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Title page:

Comparison of sun exposure versus vitamin D supplementation for pregnant women with vitamin D deficiency.

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Runing Title: Sun exposure versus vitamin D supplementation for pregnant women .

Abstract

Introduction: Maternal Vitamin D deficiency is widespread health problem which is more important in pregnant women which affects fetus growth and bone development. The aim of this study was to evaluate the effect of sun exposure versus vitamin D supplementation for pregnant women with vitamin D deficiency.

Methods and materials: This prospective clinical trial was performed on 87 pregnant women with vitamin D deficiency. Group A was treated with vitamin D 4,000 IU per day for 10 weeks, while group B was recommended for sun exposure for 30 minutes daily (30% body surface area) for 10 weeks in summer and between 10 am to 4 pm in direct sunlight. After the delivery, 25-hydroxyvitamin D_3 levels were measured in the same previous center. Moreover, weight, height and head circumference of fetus were measured at delivery in both groups and compared with each other.

Results: After 10 weeks intervention, 25-hydroxyvitamin D_3 levels was significantly higher in group treated with vitamin D as compared to sun expose group (31.27 vs 19.79 ng/ml). ($P<0.001$). However, height ($P=0.118$), weight ($P=0.245$) and head circumference ($P=0.681$) of infants in both groups did not show significant differences.

Conclusion: Vitamin D supplementation is more effective than sun exposure in increasing 25-hydroxyvitamin D_3 in pregnant women with vitamin D deficiency.

Keywords: Sunlight exposure, 25-hydroxyvitamin D_3, vitamin D deficiency.

Introduction

Maternal Vitamin D deficiency is widespread health problem which is more important in pregnant women (1). However, reduction in Vitamin D level due to minimal body exposure to sun light in pregnant women especially those wearing Hejab, can cause serious problem. Calcium level regulation in pregnant women requires appropriate vitamin D level for fetus growth and bone development to prevent any neurological disorder, also it is essential in fetal immune (2, 3). Vitamin D deficiency during pregnancy has been linked to number of health problems in offspring (3). The most important form of vitamin D is 25-hydroxyvitamin D, which introduced in the body by food intake with sufficient Vitamin D supplement. However, the major source of vitamin D is through the skin in exposure to sun light (ultraviolet B (UVB) radiation) (5) in the range of 280-320 nm which can penetrate skin and promote conversion of 7-dehydrocholesterol to pro-vitamin D3 (cholecalciferol) in the skin coupled with oral intake that is less what needed during pregnancy (3).

Moreover, near to all women of Iran have Hijab (a veil that covers the head and chest) due to culture and traditional. On the other hand, pregnant women are discouraged from outdoor activity, which causes serious problem in vitamin D levels for Iranian pregnant women. Hypovitaminosis D during pregnancy has important consequences for the newborn, including fetal hypovitaminosis D, neonatal rickets and tetany, and infantile rickets (4). Rickets during infancy has been associated with higher prevalence of lower respiratory tract infections (5), the largest cause of infant mortality in Iran. On the other hand, there is no study evaluates the complications of vitamin D supplementation in pregnancy, as well as vitamin D overdose leads to hypervitaminosis, but too much exposure to sunlight cannot reach toxic levels of vitamin D, because UV radiation make inactive the additional amounts of vitamin D_3(6). Therefore, this study was designed to evaluate the effect of sun exposure versus vitamin D supplementation in vitamin D levels for pregnant women with vitamin D deficiency, in order to find an appropriate way to regulate vitamin D levels and if sun exposure can raise vitamin D level enough?

Methods and Materials

This clinical trial was conducted in Obstetrics and Gynecology Department of Isfahan AL Zahra and Shahid Beheshti Hospitals, Center of Iran in summer 2015.

The vitamin D levels of patients receiving vitamin D supplementation (group A) were compared to patients who had sun exposure (group B). Inclusion criteria consisted of pregnant women with single fetus referred to Obstetrics and Gynecology department of AL Zahra and Shahid Beheshti hospitals with a diagnosis of vitamin D deficiency (serum levels of 25-hydroxyvitamin D_3 <30 ng/ml) (*7), signed a consent form to participate in the study and having gestational age 14 – 18 weeks and reside within the Isfahan limits. All patients were type 2 or 3 of skin color and had similar coverage and their jobs were indoor. Exclusion criteria consisted of patients with history of chronic hypertension, chronic disease such as musculoskeletal, diabetes, parathyroid, hepatitis, and kidney, any kind of malabsorption disorders, skin disease, skin cancer, having dark skin and dissatisfaction to continue participation in study, improper use of vitamin D, inappropriate exposure to sunlight, preterm labor, and lose to follow-up due to various causes.

Participants

The study flowchart is shown in figure 1. Ninety three patients with a diagnosis of vitamin D deficiency, who had been diagnosed by obstetricians and based on inclusion and exclusion criteria, were included. Sampling was performed in specific season (summer) and color of skin was similar for the patients of both groups. All patients were advised to eat fish only once a week. 25-hydroxyvitamin D_3 levels were measured in all eligible patients before intervention and in those with levels less than 30 ng/ml were randomly divided into two groups using a block randomization procedure. We used stored plasma samples to measure the circulating metabolite, 25-hydroxyvitamin D (25(OH) D), which is the accepted biomarker for vitamin D. [8] Radioimmunoassay (RIA) for 25(OH) D [7] was conducted by specific laboratory for all patients.

Eighty seven patients completed the study; 43 from vitamin D supplementation group (group A) and 44 from sun exposure group (group B). The study received ethics approval from the Ethics Committee of Isfahan University of Medical Sciences (394132), and all participants gave written informed consent.

Group A received vitamin D 4,000 IU per day for 10 weeks (Iranian Zahravi Corp.), while group B was recommended for sun exposure for 30 minutes daily (from shoulder to fingers and from thigh to toe (30% body surface area) without use of sunscreen) for 10 weeks in summer and between 10 am to 4 pm in direct sunlight. After the delivery, 25-hydroxyvitamin D_3 levels were measured in same previous center. Moreover, weight, height and head circumference of fetus were measured at delivery in both groups and compared with each other.

During this study in Isfahan, level of air pollution was investigated through Isfahan meteorological organization which was in standard range.

Data analysis

Data were analyzed and reported only for patients who completed the trial. Statistical analysis of data was performed using SPSS version 22 software. To compare qualitative variables between groups Chi-square test was performed. The normal distribution of all studied parameters was checked with Kolmogorov-Smirnov test. Student t-test and paired t-test were used for variables which were distributed in a normal way, besides Mann-Whitney and Wilcoxon test were performed for variables that have not normal distribution. The two tailed p-value less than 0.05 were considered significant. P-value <0.05 was considered significant.

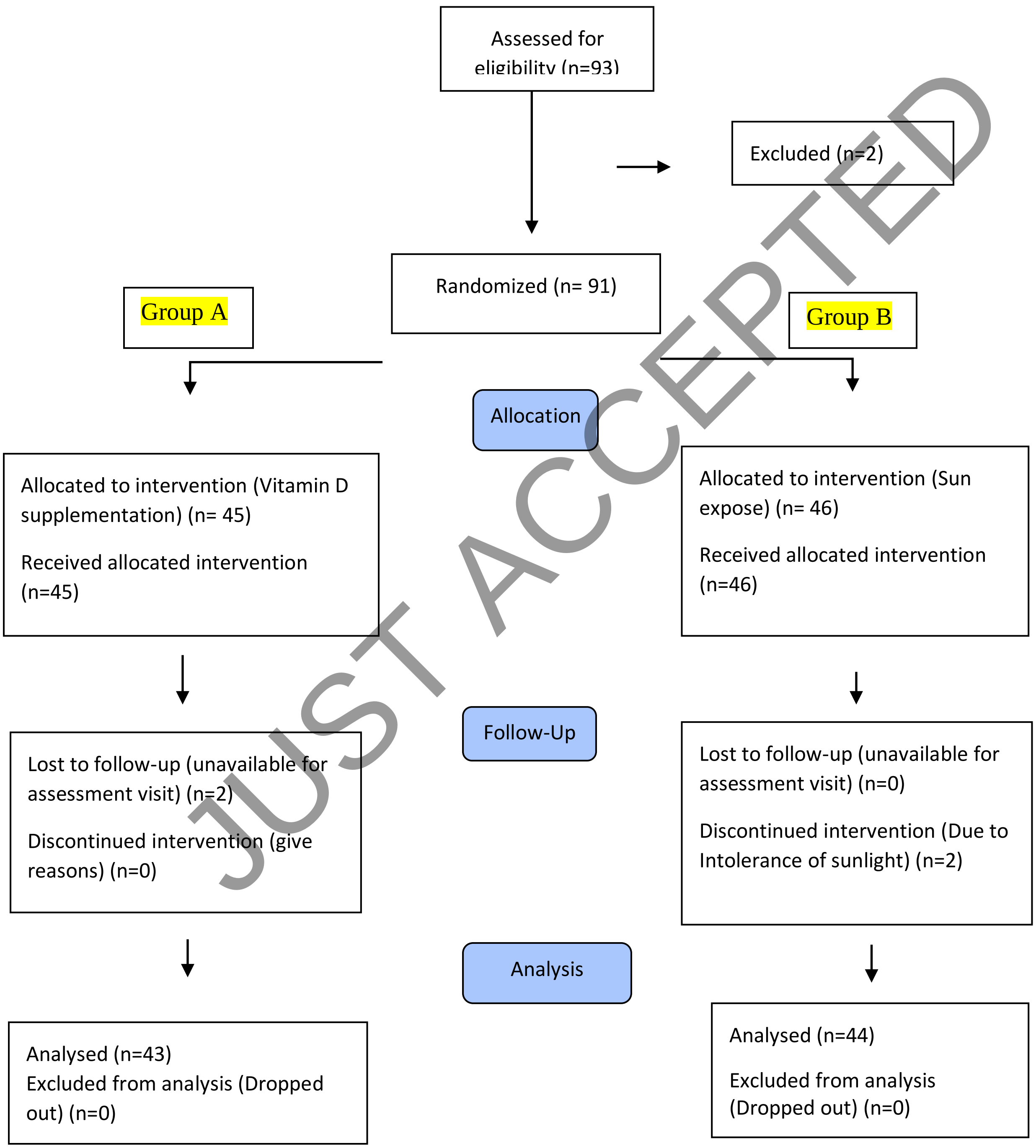


Figure 1. Study flowchart (CONSORT format)

Results

Demographic features in terms of age (P=0.844), gravity (P=0.125), gestational age (P=0.544) and history of abortion (P=0.414) in both groups were similar (Table 1). Four patients were dropped out and finally, 87 patients completed the study. Before intervention, target variable did not show significant differences between the groups. 25-hydroxyvitamin D_3 levels in vitamin D supplement and sun expose group were 15.95 ng/ml and 15.09 ng/ml, respectively (P=0.64).

As obtained, after 10 weeks intervention, 25-hydroxyvitamin D_3 levels was significantly higher in group receiving vitamin D as compared to sun expose group (31.27 vs. 19.79 ng/ml) (P<0.001). While by analyzing data with paired t test, 25-hydroxyvitamin D_3 levels in both groups significantly changed. (P<0.001, for both groups) However, height (P=0.118), weight (P=0.245) and head circumference (P=0.681) of infants in both groups did not show significant differences. (Table 2)

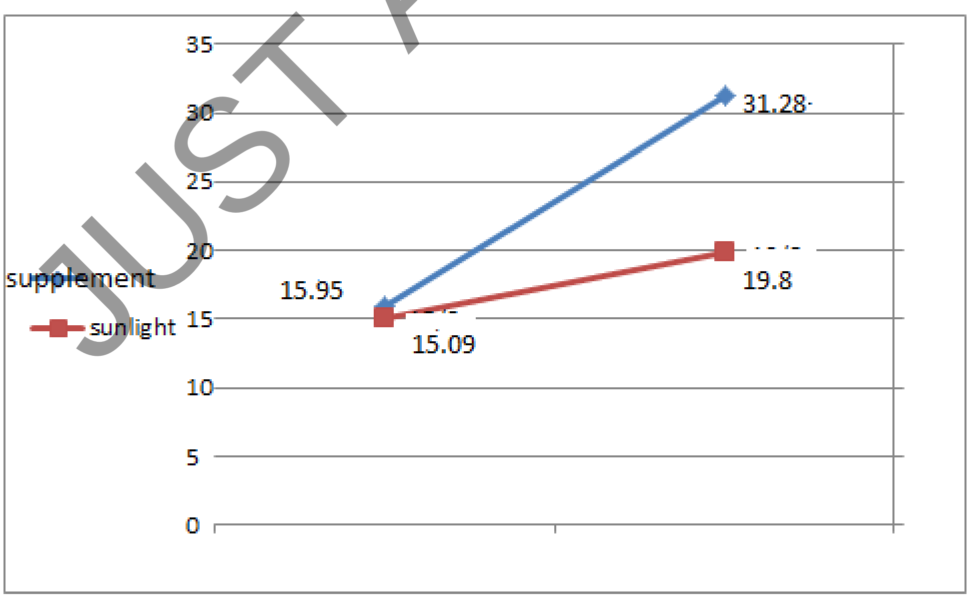
Mean change s of 25-hydroxyvitamin d3 was significantly more in vit d supplementation group. (Table 3)(Figure 2)

According table 4, by evaluation 25-hydroxyvitamin D_3 levels after intervention in both groups based on 25-hydroxyvitamin D_3 level before intervention, we found that 25-hydroxyvitamin D_3 levels after intervention in those patients had 25-hydroxyvitamin D_3 levels <10 ng/ml before intervention in both groups changed significantly (5.85 to 15.57 ng/ml in group receiving vitamin D, 5.56 to 7.93 ng/ml in sun expose group) (P<0.001). Moreover, according table 425-hydroxyvitamin D_3 levels after intervention in those patients had 25-hydroxyvitamin D_3 levels >10 ng/ml before intervention in both groups changed significantly (20.82 to 38.86 ng/ml in group receiving vitamin D, 20.53 to 26.57 ng/ml in sun expose group) (P<0.001). However, these changes were more in group receiving vitamin D as compared to sun expose group (38.86 vs 26.57 ng/ml, respectively) (P<0.001)

Table 1: Studied variables **before intervention** in both sun expose and vitamin D groups

Group Variables	Vitamin D	Sun expose	P-value
Age (year)(Mean±SD)	27.27 ± 4.47	27.09 ± 4.43	0.844
Gravity (Mean±SD)	2.04 ± 0.89	1.77 ± 0.74	0.125
Gestational age (week) (Mean±SD)	14.97 ± 0.96	15.11 ± 1.12	0.544
25-hydroxyvitamin D_3 levels (ng/ml) (Mean±SD)	15.95 ± 8.46	15.09 ± 8.66	0.64
History of abortion	2 (4.7)	4 (9.1)	0.414

Figure 2: comparison of the concentration of vitamin D in the blood (before and after treatment) in both groups.



concentration of 25-hydroxyvitamin D (ng/ml)"

Table 2: Studied variables at delivery **after intervention** in both sun expose and vitamin D groups

Group Variables	Vitamin D	Sun expose	P-value
25-hydroxyvitamin D_3 levels (ng/ml)	31.27 ± 14.54	19.79 ± 9.34	**<0/001**
Neonatal Height (cm)	49.93 ± 1.42	49.4 ± 1.64	0.118
neonatal Weight (gr)	3080.23 ± 452.12	2959 ± 509.59	0.245
neonatal Head circumference (cm)	34.83 ± 1.39	34.95 ± 1.25	0.681

Table 3: Mean change s of 25-hydroxyvitamin D3 in both sun expose and vitamin D groups

Variables	Mean	SD	Sig.
vitamin D_3	15.32	9.73	**<0.001**
Sun expose	4.7	3.63	**<0.001**

Table 4: Mean differences of 25-hydroxyvitamin D_3 levels before and after intervention in both groups .

Group 25-hydroxyvitamin D_3 before intervention		Vitamin D	Sun expose	P-value
<10ng/ml 34.48%	25-hydroxyvitamin D_3 before intervention	5.85 ± 2.07	5.56 ± 1.78	0.679
	25-hydroxyvitamin D_3 after intervention	15.57 ± 2.9	7.93 ± 1.73	**<0.001**
>10ng/ml 65.52%	25-hydroxyvitamin D_3 before intervention	20.82 ± 5.47	20.53 ± 5.76	0.845
	25-hydroxyvitamin D_3 after intervention	38.86 ± 11.41	26.57 ± 2.53	**<0.001**

Discussion

Hypovitaminosis of Vit - D and osteomalacia among pregnant South Asian women have been reported in many studies [10-12]. However, all studies but a few were from temperate regions such as the United Kingdom [12] and Norway, where the already low availability of overhead sun is compounded for Asian women by poor outdoor activity, pigmented skin, and excessive clothing [13].

Our study was performed in Iran where the culture and traditional increase vitamin D hypovitaminosis in pregnant women due to by poor outdoor activity and excessive clothing. On the other hand, in pregnancy, vitamin D concentration is 2-fold higher owing to the activity of placental 1-α-hydroxylase [12]. Therefore, increasing the level of vitamin D in Iranian pregnant women is more important than non-pregnant women and in other countries with more freedom in clothing.

There are two way to increase level of vitamin D in pregnant women. First is endogenous synthesis of vitamin D, which is more important from second method (dietary intake). Many studies in 1980 decade suggest that sun expose increased vitamin D levels more than that obtained by dietary intake [15-17], while recent studies and ours showed that receiving vitamin D supplementation increased the serum level of 25-hydroxyvitamin D_3 more. However, our study was the first investigation which evaluates two methods in pregnant women who are the most important group of society in regulating biomarkers such as 25-hydroxyvitamin D_3. Because, there is increasing evidence that vitamin D affects maternal and fetal well-being, and a deficiency is associated with a higher risk of developing pre-eclampsia, growth restriction, multiple sclerosis, schizophrenia, diabetes, and asthma [18].

Our study showed that after 10 weeks intervention, 25-hydroxyvitamin D_3 levels was significantly higher in group receiving vitamin D as compared to sun expose group (31.27 vs 19.79 ng/ml). As mentioned before, our sun exposed group receive appropriate sun light (sun exposure for 30 minutes daily (30% body surface area), without use of sunscreen for 10 weeks in summer), but at the end, group receiving vitamin D with dosage 4,000 IU per day for 10 weeks had higher levels of 25-hydroxyvitamin D3.

No consensus exists on the recommended intake and supplementation of vitamin D during pregnancy. There have been many studies with different supplementation dosage [19-23] and several authors agree that the current recommended intake of 200-600 IU (or 5-15 µg) is too low, daily requirements may be closer to 1000 IU (25 µg) or higher [24-26]. But we found that even with dosage 4,000 IU per day for 10 weeks did not increase 25-hydroxyvitamin D3 higher than 30 ng/ml at all women with vitamin D deficiency. These data suggest that, we should increase the dosage in pregnant women with vitamin D deficiency.

In a study performed on non-pregnant women, showed that the degree of association between sun exposure and serum 25(OH) D to be small (R (2) = 0.084), while the serum 25(OH) D level was significantly correlated with daily intake of dietary vitamin D (r = 0.20, P = 0.001). In the other word, they finally indicated that daily intake of dietary vitamin D and daily walking may be useful for increasing the serum 25(OH) D level, while sun exposure is not useful and cannot make sufficient levels of 25(OH) D [27], which has been proven in our study but in pregnant women. In a study conducted in Saudi Arabia in 2013, it was shown that the highest absorption of vitamin D is in the summer and between 10 am to 2 pm, while before 8 am and after 5 pm there is no absorption of vitamin D. [28] In a study conducted in Australia in 2007, it was shown that exposing 15% of the body surface for 10 to 15 minutes to sunlight, will produce 1,000 units of vitamin D [29], which has not been proven in our study. This fact may due to this fact that the absorption of vitamin D through sunlight, depends on various factors such as duration of exposure to sunlight, the surface of the body that are exposed to sunlight, the type of cover and clothes, season, geographical location and level of air pollution, the amount of melanin in the skin and use of sunscreen. [30] In totally, vitamin D administration is useful, safe and effective way to treat vitamin D deficiency in pregnant women.

Conclusions

We found that vitamin D supplementation is more effective than sun exposure in increasing 25-hydroxyvitamin D3 in pregnant women with vitamin D deficiency. Furthermore, there is still no consensus about the recommended supplementation dosage due to not reaching the levels of 25-hydroxyvitamin D3 > 30 ng/ml. A large scale study is needed to come to clinical guidelines and recommendation for obstetricians.

Conflicts of interest

The authors have indicated that they have no conflicts of interests regarding the content of this article.

Acknowledgments

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Alzahra hospital andVali –Asr Reproductive Health Research Center of Tehran University of Medical sciences.

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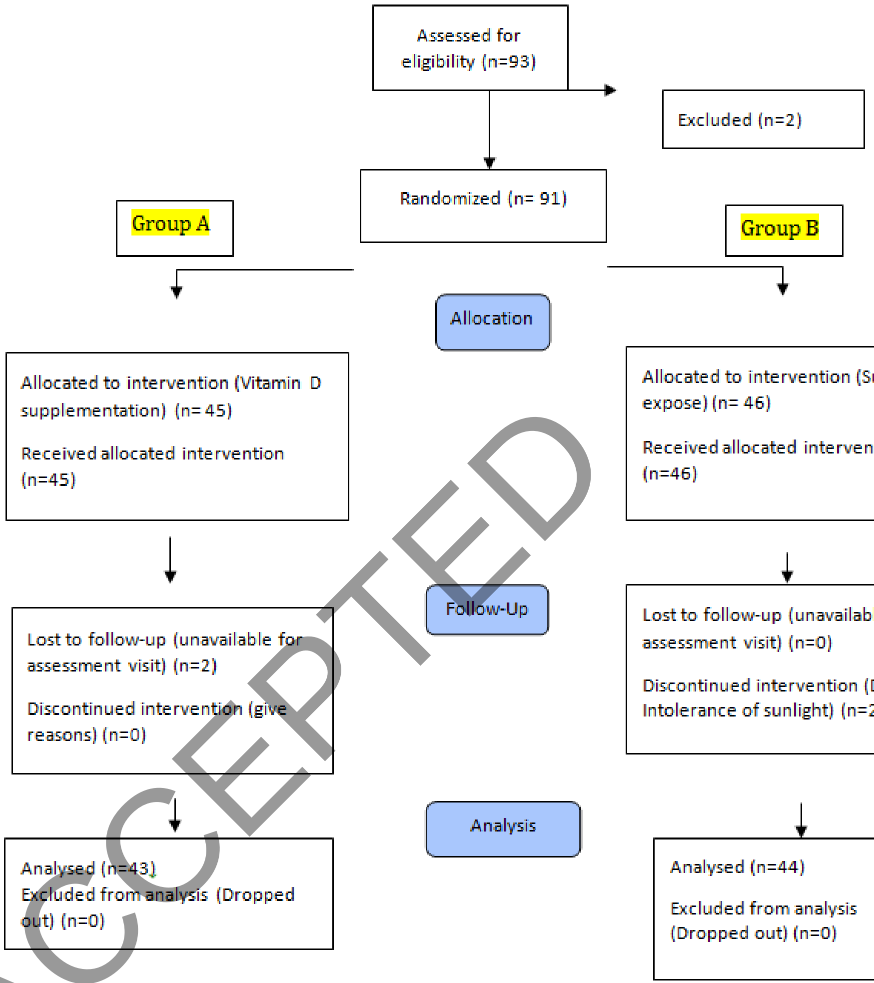

Figure 1. Study flowchart (CONSORT format)