Association between vitamin D and the risk of uterine fibroids

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Study objectives The primary objective of this part is to assess the efficacy of supplementation with vitamin D on decreasing the risk of incident uterine fibroids in one year and two years. The secondary objective of this study is to evaluate the safety of supplementation with vitamin D in subjects.

Trial design This is an open-label, randomised controlled trial. After signing of informed consent, hypovitaminosis D patients (12 ng/ml ≤ serum 25-hydroxyvitamin D_3 < 20 ng/ml) without uterine fibroids will be randomly assigned in a 1:1 ratio to intervention group or control group. Intervention group will receive an oral dose of 1600IU/day vitamin D_3 for up to 2 years. Control group will receive 2 years follow-up. Gynecologic ultrasound examinations will be performed every six months. The mount, location and size of the uterine fibroids will be documented. The safety of subjects will be evaluated, including blood routine examination, electrolyte, hepatic and renal function, liver and urinary system ultrasound, and serum 25-hydroxyvitamin D_3. Vitamin D receptor genotype of all patients will be tested. Vitamin D_3 Drops (soft capsules) are purchased from Sinopharm star shark pharmaceutical (xiamen) co., LTD and can be preserved for 2 years. An overview of the study design is shown in Figure 1 and in Table 1.

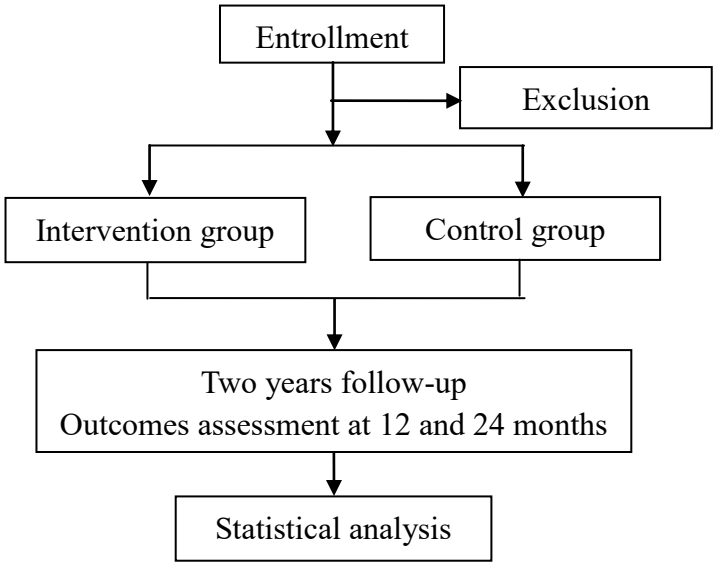

Figure 1: flow diagram.

Table 1:time of date collection

Follow-up	1	2	3	4	5	6	7	8	9
Months	0	3	6	9	12	15	18	21	24
The form of follow-up	Out-patient								
Informed consent	X								
Medical history	X								
Physical examination	X								
Serum 25-hydroxyvitamin D_3	X	X	X	X	X	X	X	X	X
Urine pregnancy test	X	X	X	X	X	X	X	X	X

Gynecologic ultrasound	X		X		X		X		X
Hepatic and renal function	X		X		X		X		X
Electrolyte	X		X		X		X		X
Blood routine examination	X		X		X		X		X
Liver and urinary System ultrasound	X				X				X
Side-effect assessment		X	X	X	X	X	X	X	X
Changes in menstruation		X	X	X	X	X	X	X	X
Adverse event assessment		X	X	X	X	X	X	X	X
Vitamin D receptor genotype	X								

Sample size The planned sample size was based on data from a previous study, in which the uterine fibroids incidence was 1.278% per year in Asia and 3.745% per year in African-American women. Women over the age of 40 years were more likely to have uterine fibroids. A study also revealed that African-American females had lower level of serum 25-hydroxyvitamin D_3 as compared to Caucasian females. Vitamin D deficiency was shown to increase the risk of uterine fibroids in vitro, in vivo animal models and in clinical trials. We assumed an one-tailed α error of 0.05 and a power (1-β) of 0.8. If the rates were 3.745% for the control group and 1.278% for the intervention group, we propose to enroll 1160 participants (580 randomized to each arm) and allow for a dropout rate of 10% for an effective sample size of 1054.

Inclusion criteria

1. Volunteer to participate in the study with informed consent;
2. Females aged 35-50 who are confirmed with a normal, fibroid-free uterine structure, by means of transvaginal or abdominal ultrasonography;
3. Serum25-hydroxyvitamin D_3 <20 ng/ml, ≥ 12ng/ml.

Exclusion criteria

1.Use of sexual hormone, mifepristone, gonadotropin-releasing hormone agonist (GnRHa), or other medication which is likely to interfere with uterine fibroids within 3 months;
2. Pregnancy, lactation, postmenopause, or planned pregnancy within two years;
3. Allergic to vitamin D_3;
4. Suspected or identified as other tumors of genital tract;
5. History of hysterectomy or myomectomy;
6. History of osteoporosis or vitamin D deficiency taking vitamin D supplements within previous one month;
7. History of hyperparathyroidism, infectious diseases (tuberculosis, AIDS), autoimmune diseases, or digestive system diseases (malabsorption, crohn disease and dysentery);
8. Alanine aminotransferase (ALT) or aspartate transaminase (AST) more than 3 times of the normal upper limit, total bilirubin (TBIL) more than 2 times of the normal upper limit;
9. Creatinine levels ≥ 1.4 mg/dL (123μmol/L) or creatinine clearance ≤ 50 ml/min;

10. History of malignant tumors;
11. Simultaneous participation in another clinical study with investigational medicinal product(s) or researcher thinks the subjects are not suitable for this trial.

Outcomes measures

The primary outcome is first diagnosis of uterine fibroids in different groups.

The secondary outcomes include hypercalcemia, abnormal liver and renal function, and urinary calculus in different groups.

Withdrawal Subjects must be withdrawn from the study when one of the following criteria occurs:

1. At their own request. At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantages as a result;
2. In the investigator's opinion, continuation of the study treatment would be harmful to the subject's health;
3. Obvious non-compliance;
4. Lost to follow-up;
5. Pregnancy;
6. Other medical or surgical treatments of uterine fibroids.
7. Receive other medical treatments which may affect the level of serum 25-hydroxyvitamin D_3 or other surgical treatments.
8. The level of serum calcium > 3.5 mmol/L or serum 25-hydroxyvitamin D_3 > 100 ng/mL.

Safety assessments Safety will be assessed by renal and liver function test, electrolyte, routine blood test, and serum 25-hydroxyvitamin D_3. Urine pregnancy test and serum 25-hydroxyvitamin D_3 level will be detected every three months. Other indicators are detected during the period of screening and after the treatment of every six months. Liver and urinary system ultrasound will be conducted after the treatment of 12 months and 24 months. The occurrence of any adverse events in trial participants will be recorded in the case report forms during each patient visit. We will withdraw patients who have severe adverse events, as it is unsafe for them to continue the trial. Meanwhile, we will give them relevant medical care and follow them up until the reaction has terminated.