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CLINICAL RESEARCH

# Effect of a Single 'Megadose' Intramuscular Vitamin D (600,000 IU) Injection on Vitamin D Concentrations and Bone Mineral Density Following Biliopancreatic Diversion Surgery

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**Abstract**
*Background* Vitamin D (VitD) deficiency is common following biliopancreatic diversion (BPD). We conducted a prospective open-label study to evaluate the efficacy of a single intramuscular injection with 600,000 IU of cholecalciferol in an arachis oil depot formulation (VitD3, Arachitol Solvay Pharmacia) as an adjunct to regular oral VitD supplementation (Citrical+D) for a period of 12 months following BPD surgery.
*Methods* Some 29 patients who had undergone BPD during 2000–2005 were recruited and received a single injection of 600,000 IU of cholecalciferol. Venous blood VitD, parathyroid hormone (PTH), alkaline phosphatase (ALP), ionised calcium and urinary N-telopeptide (NTX) were assessed at baseline and at 1.5, 3, 6, 9 and 12 months post-injection. Bone mineral density (BMD) was determined at baseline and 12 months post-injection.
*Results* VitD concentrations (mean ± SD) were significantly increased from baseline values (61.5±18.8 nmol/L) at 1.5 months (92.4±21.5, $p<0.001$), 3 months (100.5±24.4, $p<0.001$) and 6 months (79.1±20.9, $p=0.014$) post-injection, with non-significant elevations at 9 months (73.3±15.1, $p=0.248$) and 12 months (73.4±17.3, $p=0.278$). The proportion of patients with 'normalised' VitD levels was significantly higher at all post-injection time points (range, 93–100%) compared with baseline (71.4%; $p<0.01$). Ionised calcium and ALP remained within normal levels at baseline and all follow-up time points, although ionised calcium decreased by 3.4% ($p=0.015$) and ALP increased by 14.6% ($p=0.021$) at 12 months compared with baseline. No significant change in PTH, NTX or BMD was observed.
*Conclusions* Intramuscular cholecalciferol injection, as an adjunct to oral supplementation, appears a safe and effective method to increase and maintain VitD levels after BPD.

**Keywords** Vitamin D · Bone mineral density · Biliopancreatic diversion surgery

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## Introduction

Abnormalities with vitamin and nutrient absorption are well-recognised complications of malabsorptive surgical procedures for treatment of obesity [1], such as biliopancreatic diversion (BPD; with or without duodenal switch (DS)). BPD has been shown to result in effective maintenance of long-term weight loss [2, 3], but it has been well-established in the scientific literature that several undesirable metabolic consequences may occur as a result of BPD [3, 4]. Chief amongst these are

the deleterious effect on calcium homeostasis, serum vitamin D (VitD) concentrations and bone health [4–8]. Many bariatric centres commonly employ a regimen of nutritional supplements with the aim to maintain normal body physiology during the long-term post-operative follow-up [9]. However, even in patients who adhere to their supplement regimes, VitD deficiency can result [8]. One risk of long-term VitD deficiency is metabolic bone disease [10], including osteomalacia secondary to VitD deficiency and osteoporosis secondary to calcium deficiency [10]. However, Adams et al. [11] demonstrated in 18 patients that reversal of VitD deficiency improved annual bone mineral density (BMD) in the lumbar spine and femoral neck.

Two issues exist with oral fat-soluble vitamin supplementation in the post-BPD patient. Firstly, it may require a large number of tablets to be taken on a daily basis, making compliance difficult. Secondly, due to the malabsorptive nature of the procedure, vitamin deficiency is possible even if post-operative supplementation regimens are followed [8]. One possible solution is an intramuscular depot preparation of cholecalciferol (vitamin $D_3$), which may slowly release its VitD. A study of 50 nursing home patients with VitD deficiency by Diamond et al. [12] showed no serious adverse events with 'megadose' intramuscular VitD (Arachitol 600,000 IU) injection and a significant increase in the VitD level after intramuscular supplementation at 4 months ($p<0.001$) and 12 months ($p<0.001$) post-injection.

To our knowledge there are no published studies documenting the response to intramuscular VitD replacement in patients undergoing BPD. As a result, this study investigated the efficacy of a single intramuscular injection with 600,000 IU of cholecalciferol in BPD patients, as an adjunct to regular oral VitD supplementation, for maintaining serum VitD concentrations in the 12 months following injection.

## Materials and Methods

This investigation comprised a prospective open-label study, conducted in a single bariatric surgical practise, to assess the safety and effectiveness of once-yearly intramuscular VitD injection (600,000 IU) in BPD patients to supplement regular oral intake of VitD supplements in the year following injection. The safety of this dose of VitD has previously been demonstrated [13].

### Participants

All patients ($n=58$) who had undergone BPD with or without DS at Mercy Bariatrics Obesity Surgery Centre (BMOSC; Perth, WA, USA) between January 2000 and December 2005 were approached to participate in the study. All surgeries were performed by an experienced single surgeon, with >4 years experience performing BPD surgery. Patients in this series underwent either a Scopinaro type BPD with preservation of the antrum or a Duodenal Switch BPD calibrated against a 60 Fr bougie. In all cases the common channel length varied between 75 and 100 cm depending on the length of measured small bowel. The gallbladder was routinely removed at this operation. Study enrolment of the patients occurred at an average of 24 months post-surgery (range, 4–66). Due to the small number of potentially suitable participants, no exclusion criteria were implemented. A total of 29 patients (response fraction=50%) agreed to participate in the study. The participants did not differ to non-participants with regard to age, gender and pre-surgery body mass index (BMI).

### Treatment Administration

As part of the standard post-BPD protocol, all patients had been commenced on a regime of two multivitamin tablets (VitABDECK, a multivitamin preparation containing 11 mcg (440 IU) of vitamin D3, cholecalciferol per tablet) and two Citracal+D tablets (calcium 250 mg and VitD 5 mcg, 200 IU per tablet) per day. This gave a total oral dose of 1,280 IU of VitD daily. Oral supplementation compliance was however not monitored. Following blood and urine baseline measurements, patients were also given a single intramuscular injection of 600,000 IU of cholecalciferol (VitD3, "Arachitol", Solvay Pharmacia).

### Measurements

At enrolment, body mass index was calculated and baseline testing was performed prior to administration of the VitD injection. Blood was drawn at baseline and 1.5, 3, 6, 9 and 12 months post-injection from an ante-cubital vein at Mercy Hospital Pathology (Perth, Western Australia) and stored at −70°C until analysis. Concentrations of VitD, parathyroid hormone (PTH), albumin, alkaline phosphatase (ALP) and ionised calcium were determined according to standard methods. A single urine sample was also obtained at baseline and 6 and 12 months post-injection and assayed for urinary N-telopeptide (uNTX). Patients were asked to fast overnight prior to blood extraction and urine sampling. Lumbar spine and femur neck BMD was determined as absolute BMD values ($g/cm^2$) at baseline and 12 months post-injection at SKG Radiology (Perth, Western Australia) using dual-energy X-ray absorptiometry. Absolute BMD values were used in this study since its aim was to measure the change in BMD over a 12-month period. At 3, 6 and 12 months post-injection, patients were surveyed regarding any side effects experienced due to the study treatment.

Serum VitD concentrations were categorised as either 'normal' (>50 nmol/L) or 'abnormal' (<50 nmol/L) according to population normative reference ranges [14]. Normative ranges for other blood measurements were 1.3–6.8 pmol/L for PTH; 1.12–1.32 mmol/L for ionised Ca; 45–136 IU/L for ALP and <63 mmol NTX per mmol Cr for uNTX.

The study was approved by the Human Research Ethics Committee of Mercy Hospital, Perth, Western Australia.

## Statistical Analyses

Descriptive measures were obtained for all blood measures (VitD, PTH, ALP and ionised calcium) at baseline and 1.5, 3, 6, 9 and 12 months post-treatment administration, and for uNTX and BMD at baseline and 12 months post-injection.

One-way analysis of variance with repeated measures was used to evaluate changes in blood parameters across the observation period from baseline measurement. Significant differences were further evaluated with Bonferonni post-hoc analyses. Pre- and 12-month post-treatment uNTX and BMD were each compared using dependent-samples *t* tests.

Trend chi-square analysis was used to determine differences in the proportion of patients within population normative reference ranges for all blood and urine measures at each study time point. All analyses were performed using SPSS for Windows (v15.0) with the level of significance set at $p<0.05$.

## Results

Study participants ($n=29$) had a mean (±SD) age of 47.7±8.3 years (range, 32.9–67.5 years) and were mostly female ($n=23$, 79.3%). From surgery to enrolment the mean (±SD) BMI fell significantly from 47.53±6.49 kg/m$^2$ (range 37.5–58.5 kg/m$^2$) to 31.57±5.18 kg/m$^2$ (range 23.3–41.3 kg/m$^2$; $p<0.0001$), with average (±SD) percent excess weight loss of 65.5±19.6%.

Figures 1 and 2 show the VitD findings. Mean (±SD) VitD concentrations at baseline were 61.5±18.8 nmol/L (Fig. 1). A significant increase in VitD levels from baseline was evident at 1.5 months (92.4±21.5 nmol/L, $p<0.001$), 3 months (100.5±24.4 nmol/L, $p<0.001$) and 6 months (79.1±20.9 nmol/L, $p=0.014$) post-injection, but was not significant at 9 months (73.3±15.1 nmol/L, $p=0.25$) and 12 months (73.4±17.3 nmol/L, $p=0.28$) follow-up. At baseline, 28.6% ($n=8$) of patients had venous VitD concentrations outside population normative reference ranges (Fig. 2). At all post-injection time points the proportion of patients with VitD within normative reference range was significantly greater than baseline ($p<0.01$; Fig. 2). Furthermore, only two subjects were characterised with abnormal VitD levels at 12 months (45 and 49 nmol/L, respectively). The highest VitD concentration recorded was 160 nmol/L, which is well below the level associated with toxicity (>220 nmol/L) [13].

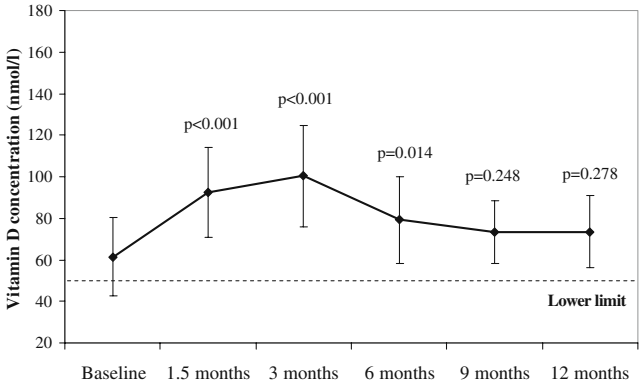


**Fig. 1** Response of serum vitamin D levels (mean ± SD) to intramuscular VitD injection in patients undergoing biliopancreatic diversion. *p* values indicate statistical difference from baseline. Lower limit specifies below which the abnormal range of VitD levels in blood lies

Results for PTH, ionised calcium, ALP and uNTX are shown in Tables 1 and 2. Mean ionised calcium and ALP levels remained within normative reference ranges at all time points (Table 1) with only 7–12% and 3–8%, respectively, of patients having abnormal levels from baseline to 12 months post-injection (Table 2). There was a significant reduction in venous ionised calcium concentrations at 12 months post-injection compared with baseline (1.201 nmol/l to 1.160 nmol/l, $p=0.015$), while ALP increased significantly from baseline (89.9 IU/L) to 12 months post-treatment (103.0 IU/L, $p=0.021$; Table 1). Mean PTH was above normative ranges at baseline, but fell

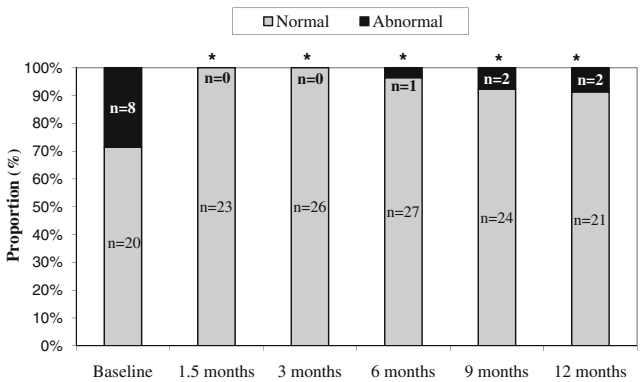


**Fig. 2** Number and proportion of patients, undergoing biliopancreatic diversion, with serum vitamin D levels within normative reference range after intramuscular injection. *$p<0.01$; proportion of patients within normative reference range significantly different from baseline

**Table 1** Mean (±SD) levels of venous PTH, ionised calcium, ALP and uNTX at baseline and during the 12 months following intramuscular injection of VitD (600,000 IU)

| | Baseline (pre-injection) | Post-injection | | | | | |
|---|---|---|---|---|---|---|---|
| | | 6weeks | 3months | 6months | 9months | 12months | Normal range[Ref] |
| PTH | 6.9±5.5 | 5.9±2.4 ($p$=0.865) | 5.6±2.4 ($p$=0.656) | 5.6±2.4 ($p$=0.607) | 5.7±2.2 ($p$=0.726) | 6.5±2.1 ($p$=0.996) | 1.3–6.8 pmol/L |
| Ionised Ca | 1.201±0.045 | – | 1.182±0.036 ($p$=0.543) | 1.195±0.040 ($p$=0.984) | 1.178±0.054 ($p$=0.327) | 1.160±0.053 ($p$=0.015) | 1.12–1.32 mmol/L |
| ALP | 89.9±24.4 | – | 91.6±29.0 ($p$=1.000) | 88.4±30.5 ($p$=0.985) | 77.3±29.5 ($p$=0.722) | 103.0±33.4 ($p$=0.021) | 45–136 IU/L |
| uNTX | 85.1±32.0 | – | – | 89.0±33.0 ($p$=0.924) | – | 100.0±48.2 ($p$=0.352) | <63 nmol NTX per mmol Cr |

*PTH* parathyroid hormone, *Ca* calcium, *ALP* alkaline phosphatase, *uNTX* urinary N-telopeptide

within the population norms at all time points post-treatment, although differences were not statistically significant (Table 1). Similarly, PTH levels were abnormally high in 12 patients (41%) at baseline, which fell to five (24%) patients at 1.5 months post-injection and increased to eight (35%) patients at 12 months, while again the differences were not significant (Table 2). Mean uNTX levels remained above the normative ranges at all time points investigated (Table 1) with 25% of patients having abnormal levels at baseline and 32% at 12 months (Table 2).

Absolute BMD (g/cm$^2$) was assessed in 66% ($n$=19) of the study participants at baseline and 12 months post-injection. Femur neck BMD was lower at 12 months compared with baseline (baseline 0.971; 12 months 0.930), with the difference observed to approach statistical significance ($p$=0.079). Lumbar spine BMD decreased non-significantly across the study period (baseline 1.237; 12 months 1.195, $p$=0.205).

No side effects or adverse outcomes were reported by study participants at 12 months post-injection as a result of the intramuscular VitD intervention.

## Discussion

Nutritional supplementation is often standard post-operative practise following malabsorptive bariatric procedures [9]. However, at present no published consensus exists regarding best-practise for supplementation when deficiencies are found. Our study clearly demonstrates that a single megadose intramuscular VitD is an effective adjunct to improving blood VitD levels after BPD in patients on regular oral supplements. This is evidenced by the significant increase (range, 29–63%) in VitD concentrations following intramuscular injection observed in our study sample. The VitD concentration elevations were highest at 1.5 and 3 months post-injection, but began to decline at 6 months. In all but two subjects tested at 12 months post-treatment, VitD concentrations remained within the healthy/normal reference range based on population norms [14] and deficiency was mild for these patients. However, given the decline in VitD concentration from 6 months post-injection, it could be argued that more frequent injections might be beneficial. As a result of this study, MBOSC have

**Table 2** Number of patients undergoing biliopancreatic diversion who experience normal/abnormal levels of PTH, ionised Ca, ALP and u NTX following VitD injection

| | Baseline | 1.5months | 3months | 6months | 9months | 12months | $p$ value* |
|---|---|---|---|---|---|---|---|
| PTH | | | | | | | |
| Normal (%) | 17 (59) | 16 (76) | 19 (68) | 22 (79) | 18 (69) | 15 (65) | 0.620 |
| Abnormal (%) | 12 (41) | 5 (24) | 7 (32) | 6 (21) | 8 (31) | 8 (35) | |
| Ionised Ca | | | | | | | |
| Normal (%) | 26 (93) | – | 24 (96) | 26 (96) | 23 (88) | 21 (88) | 0.659 |
| Abnormal (%) | 2 (7) | – | 1 (4) | 1 (4) | 3 (12) | 3 (12) | |
| ALP | | | | | | | |
| Normal (%) | 28 (97) | – | 23 (96) | 26 (93) | 22 (85) | 22 (92) | 0.498 |
| Abnormal (%) | 1 (3) | – | 1 (4) | 2 (7) | 4 (15) | 2 (8) | |
| uNTX | | | | | | | |
| Normal (%) | 21 (75) | – | – | 19 (70) | – | 15 (68) | 0.807 |
| Abnormal (%) | 7 (25) | – | – | 6 (30) | – | 7 (32) | |

*PTH* parathyroid hormone, *Ca* calcium, *ALP* alkaline phosphatase, *uNTX* urinary N-telopeptide

*$p$ values calculated using chi-square tests for comparison of proportions

subsequently implemented six monthly injections of arachitol 600,000 IU as routine practise for all BPD patients, in combination with the pre-existing oral supplementation regime.

In line with our findings, Diamond et al. [12] found that an intramuscular injection of a megadose of cholecalciferol for treatment of VitD deficiency increased and normalised VitD levels at 4 and 12 months post-injection. Their study was not performed in obese or bariatric surgery patients, but in patients who were VitD deficient for unknown reasons (but presumed due to reduced sunlight exposure in a nursing home population), which may have explained the longer lasting effect of the injection compared to our findings. Furthermore, they found that PTH levels significantly decreased in unison with the increase in VitD levels. This was corroborated in our study, although the difference was not significant.

As previously noted, the majority of VitD absorption occurs in the small intestine [15], and bile salts are required to aid absorption [16]. As such, intramuscular administration largely avoids issues related to malabsorption of VitD in the altered alimentary tract. Furthermore, intramuscular supplementation in an oily depot form may lead to VitD levels being better sustained over time. In fact, some studies of BPD patients have shown low VitD levels [7, 8, 17] and high PTH levels [7, 8, 17–19] approximately 1–4 years following surgery despite VitD oral supplementation, whereas one study found that the VitD deficiency and PTH elevation post-BPD was resolved in the majority of patients using oral supplements [20]. Also, Marceau et al. [7] found that, in a study of 33 BPD patients, one-third of study participants self-reported non-compliance with oral VitD and calcium supplements. Additionally, the authors indicated that this was likely an underestimation of the true figure due to likely reporting bias, as participants may have felt compelled to report compliance to study investigators. Consequently, a single yearly dose administered by intramuscular injection may have advantages in terms of convenience as well as efficiency compared with daily oral supplementation. In addition, the cost of a single intramuscular VitD preparation (AU$5–10 per dose) is significantly cheaper for patients compared with the cost of AU$10–15 per month for regular oral supplementation.

Intramuscular VitD injection may also be beneficial for the correction of deficiencies prior to proceeding to surgery. Compston et al. [21] studied a group of patients presenting to a clinic with a view to undergo bariatric surgery. They found that VitD levels were significantly lower in morbidly obese patients considering such procedures than age-matched healthy controls. Ybarra et al. [22] similarly found a high prevalence of VitD deficiency in morbidly obese patients prior to bariatric surgery, which did not change following surgery despite patients following a regime of oral VitD supplementation. Consequently, correcting VitD levels prior to surgery may be an important feature to maintain VitD levels normal following surgery, although further research is required.

Interestingly, maintaining normal VitD levels was not observed to improve BMD or decrease average levels of uNTX (a marker of bone turnover [23]) after BPD in the present study, despite that uNTX remained above population norms at all time points investigated. In fact, BMD decreased slightly in our study, although not significantly, but in the absence of VitD injection it may have decreased further. Marceau et al. [7] followed 33 patients for 10 years who were taking oral VitD supplements after standard BPD with a 50 cm common channel. They found significant decreases in serum VitD concentrations and lumbar spine BMD, whereas bone turnover increased [7]. Also, Compston et al. [5] found that metabolic bone disease was present in 73% of patients followed for 1–5 years after BPD despite VitD levels being maintained in normative ranges in most patients, although comparisons with the current study are complicated due to different surgery techniques used for that study. In light of the previous findings, it appears that patients undergoing oral VitD supplementation only, experience progression of bone disease post-BPD, whereas our findings indicate that the current VitD injection therapy may have some advantages in improving progression of bone disease (especially if administered annually). However, future research extending the follow-up past 12 months is necessary in order to make a conclusion as to whether VitD injection improves BMD following BPD.

We found no side effects of the VitD injection, which is in line with previous findings. Diamond et al. [12] studied the safety and efficacy of 600,000 IU cholecalciferol intramuscular injection in 50 patients with VitD deficiency. No patient in their study reported serious adverse events, but one patient developed a localised erythematous reaction at the injection site. None of the participants in our study reported any such events.

Some caution is warranted in interpreting our results. Our study did not measure hormonal status of female patients with regards to menopause, which may have influenced loss of bone mass [24]. Also, it was not felt to be ethically appropriate to include a non-VitD injection comparison group in our study. In addition, the study was unable to control for exposure to ultraviolet (UV) radiation. However, very small seasonal variation exists for sunlight exposure in Perth, Western Australia [25] and the resulting change in VitD levels or BMD throughout the 12-month study period would likely have been negligible. Lastly, inclusion of data on oral supplementation compliance may have been of interest, although this information was not collected as a part of the study and could not be empirically assessed here. However, all patients were continued on the

standard post-surgery oral regime and were reminded about the importance of compliance with oral VitD supplementation at each follow-up testing session. Although observer bias may have influenced compliance at the commencement of the trial the uniformity of the results in normalising VitD levels in all patients within 1.5 months would argue against variation in compliance with oral supplementation having a significant impact.

## Conclusion

Once-yearly injection of VitD (600,000 IU), as an adjunct to regular oral VitD supplementation, is a safe and effective means of improving serum VitD concentrations for a period 12 months in patients having undergone BPD. However, while maintained, this therapy did not significantly increase BMD in the year following commencement of treatment.

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**Conflicts of Interest Statement** Dr. Leon Cohen received payment for original treatment of the patients in this study, but did not seek financial payment for any aspect relating to this study. All other authors report no conflicts of interest.

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