>Vitamin D insufficiency, inadequate for bone status and result in rickets and osteomalacia in the longer term [82, 87,88]</td>
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<tr>
<td>30-100</td>
<td>75</td>
<td>Reference range Required to suppress serum PTH levels and for optimal bone status [82, 88,89]</td>
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<td>Ideal= 40-60</td>
<td>75</td>
<td>Reference range Required to suppress serum PTH levels and for optimal bone status [82, 88,89]</td>
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<td>&gt;150</td>
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the increased levels of adequate intake of calcium has a positive influence on bone mineral acquisition during adolescence [99-102]. Other investigators suggested that one of the important risk factor for fractures is a low calcium intake [103]. A randomized study found significant intervention effects in percent change of BMD and calcium supplementation range between 300 to 1000mg/day with 18 months or 3 years in a study on adolescents [104-106].

**Calcium Recommendation in Adolescent:** The calcium absorption is increased during puberty [107]. Most data suggested that the optimal intake of calcium in this age should be between (1200 mg/day and 1500 mg/day) for adolescents between 9-18 years of age [79, 94]. On the other hand, below this amount the PBM will not be achieved and the skeleton may not receive as much calcium as it needs [108,109]. Calcium intake can be measured with dietary questionnaires, but estimations should include consideration of bioavailability of calcium from different food products, as well as calcium from supplemental sources [110]. There is study in adolescent boys showed that the calcium supplementation group (1000 mg/d) has higher 1.3% BMC; 2.5% lumbar spine; 2.3% hip; 2.4% neck; 1.5% lumbar spine bone area than the placebo only for relatively short periods of 13 months[111]. In adolescent girls when they take calcium supplementation (1000 mg/d) for a period of 12 months the lumbar spine BMD, total hip BMD and femoral neck BMD were higher than the placebo group 1.48±0.54%, 1.37±0.56% and 1.21±0.79%, respectively [112]. It might be not long-term effect in maintaining maximum peak bone mass [113].

**Sun Exposure and Bone Growth:** The main source of vitamin D is produced by the action of solar ultraviolet B radiation (290–315 nm) [114]. The ultraviolet B radiation (UV-B) is absorbed by 7-dehydrocholesterol, which is located in the skin, in the epidermis layer, lead to transformation to pro-vitamin D3, which is rapidly converted to vitamin D3. There has been a previous study showing that there is a link between winter sun exposure and effect on bone density [115]. Another study of both sexes found that there is significant positive association between high sun exposure and higher BMD [23]. There is study in both sexes indicated that there is an association between the highest category of sunlight and BMD in males at the femoral neck and at the lumbar spine 0.9% and 4.2%, respectively compared to those in the lowest category. However, in females the sunlight exposure was significantly associated with BMD at all sites compared to those in the lowest category of sunlight exposure, at the femoral neck and at the spine 8.9% and 10.5%, respectively. A study conducted in Saudi Arabia on children and adolescents their aged ranging between 6 to 18 years with nutritional rickets status; the study showed that the most important factor for lower levels of vitamin D at this age is a lack of sun exposure [31]. There are some factors that influence the absorption of sunlight in the skin such as age, latitude, time of day and year, renal function, skin pigmentation and use of sunscreen [61]. Moreover, In Jeddah, Saudi Arabia the UV light can be affected by heavy pollution [116]. Ladies in Saudi Arabia is covered all the time and menmostly wear long sleeve so, they are not exposed enough to sunlight. In addition, Jeddah is a sunny place with relatively high latitudes, therefore adolescents try to avoid the sun as much as they can and/or use a sun cream with a sun protection factor SPF >15 (which can probably reduce vitamin D synthesis more than 99.5%) [71]. In Saudi Arabia the temperature is hot throughout the most of the year, so being outdoor is very rare [31]. Moreover, socio-cultural practices play an important role in women avoiding sun exposure because they think that it is harmful [117]. Also there is a preference for lighter skin as it more desirable and seen as more esthetically pleasing.

**Sun Exposure Recommendation:** The recommendation of sun exposure is determine by the skin type and the latitude categories [71]. The time of the day is important because the angle of the sun is different, so is difficult to make vitamin D in the early morning or later afternoon [60]. Thus, for sufficient vitamin D synthesis in the skin, at least 25 percent of the body should expose to the sun is enable the body to make enough vitamin D (without sunscreen). For instance, face, hands, arms, back and legs between at least twice a week between 10 AM and 3 PM are needed to make enough vitamin D [71, 118]. Likewise, the prolong exposure to the sunlight will not cause overproduction of previtamin D3, the reason for this is previtamin D3 is maintained in a steady state, so there is no more than 10 to 15% of the initial cutaneous concentration of 7-dehydroxcholestrol will be converted to previtamin D3[61].

**Vitamin D and Calcium Status in Saudi Arabia:** Underlying reasons for low vitamin D, calcium intake is that the fortified foods and supplementation are not wildly available if so they are very costly. Other data has demonstrated the vitamin D statues in adolescent in 1992,
since then there is no study in prevalence of vitamin D outside of their homes, was 91.6% more than 3 times a week and mostly fast food with consumption of soft drink (84.9%) [132], the increase intake of soft drink can mainly affect the bone fractures in later life [133]. That study also showed that the vegetables, fruit and dairy products were low the recommended with the calcium intake of (642.55 mg/dl), also, they found that more than 31.4% of participants were hypocalcemia [132]. Inadequate intake of milk consumption, which is the main source of calcium and vitamin D, can be one of main factor affecting the bone status in adolescent and increase the lifetime risk of fractures [134].

Culture Clothing: In Saudi Arabia the clothing is very similar in both sexes. Traditionally, they were predominantly loose and flowing, which is very helpful in Saudi Arabia’s desert climate. Men’s clothing is called “thawb” which has long-sleeves covers most of their body, except their hand and face. On the other hand, women start from menarchal period wear a long black garment known as “abaya” that completely covers their whole body when they are in public, in addition to “abaya” avery conservative women wears a face, head and hand cover. However, some women would wear “abaya” without the hand and face cover [76]. Interestingly, these clothes are made from materials that prevent the vitamin D synthesis from UV-B radiation. Studies in Middle Eastern countries have demonstrated that there is link between deficiency of vitamin D and clothing [67, 118]. A previous study test of human volunteers wearing common clothing made of different fabrics such as cotton, wool and polyester in black and white colors for 40 min, conclude that there is no elevation in vitamin D synthesis from UV-B radiation. From this study we conclude that, Saudi Arabia is at great risk of vitamin D deficiency, which could probably affect their bone status [60], from wearing one of these materials when they are in public [60].

Gaps in Knowledge: In Saudi Arabia our knowledge of nutritional problems is still insufficient. Even though there are many researches around the world investigating the effect of vitamin D and calcium supplementations and sun exposure on bone health, the majority suggests numerous relationships physiological between vitamin D, calcium and sun exposure. However, this has not been tested in my country. It might be attributed to lack of government role on nutritional polices and strategies. This study will help fill several gaps in knowledge essential to move this field forward. At this time, the vitamin D status among the
healthy adolescent in both genders is still unknown. It might be due to a lack of epidemiological data regarding the distribution of clinical trials in healthy populations amongst this age. It is still unclear the line of the collaboration between the national research and the lack of education among a general population. At the individual level there is a high level of risk factor in consuming a diet, with high fat and low fruit and vegetable and less consuming of dairy intake combine with minimum physical activity especially outdoor. This study will help fill several gaps in knowledge essential to move this field forward. The proposed research will be one of the first opportunities to measure vitamin D status, assess the calcium and dietary intake and sun exposure of school adolescents. This study includes measuring of vitamin D status and BMD, BMC in adolescents. This trail will help to understand the relationship between vitamin D, calcium and sun exposure in bone health. Moreover, this analysis will help to evaluate insight as well as quantify associations between the adequate level of vitamin D, calcium and enough sun exposure and bone status among this particular age. This will further advance new concepts in women’s health research and sex/gender differences. Knowing the differential affect of sex and gender upon women health will give us better understanding on how dietary components relate to and impact bone health.

CONCLUSION

There were link between vitamin D, calcium and sun exposure and improvement in adolescents bone health during their rapid growth. Targeting this age group may help generate a better understanding of bone health and reduce the risk of osteoporosis in later life, which is a very costly disease. Moreover, the results of the trial will help establish the value of serum 25(OH) D for defining vitamin D sufficiency and adequate sun exposure for better health in adolescent children in Saudi Arabia. Therefore, it should be educate school adolescents by developing a program for public health recommendations to improve their knowledge in health and lifestyle and increase their poor information about the nutrient intake, sunlight and bone health, which will be vital for the future of Saudi Arabia.

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