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ORIGINAL ARTICLE

The effect of intramuscular vitamin D (cholecalciferol) on serum 25OH vitamin D levels in older female acute hospital admissions

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Abstract
Introduction Many studies have demonstrated the prevalence of vitamin D insufficiency in the older population.
Objective This study sought to determine whether supplementation with intramuscular vitamin D improved 25OH vitamin D levels significantly.
Subjects Ninety female inpatients aged over 65 years were assigned to receive 300,000 IU of intramuscular vitamin D3 (cholecalciferol) or no intervention.
Methods Baseline 25OH vitamin D and intact parathyroid hormone (iPTH) levels were taken and repeated 3 months after supplementation.
Results Patients who received treatment showed a significant improvement in 25OH vitamin D levels, from 25.5 to 81 nmol/L with 11% remaining deficient. No patient became hypercalcaemic after treatment.
Conclusions Vitamin D deficiency is common throughout all age groups in the Irish population and particularly the older female population who have increased risk of osteoporosis and fractures. Intramuscular vitamin D significantly improves 25OH vitamin D levels compared to no treatment and may combat non-compliance with oral medication.

Keywords Vitamin D · Intramuscular · Old age

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Introduction

Vitamin D deficiency is a common condition which is increasingly recognised to affect the general population as well as those perceived to be at risk, such as nursing home residents and the housebound older population [1–3]. Vitamin D is essential for the absorption of calcium and maintaining bone strength. It is important in the prevention of osteoporosis. Vitamin D deficiency is recognised as a cause of reduction in muscle strength [4], increased body sway and falls risk [5] and has been linked with increased risk of cardiovascular disease, diabetes and cancer [6].

Production of vitamin D in the body is mainly from sunlight via the skin with a smaller amount absorbed through diet. Once formed it undergoes two sequential hydroxylations in the liver [25 hydroxyvitamin D (25OH vitamin D)] and the kidney [1, 25 dihydroxyvitamin D (1, $25OH^2$ vitamin D)] to form the active metabolite. This active form of vitamin D regulates bone metabolism. Deficiency in production leads to malabsorption of calcium and increased parathyroid hormone production which causes reduced bone mineral density and increased fracture risk. Serum 25OH vitamin D is the standard measure of vitamin D status. Although 1, $25OH^2$ vitamin D is the

active form it should not be measured as it is often normal or elevated in patients with vitamin D deficiency [7].

Recommended levels of adequate vitamin D intake are between 400 IU and 600 IU daily (adequate intake, 600 IU >70 years and 400 IU <70 years, [8], Scientific Committee for Food in the European Union (400 IU) [9]). However, routine oral supplementation at commonly prescribed doses does not result in sufficient repletion of 25OH vitamin D levels in older, community dwelling, female acute hospital admissions [10]. The aim of this study is to establish if vitamin D intramuscular administration results in normalisation of 25OH vitamin D levels in this population.

Methods

All female acute admissions aged over 65 years admitted to University Hospital Galway during the period 1st November 2005 to 20th February 2006 were invited to take part in the study. The study was approved by the Clinical Research Ethics Committee and all patients gave written, informed consent. Any patients with known metabolic bone disease (other than osteoporosis or osteomalacia) or documented hypercalcaemia were excluded. Those with overt renal impairment (creatinine >150 μmol/L) were also excluded because this results in impaired hydroxylation of 25OH vitamin D to 1, $25OH^2$ vitamin D. Patients with bleeding disorders or those on anticoagulants were excluded due to the risk of haematoma formation at the injection site. Patients already receiving calcium/vitamin D supplements were not offered vitamin D injection but were asked to participate in a control arm of the study.

Initially 100 patients were recruited, 90 of these being suitable for inclusion in the study. Of these patients, 72 were administered 300,000 IU of intramuscular vitamin D3 (cholecalciferol—Streuli Pharma). Eighteen patients were recruited to a control group and not administered any treatment. Full clinical evaluation was undertaken at initial recruitment followed by haematological and biochemical assessment. Blood was collected and transported to the laboratory on ice, centrifuged and stored frozen at −80°C for later measurement of 25OH vitamin D and intact parathyroid hormone (iPTH) concentrations. Blood was also analysed on the day of sampling for a biochemical and bone profile including calcium, alkaline phosphatase and phosphate. Biochemical and bone profile with vitamin D and iPTH concentration was repeated after an interval of 3–6 months.

The methods used for analysing the blood results were the same as that used in the previous study by DeLappe et al. [10]. The laboratory in University Hospital Galway participates in UK external Quality Assessment Schemes for all parameters measured. Serum 25OH vitamin D was measured using the manual Diasorin 25 hydroxyvitamin D ^{125}I RIA kit (a two-step process involving an extraction step followed by an equilibrium radio-immunoassay procedure). The Diasorin method for 25OH vitamin D has a negligible bias. The level of vitamin D considered insufficient was taken as <50 nmol/L as per the hospital reference range.

Serum iPTH was measured using the automated DPC Immulite 2000 method for quantitative assessment of intact PTH in serum or plasma using a solid-phase, two-site chemoluminescent enzyme-labelled immunometric assay.

A statistical software programme SPSS was used to analyse the data. A one-tailed paired *t*-test was carried out for pre- and post-treatment groups.

Results

The mean age of those recruited was 79 ± 7 years for the injection group, and 76 ± 7 years for the control group. The baseline characteristics of the patients in the treatment and control groups are demonstrated in Table 1.

Baseline assessment

Mean calcium levels in the control and treatment groups were 2.29 ± 0.14 and 2.24 ± 0.14 mmol/L, respectively, with mean vitamin D levels at 27.72 ± 15.25 and 25.43 ± 16.05 nmol/L. Hydroxyvitamin D deficiency was identified in 87.7% of all patients recruited as defined by our cut off point of 50 nmol/L. Plasma levels of iPTH at baseline were 64.28 ± 47.42 and 80.84 ± 84.51 pmol/L for the control and treatment groups, respectively.

3-Monthly assessment

Patients who received treatment showed a significant improvement in 25OH vitamin D levels, from 25.5 ± 16 to 81 ± 25 nmol/L ($p < 0.0001$, paired *t*-test) with only 11% remaining deficient. Serum 25OH vitamin D levels in the control group also increased (27 ± 15 to 37 ±22 nmol/L, $p = 0.006$), but 66% were insufficient at 3 months.

Plasma levels of iPTH in the control group were not statistically different from baseline after 3 months ($p = 0.49$, paired *t*-test). Plasma levels of iPTH fell significantly from 80.8 ± 84.2 to 51.2 ± 39.8 pmol/L ($p = 0.001$, paired *t*-test) in the treatment group. No patient became hypercalcaemic after treatment, with calcium levels at 2.37 ± 0.14 and 2.36 ± 0.11 mmol/L for the control and treatment group, respectively.

Results and paired analyses are summarised in Figs. 1 and 2 below.

Table 1 Mean plus one standard deviation of all characteristics baseline, and at 3 months of control and treatment groups

Mean	Treatment baseline	Treatment: 3 months	Control baseline	Control: 3 months
Age	79.58 ± 7.01		76.16 ± 7.18	
Serum Ca	2.24 ± 0.14	2.37 ± 0.11	2.30 ± 0.14	2.38 ± 0.00
Serum Phos	1.12 ± 0.20	1.29 ± 0.20	1.24 ± 0.44	1.24 ± 0.15
ALP	103.64 ± 55.55	94.44 ± 35.78	85.78 ± 24.00	88.06 ± 0.17

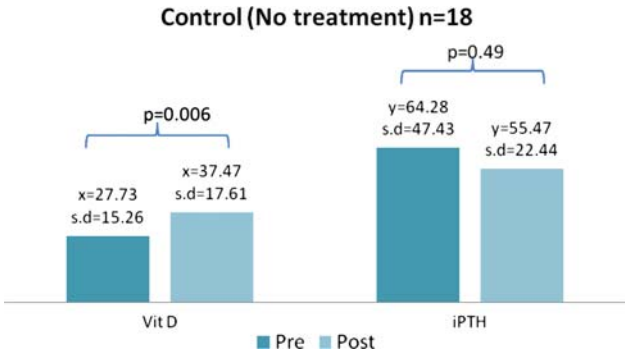

Fig. 1 Changes in mean plasma 25OH vitamin D (x) and iPTH (y) levels during treatment period in the control group

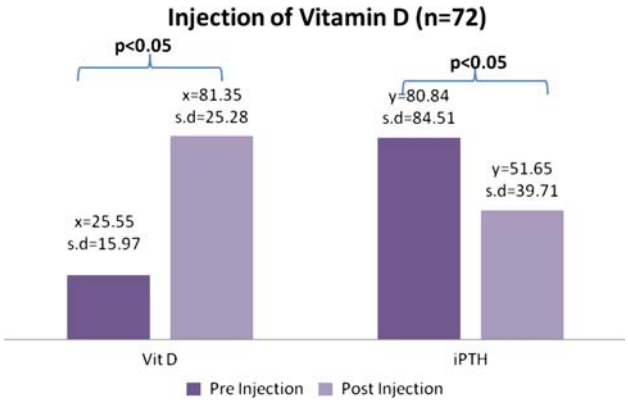

Fig. 2 Changes in mean plasma 25OH vitamin D (x) and iPTH (y) levels during treatment period in treatment group

Discussion

Our study demonstrates that a single injection of vitamin D3 (300,000 IU cholecalciferol) results in a significant rise in plasma 25OH vitamin D levels in the majority of community dwelling older female acute inpatients after 3 months. The increment in plasma levels occurred without any significant biochemical derangement and specifically the bone profile of all patients remained unchanged. A previous study performed in our centre demonstrated that oral calcium and vitamin D supplementation in a similar population failed to normalise plasma levels in most patients [10].

There is a high prevalence of vitamin D deficiency among all age groups but especially so in the older female population who are more at risk of osteoporosis and its complications [11]. Our study confirms the high level of vitamin D deficiency in an older Irish female population admitted to hospital, even among those taking vitamin D supplements at the recommended level, as shown in the baseline results for those women in the control group.

Studies on intramuscular injection of vitamin D are few with inconsistent results. Heikenheimo et al. [12] showed that an annual injection of vitamin D2 normalised vitamin D concentrations in older people for 1 year. Smith et al. [13] concluded that an annual injection of vitamin D2 (300,000 IU) was not effective in preventing non-vertebral fractures among older men and women resident in the community. The Nottingham Neck of Femur (NoNOF) study [14] found that levels of vitamin D were raised at one year following intramuscular injection of vitamin D2 in women with previous fracture and they had a reduced risk of falls and fracture. We used intramuscular vitamin D3 (cholecalciferol) in our study. Follow on studies are needed to show whether the increased plasma level of vitamin D after vitamin D3 intramuscular injection leads to a reduced risk of fractures and falls.

There is conflicting evidence for the role of vitamin D supplementation in the reduction of fractures. Chapuy's [15] paper was the original indication to use calcium and vitamin D to prevent fracture. It showed that daily oral calcium and vitamin D reduced substantially (17–23%) the number of hip fractures over a period of 3 years. Trivedi et al. [16] showed a fracture reduction of 22% after 5 years. Porthouse [17] et al. found no evidence of reduction of fractures in a primary care population supplemented with calcium and vitamin D3 (800 IU) orally. The randomised evaluation of calcium or vitamin D (RECORD) trial [18] group found no reduction in fractures. A large randomised controlled trial by Lips et al. found no reduction in fracture risk for vitamin D, but the population studied did not have a high prevalence of vitamin D deficiency [19].

Besides fracture prevention, studies have shown that supplementation of vitamin D reduces the risk of falls in an older population [20], thus demonstrating the importance of vitamin D in muscle power and body sway. Bischoff-Ferrari found that combined supplementation with calcium

and vitamin D reduced the odds of falling in an ambulatory older female population by 46% [21].

A major issue affecting trials with vitamin D is compliance. Porthouse et al. found that compliance with vitamin D supplements was 54.5% at 2 years. Importantly 45.2% of patients receiving osteoporosis medications were not filling their prescription one year after initiation of therapy [22]. We feel the intramuscular route is a solution to the issue of non-compliance.

There are a number of shortcomings in our trial of which we are aware. The time span was short with the majority of patients recruited during winter months when vitamin D levels would be low. The follow-up level of vitamin D was performed in the summer months when levels would be expected to rise. This may have lead to bias in the results. Our control group was small and did show a rise in vitamin D but not as large an increase as those who received the intramuscular injection of vitamin D. It would be interesting to have recruited patients over a calendar year to remove some of this bias.

Conclusion

There are a number of difficulties arising in correcting vitamin D deficiency in the population. Even with appropriate diagnosis and treatment, poor absorption of vitamin D from the gastrointestinal tract and non-compliance with medication leads to unsatisfactory results.

We feel that vitamin D supplementation via the intramuscular route has the potential to aid the older female population. Besides reduction in fractures, vitamin D reduces the risk of body sway and falls. Intramuscular injection is a safe and effective way to increase vitamin D levels. It is well tolerated in a population known to have low vitamin D levels and who are at risk for complications of vitamin D deficiency. This group of older women have also been shown to be largely non-compliant with oral supplementation and an injection offers advantages for both patient and clinician.

Our study has demonstrated that a single intramuscular injection of vitamin D3 safely and successfully repletes plasma 25OH vitamin D levels in a group of community dwelling older female patients on admission to hospital. Further studies are required to establish the feasibility of such an intervention in the older population on a routine basis.

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