Effect of Higher vs Standard Dosage of Vitamin D3 Supplementation on Bone Strength and bone metabolism in child with chronic kidney disease

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Research Article

Keywords: Chronic kidney disease, vitamin D, bone metabolism

Posted Date: July 20th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1843828/v1

Abstract

We investigated the effects of high VS. standard dose of vitamin D supplementation on kidney function and bone metabolism in children with chronic kidney disease (CKD). In all, 75 participants receive 2000 IU/D of vitamin D oral supplementation vs 75 participants who were randomized to receive 400 IU/d for a minimum of 4 months. We investigated the effects of vitamin D supplementation on kidney-related indicators and bone metabolism-related indicators at different doses. A total of 158 participants were screened and 150 met inclusion criteria. The indicators of chronic kidney disease, such as eGFR and serum uric acid, was negatively correlated with 25(OH)D levels and BMD. Serum 25(OH)D level and osteocalcin were positively correlated with spine BMD. The standard dose of vitamin D can improve serum uric acid levels, but high doses of vitamin D supplementation had no significant effect on serum uric acid. The high doses of vitamin D supplementation also improve alkaline phosphatase levels. When comparing the results of different doses of vitamin D supplementation, it was found that high-dose vitamin D supplementation did not improve bone density in the spine and femur neck relative to the standard dose of vitamin D, but improved low calciumemia and PINP levels. Among the children with clinical kidney disease, treatment with Vitamin D for 4 months at high dose, compare with standard dose of Vitamin D treatment, resulted in statistically significantly improve kidney function but no significantly different in bone metabolism.

Significance Of This Study

What is already known about this subject:

1. Epidemiological studies support the correlation between dose of 25-hydroxyvitamin D levels and chronic kidney disease.
2. The key players of the chronic kidney disease-mineral and bone disorders (CKD-MBD) are calcium, phosphate, the vitamin D hormonal system. vitamin D play important role in kidney and bone health.
3. Osteoporosis is only part of a spectrum of skeletal complications that includes osteomalacia and the various forms of renal osteodystrophy of chronic kidney disease-mineral and bone disorder (CKD-MBD).

What are the new findings:

1. The indicators of chronic kidney disease, such as renal globall filtration rate and serum uric acid, was negatively correlated with 25(OH)D levels and BMD. Serum 25(OH)D level and osteocalcin were positively correlated with spine BMD.
2. The standard dose of vitamin D can improved serum uric acid levels, but high doses of vitamin D supplementation had no significant effect on serum uric acid.
3. When comparing the results of different doses of vitamin D supplementation, it was found that high-dose vitamin D supplementation did not improve bone density in the spine and femur neck relative to the standard dose of vitamin D, but improved low calciumemia and PINP levels.

How might it impact on clinical practice in the foreseeable future?

1. This study provides suggestion for bone volume changes caused by different doses of vitamin D therapy in children with chronic kidney disease

Introduction

Chronic kidney disease(CKD) is a disease that seriously affects public health(1). The incidence and prevalence of chronic kidney disease is also increasing in children. In children, chronic kidney disease increases mortality (2, 3). CKD has a significant impact on a variety of factors, including growth, cognition and behavior, and cardiovascular health(4-7). It will have a significant impact on the quality of life of the children(8). The burden of chronic kidney disease (CKD) and its treatment may severely limit the ability of children with CKD to do daily tasks and participate in family, school, sporting and recreational activities(9). Chronic kidney disease has a significant effect on the absorption of calcium and phosphorus, which in turn affects bone system health(10). Osteoporosis is only part of a spectrum of skeletal complications that includes osteomalacia and the various forms of renal osteodystrophy of chronic kidney disease-mineral and bone disorder (CKD-MBD). Therefore, the label "kidney-induced osteoporosis" has been proposed. CKD is also associated with an increased risk of osteoporosis fractures(11). However, studies have also found that the relationship between osteoporosis and CKD is not very close(12).

The key players of the chronic kidney disease-mineral and bone disorders (CKD-MBD) are calcium, phosphate, the vitamin D hormonal system. vitamin D play important role in kidney and bone health. Vitamin D deficiency is very common in patients with CKD and has a significant impact on the progression of CKD. Besides, vitamin D influences skeletal mineralization principally through the regulation of intestinal calcium absorption. It has been proposed that vitamin D has direct beneficial effects on bone (besides the prevention of osteomalacia)(13). However,

meta-analyses of vitamin D trials show no effects on bone density or fracture risk when the baseline 25-hydroxyvitamin D is >40 nmol/L and A daily dose of 400 to 800 IU vitamin D3 is usually adequate to correct such deficiency(14). A Randomized Clinical Trial found that it is not helpful for high-dose vitamin D supplementation for bone health(15). The effect of different doses of vitamin D3 on bone metabolism in children with chronic kidney disease is not yet known.

Therefore, in order to determine the effects of different doses of VitD3 on the skeletal system. Our study analyzed the effects of high-dose and standard-dose VitD3 supplements on bone strength and bone metabolism in children with CKD.

Materials And Methods

Study design and human research

This study is a single-center randomized controlled study. This study was included in patients from 2011.1 to 2018.1 by 1: 1, and was approved by our Hospital Ethics Committee. All children have the consent of the guardian and sign an informed consent form. Clinical trial registration number is NO:DSE209931.

Partcipants

Children(1-18 year old) with 158 cases of vitamin D deficiency in this study were given a CKD stage of 2-5, which recived vitamin D supplementation or placebo control, respectively. The exclusion criteria are receiving vitamin D therapy or growth hormone or other receiving renal replacement therapy. Children were randomized to receive 1 of 2 formulations: the standard dose, 400 IU/d of vitamin D, or the high dose, 2000 IU/d. The standard dose was chosen to be consistent with vitamin D guidelines from the American Academy of Pediatrics (AAP)(16) and high dose was chosen to be within the tolerable upper vitamin D intake specified by the Institute of Medicine(17). Children could only be randomized into the trial during 4 months. Parents of participants received a drop-based formulation in order to ease administration of the study drug (Kids Ddrops containing Vitamin D3). Informed written consent was obtained from all caregivers, with assent from children as appropriate. All local research ethics committees approved the studies.

The sample size is estimated to be estimated at a potential 15% loss rate in 150 patients. The proportions were compared using the type of unilateral test, with a 95% confidence level, 90% statistical power and 15% accuracy. Subjects were taken consecutively from nephrology services. They continued with their medical, nutritional and physical activity protocolized treatment corresponding to their nutritional and CKD status provided by their nephrology service, which was not modified by researchers. Acute infection, hospitalization and refusal to participate were exclusion criteria.

Randomization and masking

The randomization sequence was generated using a computer-basedrandom-numbergenerator by the SickKids research pharmacy. The study biostatistician was unaware of the randomization sequence. Randomization was stratified by practice site with blocks of size 4. The research pharmacy prepared the vitamin D formulations in sealed, serially numbered bottles identical in appearance andweight to maintain allocation concealment. Study personnel, parents, attending physicians, laboratory personnel, investigators, and data analystswere all blinded to group allocation throughout the study period. Research assistants at each site approached participants for entry into the study.

Procedures and Outcomes

Figure1 shows flowchart of study enrollment. After providing informed consent, parents completed a standardized data collection form with questions. These included age, sex, birth weight, birth height, Body mass index, SBP and DBP. The mean baseline and 4 month follow-up were compared between the study and control group participant.

Bone mineral density were detected by DXA(GE Medical Instruments) and measurement sites included the lumbar spine 2-4 and femoral neck. CVs that were based on phantom scans ranged from 0.59% (spine) to 5.36% (femoral neck) for BMD. eGFR was determined by the Schwartz formula using locally determined k value of 0.33. Vitamin D deficiency was defined as 25(OH)D <75 nmol/L and vitamin D sufficiency as 75 nmol/L. Hyperphosphataemia and hyper-/hypocalcaemia were defined according to KDOQI guidelines(18). Since vitamin D3 is thought to have equivalent potency, their respective dosages were used to assess associations between vitamin D dosage and other parameters.

Details of Laboratory outcome collection, including routine clinical biochemistries (serum 25(OH)D, serum calcium, serum phosphorus, magnesium, uric acid, hsCRP, creatinine, albumin, parathyroid hormone (PTH)). bone health parameters (specific alkaline phosphatase (ALP), osteocalcin (OC), Procollagen I N-Terminal Propeptide (PINP) were measured using validated methodologies.

Statistical analysis

Data was analyzed on a per-protocol and intent-to-treat (ITT) basis; with missing data replaced by median values from the opposite group for each primary outcome variable (at each time point) in the ITT analysis. Comparison between two groups was performed with t tests for normally distributed variables and $\chi 2$ analyses for categorical data. Multivariable regression analyses were used to investigate covariates including baseline Body mass index eGFR, Serum uric acid, Hypocalcaemia, Serum phosphate, Serum 25(OH)D, ALP, Osteocalcin, spine BMD and Fummer-BMD. Comparison between two groups was performed with t tests for normally distributed variables and $\chi 2$ analyses for categorical data. Age, eGFR, Serum iPTH, Albuminuria, Serum uric acid, Osteocalcin and spine BMD were as factors associated with final 25(OH)D and $\triangle$25(OH)D were assessed by Spearman's rank correlations. Data are presented as mean ± standard deviation (SD) or median (25th-75th percentile) for variables demonstrating parametric and non-parametric distributions, respectively. Statistical significance was determined at a $p \leq 0.05$. SAS 9.3 (SAS Institute, Cary, NC, USA) or R version 3.3.3 (R Project for Statistical Computing, Vienna, Austria) was used.

Results

The flow of participants is presented in Figure 1. A total of 158 paeticipants were screened and 150 met inclusion criteria and randomized. Besides, 145 completed all aspects of 4 month trial. We found no significant difference in age(56 VS. 51, P=0.231), BMI(17.32±7.92 VS. 18.42±6.23, P=0.732), eGFR(49.23±2.93 VS. 51.92±5.62, P=0.334), serum 25(OH)D (12.92 VS. 13.83, P=0.573) and spine BMD(0.731±0.113 VS. 0.739±0.098, P=0.553) between high dose and standard dose of Vit D supplement. The others patient's baseline data is represented in Table 1.

The primary analyse included 150 participants. We further analyzed the correlation between multiple baseline data. The results showed that the index of chronic kidney disease, such as renal globall filtration rate and serum uric acid, was negatively correlated with 25(OH)D levels and BMD. Serum 25(OH)D level and osteocalcin were positively correlated with spine BMD(Table 2).

Effect of vitamin D supplemention on kidney function

Both high and standard doses of vitamin D improved serum 25(OH)D levels in children, but there was no significant difference in 25(OH)D levels between the two groups. We first analyzed the improvement of renal globall filtration rate and the albuminuria/creatinine ratio of vitamin D supplementation over a four-week high dose and standard dose. The standard dose of vitamin D can improved serum uric acid levels, but high doses of vitamin D supplementation had no significant effect on serum uric acid. We further compare the effects of high doses and standard doses of vitamin D on kidney function. It was found that high doses of vitamin D were compared to the standard doses of hsCRP and creatinine levels(**table 3**).

Effect of vitamin D supplemention on bone metabolism

Standard and high doses of vitamin D supplementation after 4 months will improve hypocalcemia, spinal bone density and femur neck bone density. At the same time, high doses of vitamin D supplementation also improve alkaline phosphatase levels. When comparing the results of different doses of vitamin D supplementation, it was found that high-dose vitamin D supplementation did not improve bone density in the spine and femur neck relative to the standard dose of vitamin D, but improved low calciumemia and PINP levels(**table 4**).

Discussion

Chronic kidney disease in children often leads to abnormal bone metabolism, which in turn affects the health of the bone system. Our study analyzed the effects of different doses of vitamin D on kidney function and bone metabolism in children with chronic kidney disease, and found that vitamin D supplementation improved kidney and bone metabolism abnormalities. Besides, compare with standard dose of vitamin D, high doses of vitamin D supplementation can improved kidney function and alkaline phosphatase levels only but there are no significantly different in bone density.

Bone metabolism in children of chronic kidney disease is a triad of biochemical imbalances of calcium, phosphate, parathyroid hormone and vitamin D, bone abnormalities and soft tissue calcification. The Kidney Disease: Improving Global Outcomes (KDIGO) 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) is a selective update of the prior CKD-MBD guideline published in 2009(19). Annika et al. found that patients with nephropathic cystinosis show more severe skeletal comorbidity associated with distinct CKD stage-dependent alterations of bone metabolism than CKD controls, suggesting impaired mineralization and increased bone resorption, which is only partially normalized after renal transplantation(20). Huang et al. investigated that higher prevalence of hip fracture, relative to that of the spine, among CKD patients and generate meaningful insights to guide care, prevention, and treatment regimens for CKD patients(12). Our analysis also found a significant correlation between kidney disease indicators and bone metabolism-related indicators.

Vitamin D deficiency (<20 ng/mL) and insufficiency (20-29 ng/mL) are common among patients with chronic kidney disease (CKD) or undergoing dialysis(21). Vitamin D supplement may play important role in CKD. Anna et al. found that multiple observational studies have demonstrated an association between the use of active vitamin D therapy in patients on dialysis and with CKD and improved survival(22). Meta-analysis found that The use of vitamin D supplement, especially vitamin D3 could reduce incidence of fall. Only vitamin D with calcium supplement showed benefit in fracture reduction(23). Patients with stage 3-4 CKD and vitamin D deficiency, vitamin D supplementation may improve vascular function(24). However, Among adults with type 2 diabetes, supplementation with vitamin D3, compared with placebo, resulted in no significant difference in change in eGFR at 5 years(25). This is also consistent with our finding that vitamin D supplementation also improves kidney function.

Vitamin D deficiency also is associated with many diseases such as enhances the risk of osteoporotic fractures. Randomized controlled trials in childhood and adolescents are urgently needed to support the potential of vitamin D as a complementary therapeutic option in mental disorders(26). For breastfed infants, vitamin D supplementation 400 IU/day for up to six months increases 25-OH vitamin D levels and reduces vitamin D insufficiency, but there was insufficient evidence to assess its effect on vitamin D deficiency and bone health. For higher-risk infants who are breastfeeding, maternal vitamin D supplementation reduces vitamin D insufficiency and vitamin D deficiency, but there was insufficient evidence to determine an effect on bone health(27).

In our study, we further analyzed the effects of different doses of vitamin D on the bone system of children with chronic kidney disease. It was found that the effect of high dose vitamin D on bone system has no significantly effect in bone metabolism with chronic kidney disease. This is also consistent with previous results. Lauren et al. found that high-dose vitamin D supplementation can not improve the bone health in adult(15). Not only that, but for adult women, studies have found that high doses of vitamin D have a greater adverse effecton the volumetric bone density(28). Besides, High doses of vitamin D also have a significant effect on kidney indicators. Thierry et al found that small (- 15%) but significant decrease in albuminuria after high dose vitamin D supplementation(29). A similar results has been found in our results. In animal experiments, Wang et al. showed that exposure to high dose of vitamin D3 decreased the levels of serum creatine, urea nitrogen and urine protein and restored the homeostasis of calcium and parathormone and vitamin D3 is a potential antifibrotic drug in chronic kidney disease via the vitmin D receptor and inhibiting TGF-β1/Smad3 signaling pathway(30).

There are several limitations of this study. First, this study was a single-center RCT study. Second, 5 patients were discharged between 4 month. Finally, 145 patients were ultimately analyzed in our study. The modest sample size could have affected the accuracy of the analysis. Additionally, the use of DXA in our CKD pediatric group is of limitations due to the unique growth and stature of our patients. Future studies should include multi-center studies with larger sample sizes to evaluate the performance of the different definitions.

Conclusion

Among the children with clinical kidney disease, treatment with Vitamin D for 4 months at high dose, compare with standard dose of Vitamin D treatment, resulted in statistically significantly improve kidney function but no significantly different in bone metabolism.

Declarations

Ethical Approval

This study was approved by Ethics Committee of Shandong First Medical University (NCSD2031233).

Preprint availability and repository

All participate approve this study.

Consent to Publish

All authors agree to publish.

Author Contributions

guarantor of integrity of the entire study Yan Fu, Kunna Lu, Yan Ma

study concepts Yan Ma, Feng Liu, Xinhuan Zhang

study design Zhiqiang Feng, Yan Ma, Feng Liu, Xinhuan Zhang, Yan Fu, Kunna Lu

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Funding sources

This research was funded by Academic Promotion Program of Shandong First Medical University (Grant No. 2019QL017).

Competing Interests

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Data availability

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Tables

Table1 baseline demographic, Health characteristic and laboratory values

variable	High dose of Vitamin D3	Standard dose of Vitamin D3	P value
no. of participants	75	75	
demograhics			
Men(%)	56	51	0.231
Age, mean(SD),y	9.2±2.3	10.3±1.9	0.123
Body mass index, mean (SD), kg/m2	17.32±7.92	18.42±6.23	0.732
Weight, mean (SD), kg	14.22±2,31	13.92±2.34	0.832
Height, mean (SD), cm	132.22±10.23	136.12±11.34	0.532
Birth weight, mean (SD), kg	17.62±5.34	18.12±6.52	0.346
SBP(mmHg)	115.92±11.23	113.82±8.32	0.122
DBP(mmHg)	63.92±2.35	59.12±7.32	0.324
eGFR (mL/min/1.73 m2)	49.23±2.93	51.92±5.62	0.334
hsCRP(mg/L)	9.23±3.11	9.89±1.32	0.452
Serum uric acid (mg/dL)	6.73±1.02	6.02±1.83	0.562
CKD causes			
Glomerulonephritis, n (%)	14(18.6)	13(17.3)	0.109
Cystic kidney disease, n (%)	19(25.3)	21(28)	0.335
CAKUT (%)	34(45.3)	31(41.3)	0.393
Chronic recurrent UTIs associated with reflux	8(10.6)	10(13.3)	0.452
Adjusted serum calcium (mmol/L)	2.22±0.12	2.62±0.21	0.552
Hypocalcaemia (%)	9(12.0)	10(13.3)	0.632
Serum phosphate (mmol/L)	1.50±0.12	1.73±0.32	0.345
Hyperphosphataemia (%)	19(25.3)	21(28.0)	0.123
Serum iPTH (pmol/L)	12.23(9.21, 23.12)	13.55(6.23, 19.23)	0.348
Serum 25(OH)D (nmol/L)	12.92(4.23,18.12)	13.83(6.32,23.23)	0.573
Serum bicarbonate (mmol/L)	21.93±4.23	22.12±3.23	0.632
CRP (mg/L)	0.56(0.21, 2.01)	0.61(0.27, 2.66)	0.183
Sclerostin (ng/mL)	0.28(0.11-0.53)	0.32(0.23-0.42)	0.732
Alkaline phosphatase(U/L)	510.92±210.23	518.12±183.23	0.328
Osteocalcin(ng/L)	62.92±17.32	69.12±19.23	0.893
PINP(μg/L)	391.92±112.23	434.12±102.32	0.119
Albuminuria (g/molcreatinine)	323(76, 783)	412(34,992)	0.763
Alkaline phosphatase(U/L)	510.92±210.23	518.12±183.23	0.832
Osteocalcin(ng/L)	62.92±17.32	69.12±19.23	0.332
spine BMD (g/cm2)	0.731±0.113	0.739±0.098	0.553
Fummer-BMD (g/cm2)	0.783±0.173	0.773±0.121	0.763

CKD, Chronic kidney disease; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; hsCRP, high-sensitivity C-reactive protein; eGFR, glomerular filtration rate; CAKUT, congenital anomalies of the kidney and urinary tract. CPR, C-reactive protein; PINP, procollagen IN-terminal peptide. BMD, bone mineral density

Table 2. Correlation analysis between kidney and bone metabolism measurements at high or standard dose of Vit D

	Body mass index	eGFR	Serum uric acid	Hypocalcaemia	Serum phosphate	Serum 25(OH)D	ALP	Osteocalcin	spine BMD	Fummer-BMD
Body mass index	1									
eGFR	0.32	1								
Serum uric acid	0.31	0.39	1							
Hypocalcaemia	&-0.83*	0.12	0.34	1						
Serum phosphate	&-0.12	0.93	0.11	0.45	1					
Serum 25(OH)D	0.78	&-0.32	&-0.34*	&-0.94	0.45	1				
ALP	&-0.12	0.21	0.78	0.23	0.78	0.21	1			
Osteocalcin	0.83	&-0.88	&-0.34*	&-0.33	0.84	0.22	0.23	1		
spine BMD	0.28	&-0.31	&-0.23*	&-0.11	0.67	0.25*	0.53	0.29**	1	
Fummer-BMD	0.34	&-0.45*	&-0.83	&-0.43	0.43	0.53	0.34	0.35	0.75	1

CKD, Chronic kidney disease; SBP,Systolic Blood Pressure; DBP,Diastolic Blood Pressure; hsCRP, high-sensitivity C-reactive protein; eGFR,glomerular filtration rate; CAKUT,congenital anomalies of the kidney and urinary tract. CPR,C-reactive protein; PINP,procollagen I N-terminal peptide. BMD, bone mineral density

Table 3. Changes in biochemical parameters of high dose and standard dose of Vitamin D3

Variables	High dose of Vitamin D3			Standard dose of Vitamin D3		
	baseline	4 months	p value	baseline	4 months	p value
Serum 25(OH)D (nmol/L)	12.92(4.23, 18.12)	15.23(7.23, 27.23)	**0.02**	13.83(6.32,23.23)	14.93(7.23, 24.32)	**0.04**
eGFR (mL/min/1.73 m2)	49.23±2.93	59.23±2.31	**0.03**	51.92±5.62	56.92±8.32	**0.01**
hsCRP(mg/L)@	9.23±3.11	8.32±1.23	0.33	9.89±1.32	8.89±0.93	0.42
Serum uric acid (mg/dL)	6.73±1.02	5.11±1.02	0.31	6.02±1.83	5.32±2.31	**0.03**
Albuminuria (g/mol creatinine)@	323(76, 783)	283(52,673)	**0.011**	412(34,992)	335(53, 732)	**0.013**
Serum phosphate (mmol/L)	1.50±0.12	1.49±0.21	0.832	1.73±0.32	1.62±0.23	0.341
Hyperphosphataemia (%)	19(25.3)	13(17.8)	0.138	21(28.0)	18(25)	0.329
Serum PTH (pmol/L)	12.23(9.21, 23.12)	12.93(8.92, 25.23)	0.877	13.55(6.23, 19.23)	12.92(3.23,21.34)	0.884
serum calcium (mmol/L)	2.22±0.12	2.52±0.32	0.348	2.62±0.21	2.93±0.42	0.423
Hypocalcaemia (%)@	9(12.0)	4(5.6)	**0.02**	10(13.3)	2(2.7)	**0.031**
Alkaline phosphatase(U/L)	510.92±210.23	419.21±113.23	**0.023**	518.12±183.23	529.22±112.31	0.341
Osteocalcin(ng/L)	62.92±17.32	69.22±11.32	0.126	69.12±19.23	74.92±11.34	0.123
PINP(μg/L)@	391.92±112.23	443.92±67.23	0.653	434.12±102.32	402.19±103.88	0.543
spine BMD(g/cm2)	0.731±0.113	0.812±0.034	**0.023**	0.739±0.098	0.883±0.012	**0.032**
Fummer-BMD(g/cm2)	0.783±0.173	0.804±0.034	**0.046**	0.773±0.121	0.799±0.073	**0.028**

CKD, Chronic kidney disease; SBP,Systolic Blood Pressure; DBP,Diastolic Blood Pressure; hsCRP, high-sensitivity C-reactive protein; eGFR,glomerular filtration rate; CAKUT,congenital anomalies of the kidney and urinary tract. CPR,C-reactive protein; PINP,procollagen I N-terminal peptide. BMD, bone mineral density

Table 4. Predictors of final 25(OH)D levels and changes in serum concentrations of 25(OH)D during vitamin D supplementation; results of multiple linear regression analyses

Outcome	Predictor	β(standard error)	P value
Final 25(OH)D	Age	&-3.732 0.231	0.023
	eGFR	&-5.231(0.832)	0.012
	Serum iPTH	&-0.563(0.032)	0.041
	Albuminuria	&-21.23(1.341)	0.023
	Serum uric acid	&-3.21(0.233)	0.011
	Osteocalcin	&73.23(10.332)	0.001
	spine BMD	&3.23(0.342)	0.031
△25(OH)D	eGFR	&-3.529(0.732)	0.042
	serum calcium	&2.31(0.232)	0.023

CKD, Chronic kidney disease; SBP,Systolic Blood Pressure; DBP,Diastolic Blood Pressure; hsCRP, high-sensitivity C-reactive protein; eGFR,glomerular filtration rate; CAKUT,congenital anomalies of the kidney and urinary tract. CPR,C-reactive protein; PINP,procollagen I N-terminal peptide. BMD, bone mineral density

Figures

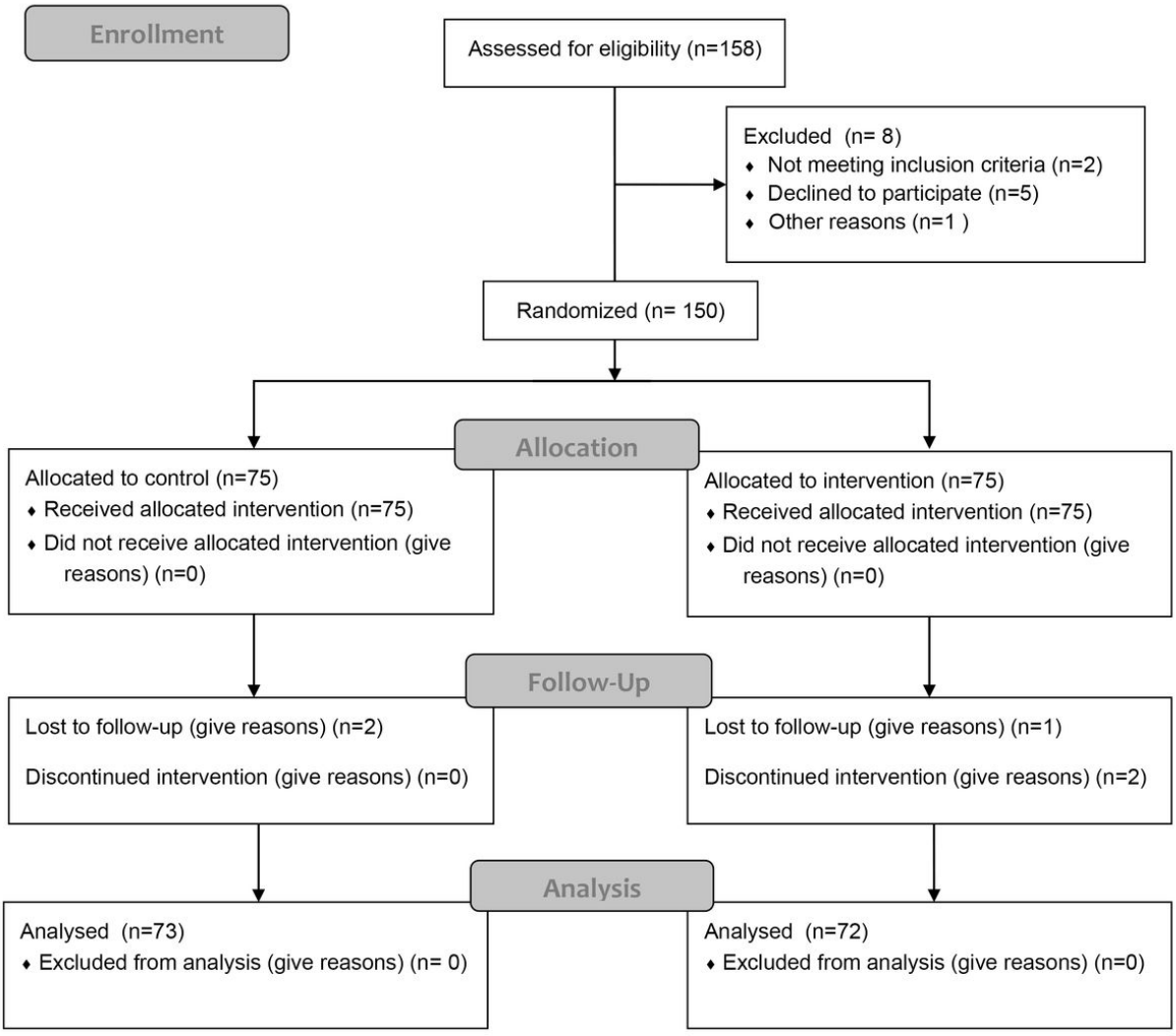

Figure 1

CONSORT 2010 Flow Diagram