Relationship between serum vitamin D and calcium levels in women of reproductive age in Taiwan – A pilot study

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Abstract: **Purpose**: We tried to evaluate the level of Vitamin D and calcium in serum in women of reproductive age in Taiwan. **Methods**: A cross-sectional was performed on a total of 125 healthy non-pregnancy and non-lactating women in 20-49 years in southern and northern Taiwan. Therefore, demographic, socioeconomic, and biochemical parameters for the estimation of serum 25(OH) D and calcium levels in female of reproductive age were studies. **Results:** Vitamin D deficiency (< 20 ng/ml) was present in 72% of total women. Women from middle socioeconomic class had the lowest mean serum 25(OH) D level (9.2± 5.4ng/ml) as compared to women from upper middle (11.2±5.2 ng/ml), lower (12.9±4.4 ng/ml), and upper (10.4±2.8ng/ml) socioeconomic class. Serum calcium levels were found in the normal range for all volunteers. Moreover, the mean vitamin D level in serum of women lived in southern Taiwan is higher than those in northern Taiwan. **Conclusion**: This is a high prevalence of hypovitaminosis D among women of reproductive age. These women had the tendency to develop the osteoporosis and associated complications. Enough intake of vitamin D supplements become necessary and important for the women aged 20-49 years.
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Introduction

Vitamin D is an important steroid hormone with endocrine, paracrine, and autocrine effects. It is produced endogegeously in the skin by exposure to ultraviolet rays or can be taken from exogenous source such as some food items and vitamin D preparations〔1〕. However, calcium is an essential component of bone mineral and thus, adequate calcium intake is considered important for skeletal health. Therefore, enough calcium intake, or use of calcium supplements, has become a fundamental strategy in the treatment of prevention of osteoporosis and even cataract recently〔17,18,40,50〕. Vitamin D is well known for its role in bone and mineral metabolism. Besides, it also plays an important role in the physiological field in our body both in skeletal function and extra-skeletal tissues. The vitamin deficiency is a major problem which may be associated with disorders of calcium, DM (type 1 and type 2), rickets, hip or other bones fractures, stunting in younger children, age-related macular degeneration, metabolic syndrome, cancers (e.g. prostate cancer), cardiovascular disorders, infectious diseases, several autoimmune diseases and even decreased mammographic breast density among premenopausal women〔2,3,20,26,27,29,42〕. In reproductive stage, vitamin D status is particularly important. Maternal deficiency has been associated with poor bone density, higher risk of osteoporosis particular in women who have repeated episodes of pregnancy and laceration.

Short- and long-term adverse effects in developing and offspring are associated with vitamin D deficiency. Furthermore, maternal vitamin D deficiency in pregnancy has also associated with an increased risk of pre-eclampsia and gestation diabetes mellitus〔6,7〕. The major source of sunshine exposure even though some of the women in Taiwan is suffering from vitamin D deficiency because that they are afraid from the photo-damage and stayed at home.

It is reported that hypo-calcium is frequently found in Northern Europe and North America. Lower calcium intake may result in hypertension〔43〕. Furthermore, hypo-vitamin D occurred significantly in Middle East North Africa and South Asia〔28,30〕. Goswami et al. women from reproductive age group are exposed to higher risk of developing abnormalities and other dissociated due to lower vitamin D levels〔8〕. However, there is a lack of scientific literature of vitamin D or calcium in women of reproductive age in Taiwan. Therefore, we designed a cross-sectional study to conduct to evaluate the status of serum vitamin D and calcium levels in women age.

Material and methods

A cross-sectional study was conducted on a total 125 healthy women in the reproductive stage of 20 - 49 years (55 subjects in northern Taiwan and 70 subjects lived in southern Taiwan). The participants included were attendant of patients receiving regular treatment from OPD services of different hospitals several years ago. The procedures were after informed consent for the patients was obtained.

The subjects were included on the basis of availability over a period of 6 months. Inclusion criteria adopted was non-pregnant, non-lactating women of reproductive age without any history of chronic diseases, vitamin D intake or any other dietary supplement. A pretested structured questionnaire was administered to each participant to get the information on socio-demographic profiles such as name, age, educational qualification, present occupation, and monthly income of the family.

The socieoeconomic status of the individuals were evaluated by Kuppusswamy classification〔9〕. Furthermore, non-fasting blood for the biochemical for the 25(OH)D and total calcium were checked. The procedure was following: 3 mL of blood was withdrawn from the median cubital vein from everybody. Then, the serum separation was carried out within 2 h after collection by centrifugation at 2100 rpm for 7 min. Serum sample were then stored at minus 80 degree Celsius till further analysis was done. Serum 25(OH)D and total calcium levels were estimated by chemiluminescent immunoassay (chemiluminescence) and colorimetetric assay (Roche Cobas) technique. The values were documented in ng/ml and mg/dl. Moreover, the vitamin D deficiency was defined as serum 25(OH)D level < 20 ng/ml〔10,11,12〕. The level were further categorized under three classification: mild deficiency (10 -- < 20 ng/ml), moderate deficiency (5--- < 10 ng/ml) and severe deficiency (< 5 ng/ml).

How to measure the serum (25(OH)D) levels

25(OH) D levels in serum were measured as a standard procedure. The LIAISON 25-hydroxyvitamin D Assay (DiaSorin) uses chemiluminescent immunoassay technology. The lower limit Quantitation of the assay was 4.0 ng/mL (DiaSorin LIAISON 25 OH Vitamin D TOTAL ASSAY, DIaSorin, Stillwater, MN, USA,2012) Specific antibody to vitamin D is used for coating magnetic particles (solid phase), and Vitamin is linked to an isoluminol derivative. During the incubation, 25 (OH)D was dissociated from its binding protein and competed with labeled vitamin D for binding sites on the antibody. After the incubation, the unbound material was added, and a flash chemiluminescent reaction was initiated. The light signals was measured by a photomultiplier as relative light units and was inversely proportional to the concentration of 25(OH)D present in sample. Internal and external quality control was maintained by running a sample of known concentration of 25(OH)D along with the samples for analysis.

How to measure the serum calcium levels

Serum total calcium estimation was done on automated analyzer, COBAS INTEGRA 400 Plus. Roche Integra auto analyzer (Roche Diagnostics India Pvt. Ltd., Mumbai India). Calcium ions react with O-ceresolphthelein under alkaline conditions to form a violet colored complex. The addition of 8-hydroxylquinoline prevents interference by mg magnesium and ferric ions. The color intensity of the complex formed was directly proportional to the calcium concentration. It was determined by measuring the increasing in absorbance at 552 nm. The value was expected in mg/dl.

Statistical analysis

Statistical package for social science (SPSS) version 20.0 was utilized for conducting the statistical analysis of the data (IBM Corp., Armonk, NY, USA). Data were expressed as mean ± standard deviation (SD), median (lowest to highest) and frequency.

Results

The mean age of all female volunteers (n=125) was 36.6 ± 2.5 years. The subjects (55%, 67 female) in this experiment were from urban areas, and a few subjects (45%,58female) were from rural areas. The percentage of individuals from the upper

socioeconomic class were (21%, n=26), upper middle (32%, n=40), middle (26%, n=33) and lower socioeconomic class (21%, n=26). The medium values for serum 25(OH)D and calcium level was found to be 7.3 (4-45) ng/dl and 9.8 (8.5-11.3) mg/dl. Moreover, it was found that 34% (n=42) patients had severe vitamin D deficiency followed by 33% (n=41) patients with moderate deficiency and 22% (n=28) with mild deficiency. Therefore, only 11% (n=14) of subjects had serum 25(OH) D levels equal to or more than 20 ng/ml.

Mean serum 25(OH)D and calcium level for individuals from upper socioeconomic class was (10.4± 2.8ng/ml) and (10.0±0.5 ng/ml), upper middle (11.2±5.2 ng/ml) and (9.7±0.2 mg/dl), and lower socioeconomic class (12.9±4.4 ng/ml) and (9.5±0.4), respectively. Serum calcium levels were found in the normal range for all volunteers. In result, it revealed that female volunteers from middle socioeconomic class had the lowest serum 25(OH)D level as compared to subject from upper, upper middle, and lower socioeconomic class. We further compared the results of subjects from southern or northern Taiwan. The mean serum 25(OH)D and calcium level from northern Taiwan group class was (12.1 ± 1.8ng/ml) and (9.0±0.4 ng/ml), however, the mean serum 25(OH)D and calcium level from southern Taiwan group class was (12.2 ± 1.8 ng/ml) and (11.0±0.4 ng/ml). Therefore, we found that serum calcium levels were found in the normal range for all volunteers in any place. Moreover, the vitamin D of women lived in southern Taiwan is all higher than those in northern Taiwan.

Discussions

The source of the Vitamin D is from sunshine exposure and dietary calcium intake〔4,5〕. At first, vitamin D can be produced endogeneously in the skin following sufficient and enough sunlight exposure (UVA and UVB); specifically exposure to UVB radiation (280-315 nm) 〔6〕. Dawson-Hughes B et al. reported that more than 80% of vitamin D intake is from sun exposure〔11〕. Other calcium source is from dietary intake. It is reported that increasing calcium intake increases passive calcium absorption from the gastrointestinal tract〔13〕. A higher cilium intake also increases the half-life of 25(OH)D in circulation〔14〕 and together these actions may explain the effect of high calcium in the lowest 25(OH)D tertile. However, a key physiological function of 25(OH)D is the maintenance of Ca homeostasis via active intestinal absorption. While 25(OH)D and calcium absorption have a positive relationship, there is a plateau to this effect.

The major source of vitamin D is a secosteroid that is produced cutaneously through solar UV-B irradiation of 7-dehydrocholesterol present in the skin. The second source of vitamin D is via food intake and like for calcium, the major component from the milk and other dietary products. Vitamin D undergoes two hydroxylation steps, one in the liver, one in the kidney 〔13,14〕. The final hydroxylation step in the kidney convert 25-hydroxyvitamin D (25(OH)D) to its active metabolite, 1,25-dihydroxyvitamin D (1,25(OH_2D), and the enzyme 1-α-hydroxylase catalyses this conversion〔15〕.

The role of vitamin D may maintain calcium and phosphorus homeostasis, promote healthy bone mineralization, induction of cell differentiation, inhibition of cell growth, inhibition of cell growth, and regulation of apoptosis. Furthermore, vitamin D is involved in regulating the function of the female reproductive system. Liu et al. observed many female with pregnancy and found that hormones regulated by the vitamin D system include estradiol, progesterone, human chorionic gonadotropin, and human placental lactogen, all of which are critical in maintaining regulation of reproductive health〔16〕. Besides, high intakes of dietary vitamin D and calcium may be moderately associated with a lower risk of early menopause〔21〕. Furthermore, calcium and vitamin D have been implicated in several gynecologic and reproductive conditions including polycystic ovary syndrome, endometriosis, premenstrual syndrome and even fertility〔22,23,24,25〕.

Maternal vitamin D deficiency or insufficiency during pregnancy has been related to preeclampsia, or gestational diabetes condition in bone disorder greater risk of cesarean diabetes delivery and preterm birth 〔31,32,33,34,35〕. Southern Taiwan is a place with ample sunshine, despite the fact; vitamin D deficiency continues to be a growing public health concern. Other than geographic factors and ambient UVB radiation there are individual-specific variables that affect endogenous production of vitamin D, such as limited access to sunlight, air pollution, skin condition, skin condition, pigmentation of skin, time spent outdoors, types of clothing, and sun protection practices〔36〕. People with darker skin require more UVB (e.g., longer time outdoors) to produce vitamin D. Exogenous sources of vitamin D include foods and supplements. Denova-Gutierrez et al. reported that milk, whole grains, and some types of fishes contain calcium〔37〕. In addition, Calvo et al. demonstrated that very few food contain vitamin D naturally〔38〕. However, fatty fish such as samon or mackerel; contain relatively high amounts, whereas other foods, such as meats, eggs, and shellfish, contain low quantities〔39〕. The calcium and vitamin D intake is very important. Kim et al. recommend that

daily calcium intake is 800-1000 mg per day and vitamin D intake of more than 800 IU per day, which appears to reduce the risk of fracture〔17〕.

In the past studies, the final result varies. For example, Sofi et al. reported that 88% of women of reproductive age group suffered from vitamin D deficiency (< 20 ng/ml) in India〔44〕. Moreover, other research conducted across the country have documented similar results of 96%, 76%, 58.5%, and 83% among women of reproductive age 〔45,46,47,48〕. In our study, we found that 72% of women (20-49 years old) was the victim of vitamin D deficiency. The data was similar as the above articles. In addition, it is interesting to find that the subjects from low socioeconomic position had higher mean serum (25(OH)D) level (12.9±4.4 ng/ml). We supposed that this phenomen is possibly due to higher sun exposure and active lifestyle in this group. A high prevalence of vitamin D deficiency and poor dietary calcium intake is likely to worse during pregnancy and may result in significant adverse health consequences in the newborn, including rickets and tetany. A recent meta-analysis concluded that vitamin D concentrations were lower in women with polycystic ovary syndrome compared with those without polycystic ovary syndrome, independently of body mass index〔49〕. The present study showed that we must pay attention to the phenomen and associated problems that high prevalence of vitamin D deficiency among the women aged 20-49 years in Taiwan. Moreover, the serum vitamin D of women lived in southern Taiwan is higher than those in northern Taiwan. We suggested that the reason is because of the amount of sunshine. However, the sample numbers in our study is relatively small. The more exact level needs further intervention in the future.

Conclusion

In our study, vitamin D deficiency is highly prevalent across all socioeconomic groups in southern Taiwan women of reproductive age. These women may possibly have a higher risk of developing osteoporosis, other diseases and pregnancy-related complications in future when the serum 25(OH)D is lower than 20 ng/dl.

In the presence of lack of naturally occurring vitamin rich foods in the country, food fortification and supplementation (e.g. milk) with vitamin and adequate sunshine exposure should be given a higher priority among these women, even men older than 50 years〔17〕.

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