Standard vs Cyclic Teriparatide and Denosumab Treatment for Osteoporosis: A Randomized Trial

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DM: NONE

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Abstract: In the absence of an intervening antiresorptive agent, cyclic administration of teriparatide does not increase BMD more than standard daily therapy. Since denosumab is a potent antiresorptive agent with a rapid off-effect, we hypothesized that it might be the optimal agent to help maximize bone gains with cyclic teriparatide. In this 3 year protocol, 70 postmenopausal women with osteoporosis were randomized to: 18 months teriparatide followed by 18 months denosumab (Standard) or 3 separate 12 month cycles of 6 months teriparatide followed by 6 months denosumab (Cyclic). BMD (DXA) measurements of lumbar spine (LS), total hip (TH), femoral neck (FN), and 1/3 radius (RAD) were performed every 6 months and Total Body Bone Mineral (TBBM) at 18 and 36 months. Baseline descriptive characteristics did not differ between groups except for a minimal difference in LS BMD, but not T-Score (mean age 65, mean LS T-Score -2.7). In the Standard group, BMD increments at 36 months were: LS 16%, TH 4%, FN 3% and TBBM 4.8% (all $p<0.001$ vs baseline). In the Cyclic group, 36-month BMD increments were similar: LS 12%, TH 4%, FN 4%, TBBM 4.1% (all $p<0.001$ vs baseline). At 36 months, the LS BMD increase with Standard was slightly larger than with Cyclic ($p=0.04$), but at 18 months, in the Cyclic group, there was no decline in RAD or TBBM ($p=0.007$ and <0.001, respectively vs Standard). Although the Cyclic regimen did not improve BMD compared with Standard at 36 months, there appeared to be a benefit at 18 months, especially in the highly cortical skeletal sites. This could be clinically relevant in patients at high imminent risk of fracture, particularly at nonvertebral sites.

Key words: Teriparatide, Denosumab, Anabolic, Antiresorptive, Sequential

Introduction:

Anabolic agents, which stimulate bone formation and reduce fractures rapidly, are particularly appropriate for patients at high imminent risk of recurrent fracture.[1-8] Teriparatide (TPTD) stimulates both modeling-based and remodeling based bone formation throughout 24 months of administration [9-14], resulting in increased BMD and improved bone microarchitecture. Modeling-based formation predominates during the first 6 months;[14] during that period, increments in biochemical markers of formation are increased proportionately more than those of bone resorption, and BMD increases most rapidly.[15-17] Histomorphometric data are consistent with the biochemical marker and BMD data, showing that the maximal effect on bone formation rate is early, with peak activity seen after 3 to 6 months of TPTD in the endocortical envelope. [14,18-21]

In an effort to maximize BMD improvement with TPTD, we have previously tested a cyclic approach. [17,18] In women who received short cyclic courses of TPTD, BMD declined during the off-TPTD periods, in the absence of an antiresorptive agent. We hypothesized that administration of cyclic TPTD might be optimized by using an intervening antiresorptive agent during these off-TPTD periods. Denosumab, a RANK Ligand inhibitor that suppresses osteoclast differentiation, activation, and survival,[22] is rapidly reversible and therefore might be the best agent to optimize BMD gains with cyclic TPTD/antiresorptive therapy.

The primary hypothesis was that the increment in spine BMD would be greater in women randomized to receive the cyclic regimen, compared with a standard sequence.

Materials and Methods:

This three-year randomized parallel design study evaluated the effect of sequential therapy with TPTD and Denosumab (Dmab) on BMD and bone turnover markers when the treatments were given in Standard Sequence (TPTD for 18 months followed by Dmab for 18 months) versus a Cyclic Regimen (three separate 6 month cycles of daily subcutaneous TPTD, each followed by one subcutaneous injection of Dmab). Both groups received the same cumulative doses of TPTD and Dmab, given over the same total time period. The study was approved by the Helen Hayes Hospital Institutional Review Board. All study visits and outcome assessments occurred at Helen Hayes Hospital.

Inclusion and Exclusion Criteria:

Individuals were recruited from our ambulatory care osteoporosis service, bone density screening program, and from the surrounding community by advertisement, public educational programs, and support group meetings. Recruitment began in January 2013 and the last subject was recruited in May 2015. At screening, volunteers provided a comprehensive medical history and fasting blood samples. BMD of the spine, hip and radius were measured by DXA.

Included were postmenopausal women $\geq$age 45 years old with a diagnosis of osteoporosis on no current osteoporosis medication. Osteoporosis was defined by BMD T-Score $\leq$ -2.5 at lumbar spine ($\geq$2 evaluable vertebrae), total hip or femoral neck or radiographically confirmed vertebral deformity or prior osteoporosis-related

fracture with T-Score $\leq$ -1.5 in at least one skeletal site. Volunteers were required to have normal serum levels of calcium, parathyroid hormone, and bone alkaline phosphatase and 25(OH)D $\geq$30 ng/ml.

For patients who had low screening 25OHD levels, Vitamin D replacement and retesting was performed using the following protocol: for serum 25OHD levels of 25-29ng/ml, 50,000 IU vitamin D_2 was prescribed once weekly for 6 weeks followed by 2000 IU vitamin D_3 daily. For initial serum 25OHD levels of 10-24ng/ml, 50,000 IU vitamin D_2 was given twice weekly and for serum 25OHD <10 ng/ml, 50,000 IU vitamin D_2 was prescribed three times weekly. Levels were rechecked at 6 weeks and every 6 months for those with low initial serum 25OHD levels and maintenance Vitamin D doses adjusted as needed.

Exclusions included multiple vertebral fractures or severe lumbar degenerative changes with fewer than 2 evaluable lumbar vertebrae and current use of osteoporosis medication. Also excluded were use of hormone/estrogen therapy, raloxifene or calcitonin within the preceding 3 months; prior use of oral bisphosphonates >4 months within the previous 2 years or >5 years total in the previous 10 years; intravenous ibandronate within the prior 18 months; or intravenous zoledronic acid within the prior 4 years. Women with symptomatic renal stones within the prior 3 years or history of multiple symptomatic renal stones were excluded, as were those with skeletal disorders other than osteoporosis (hypercalcemia, hyperparathyroidism, Paget's

Disease). Women were also excluded if they had contraindications to the use of either TPTD (history of skeletal radiation exposure) or Dmab (hypersensitivity, hypocalcemia).

Baseline Assessments:

At the baseline visit, dietary calcium and vitamin D intakes were ascertained. Calcium supplements were recommended as needed to bring total calcium intake to ≥1200 mg daily. Appropriate maintenance oral doses of Vitamin D were provided and levels retested on an individual basis to ensure serum 25OHD levels were maintained ≥30ng/ml. Total body bone mineral assessment (TBBM) and vertebral imaging for diagnosis of compression fracture were performed by DXA. Baseline blood samples were obtained for measurement of biochemical indices of bone turnover (BTMs).

Treatment assignment, randomization and blinding:

Once volunteers were determined to meet all inclusion and exclusion criteria, the research nurse requested group allocation. Subjects were randomized (computer allocation) in a 1:1 ratio to one of two treatment arms: Cyclic Regimen (three separate 6 month cycles of daily subcutaneous TPTD, each followed by one injection of Dmab) or Standard Sequence (18 months of daily subcutaneous TPTD followed by 18 months Dmab). Participants and care providers were not blinded to intervention, but those evaluating the outcomes (bone turnover markers and bone density) were blinded to the treatment group assignment.

Study Visits and Assessments:

Subjects were seen every 3 months for assessment of interval medical history, compliance and adverse events. Blood samples were obtained, in the morning after an overnight fast, for BTMs (serum Propeptide of type I procollagen [PINP] for bone formation and serum crosslinked c-telopeptide [CTX] for bone resorption). Blood samples were centrifuged, and serum was separated into 0.5 ml aliquots and stored in a -70-degree freezer. Samples were batched and all samples for individual patients were assayed in the same batch using Elecsys Cobas (Roche Diagnostics Corporation, Indianapolis, USA). Reagents for these biochemical markers were also provided by Roche Diagnostics Corporation. The ranges of intra and inter-assay coefficients of variation, based on the analysis of control samples with high, medium and low concentrations were for PINP: 1·6-2·5% and 1·9-3%; and for CTX: 1·0-1·6% and 2·9–4·2%.

BMD was measured at lumbar spine (LS), total hip (TH), femoral neck (FN), and 1/3 radius (RAD) by dual x-ray absorptiometry (DXA) every 6 months. DXA measurements of TBBM and lateral vertebral imaging were performed at 18 and 36 months. All BMD testing was completed on the Hologic Discovery (Hologic Inc, Waltham, MA). In vivo precision calculations for specific skeletal sites using coefficients of variation were as follows: LS 1.1%, TH 1.5%, TR 1.5%, FN 2.0%, and RAD 2.2%. T-scores were calculated as compared to the NHANES reference database.

TPTD was distributed and Dmab administered as indicated at appropriate study visits. The last study visit was in May 2018.

Statistical Analyses:

The primary outcome was the group difference in spine BMD increment at 36 months. Secondary outcomes were group differences in BMD changes at the TH, FN, RAD and TBBM at 36 months and at 18 months and group difference in spine BMD increment at 18 months. Additional outcomes were biochemical marker changes at multiple time points.

T-tests and Fisher's Exact tests were used to assess group differences at baseline. DXA was measured twice at baseline, and the mean reading used for analysis. For BTMs, means, medians and standard errors of the mean were calculated for each variable at baseline and during treatment. Non-normally distributed variables were log transformed prior to analysis. Group differences in the longitudinal change in DXA BMDs and BTMs (log-transformed) were analyzed with linear mixed models for repeated measures, with treatment group, visit month and group by visit interaction, entered as fixed effects and the baseline value of the dependent variable entered as a continuous covariate. Between-group comparisons of percent change in DXA BMD at specific study time points used the model-estimated mean difference and weighted standard errors with and without covariate adjustment. Covariates were examined to assess whether outcomes changed independently of factors such as age, baseline BMD and body weight.

Analyses were performed using intention to treat as well as per protocol analyses. Per protocol analyses included all subjects who received at least 80 percent of their TPTD

doses and three Dmab treatments. Missing data were handled by interpolating levels between the nearest levels before and after the missing point for both BMD and BTM measurements. Means and standard errors of percent change and raw scores are reported. No adjustments for multiple comparisons were made.

The sample size of 70 women was determined based on the expectation that 56 women would complete the study (assuming 20% withdrawal). We expected to see a 4% greater BMD gain in the lumbar spine in the Cyclic Arm vs the Standard arm at 3 years. With a standard deviation of 4.5% for spine BMD change, we anticipated we would have more than 90% power to see this difference with 56 participants completing the trial.

Results:

Of the 70 women randomized, 63 (90%) completed the 3-year study (Figure 1). Withdrawals (n=7) were similar between the groups. Only 2 women discontinued because of adverse events; both were unrelated to study drug.

Baseline descriptive characteristics (Table 1) did not differ between groups, except for a minor difference in baseline LS BMD, but not LS T-Score. Mean age was 65 years, mean LS T-Score -2.7 and mean TH T-Score -1.7. About half of the volunteers for this study had had remote bisphosphonate exposure, but none had recent exposure, consistent with the exclusions described above. 21% of subjects had a history of low trauma nonvertebral fracture that occurred at ≥50 years of age and 16% had prevalent vertebral

fracture confirmed radiographically. Serum BTM levels were on average within the respective normal premenopausal ranges and similar between groups.

Biochemical Marker Changes: (Figure 2)

In the Standard regimen, on TPTD treatment, serum PINP levels increased and plateaued at 6-18 m, with slight decrements after 6 m for both serum PINP and CTX. Both markers declined promptly after Dmab treatment was initiated. In the Cyclic group, serum CTX increments during the 2nd and 3rd cycles were greater than seen during the 1st cycle (associated with lower baseline levels), whereas formation marker responses were similar during all 3 cycles.

Bone Density Changes: (Figure 3)

At 36 months, the Standard regimen increased BMD at all skeletal sites, except the radius, as follows: LS 16%, TH 4%, FN 3% and TBBM 4.8% (all $p<0.001$); RAD -0.4%. The Cyclic regimen increased BMD to a similar extent: LS 12%, TH 4%, FN 4%, and TBBM 4.1% (all $p<0.001$); RAD increased 1.5%. At 36 m, there was a slightly greater increase in LS BMD with Standard ($p=0.04$, after controlling for baseline BMD), but no significant differences were seen in hip BMD or TBBM. There was a slight decrease in RAD BMD with standard vs an increase with Cyclic at 36 months ($p=0.10$). At 18 m, the Cyclic regimen obviated the declines at RAD and TBBM seen with the Standard regimen (group differences 0.007 and $p<0.001$, respectively, after controlling for baseline BMD).

Safety and Fractures:

Both treatments were well tolerated in both arms of the study. There were no deaths in either group and no group differences in adverse events or serious adverse events. There were nine serious adverse events, 5 in the standard group and 4 in the cyclic group and none of these were thought to relate to study drug. Only 5 patients had osteoporosis-related fractures during the 3-year study: 3 in the standard group (clavicle; intertrochanteric and wrist) and 2 in the cyclic group (rib and elbow). In addition, one person in the standard group had traumatic fractures in a motor vehicle accident (pelvis and cervical spine) and one patient in the cyclic group had a toe fracture. Furthermore, there were no new vertebral fractures by VFA in either group.

Discussion:

Our findings indicate that over 36 months, a cyclic regimen alternating 6 months of TPTD with 6 months of Dmab did not increase BMD significantly more than a standard sequence of 18 months of TPTD followed by 18 months of Dmab treatment. However, at 18 months, there was an apparent benefit of the cyclic regimen in the more cortical sites, particularly the 1/3 Radius and TBBM. The BMD findings seen in this trial in the cyclic arm are superior to those seen in our prior study where women received cyclic TPTD without any intervening antiresorptive therapy.[17] This cyclic approach could potentially be appropriate for some patients who are at particularly high imminent risk of fracture, especially at cortical predominant nonvertebral skeletal sites.

In the DATA switch study,[23] hip BMD declined precipitously upon transition from Dmab (after 2 years of treatment) to TPTD administration. This finding is consistent with data indicating that cessation of Dmab after two or more treatments is associated with a rapid rise in bone turnover and rapid loss of BMD. The difference in effect of stopping Dmab after one, compared with multiple, treatments has been reviewed recently.[24] Accordingly, we did not see any dramatic BMD loss upon returning to TPTD after a single Dmab injection, however, the BMD improvements in both hip and spine were muted at 12-18 months, and were absent completely at 24-30 months, upon transition back from Dmab to TPTD. This is consistent with the biochemical marker effects; PINP increments were similar with each TPTD cycle (from respective baseline levels), while CTX increments were larger at 12-18 months and 24-30 months compared with the first cycle at 0-6 months (vs respective baseline levels at months 0, 12 and 24). The effect of Dmab withdrawal on bone remodeling might overwhelm the TPTD-induced stimulation of bone formation, even after just one Dmab treatment, however, it is also possible that 6 months of TPTD is just too short a treatment period to show a beneficial effect on BMD of the TH and FN. There was no increase in BMD at these sites over the first 6 months after initiation of TPTD, even in the absence of prior Dmab. No benefit of the cyclic regimen was seen at any site at 36 months; in fact, the spine BMD increment was slightly lower in the women who received cyclic (12%) rather than standard treatment (14%).

It is interesting to note that the BMD increments seen with 18 months of Dmab treatment after 18 months of TPTD were quite large, especially in the spine and total hip. These BMD gains appear larger than those seen in other studies when alendronate is

administered after teriparatide [25] or abaloparatide [26,27]. Several other studies suggest that Dmab treatment enhances BMD gain after TPTD to a greater degree than bisphosphonates [23,28, 29]. The explanation is likely due to a more potent antiresorptive effect of Dmab compared to bisphosphonates [30].

Most of the women in this trial were healthy aside from osteoporosis. This might affect generalizability to patients with multiple other serious comorbidities or who take multiple medications. Furthermore, to enroll in this study, there was a substantial washout period required for prior use of bisphosphonates. Our results would not apply to patients who have recently transitioned from a bisphosphonate or denosumab.

Although the cyclic regimen did not improve BMD compared with Standard at 36 months, there might have been a benefit up to 18 months in the highly cortical skeletal sites (TBBM, RAD and perhaps hip). This is likely due to a reduction in TPTD-mediated remodeling and cortical porosity as a result of the Dmab treatment given at 6 months. This observation is potentially relevant in some patients at high imminent risk of fracture due to recent incident nonvertebral fracture, however, further study would be required before a recommendation could be made to utilize this regimen. Other approaches to optimize cortical BMD could also be considered in these patients, such as concurrent administration of zoledronic acid or Dmab with TPTD [23,31] however the cumulative doses of antiresorptive medications are higher with these concurrent regimens. Upcoming analyses of high-resolution peripheral computed tomography data from this study will also help inform this issue.

We conclude that cyclic therapy with 6 months of TPTD followed by 6 months of Dmab might have promise for some patients, particularly those with very low BMD at predominantly cortical sites, since cortical BMD outcomes appear superior over the first 18 months with cyclic therapy compared to daily TPTD alone. At the current time, however, for the vast majority of high risk patients, standard monotherapy sequences should be utilized, with anabolic treatment for 18-24 months, followed by potent antiresorptive therapy for several years[23, 25-27] to achieve expected BMD gains and expected fracture risk reductions.

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Authors' roles: Study design: FC and JN. Study conduct: FC and JN. Data collection: FC and JN. Data analysis: JN and DM. Data interpretation: FC, JN, DWD. Drafting manuscript: FC. Revising manuscript content: FC, JN, DWD. Approving final version of manuscript: FC, JN, DM, DWD. All authors take responsibility for the integrity of the data analysis.

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Figure Legends

Figure 1. Consort Diagram.

Figure 2. Changes in Biochemical Markers of Bone Turnover over 36 months.

Changes in serum Propeptide of type I procollagen [PINP] and serum crosslinked c-telopeptide [CTX] over 36 months. Values are Means +SEM.

Figure 3. Changes in BMD of the spine, total hip, femoral neck, 1/3 radius and Total Body Bone Mineral (TBBM) over 36 months. At 36 months, LS BMD Standard vs cyclic group difference was p=0.04; no other significant differences were seen. At 18 months, in the Cyclic regimen, BMD levels at the RAD and TBBM were different vs the Standard (group differences p=0.007 and p<0.001, respectively). Values are Mean+SEM.

Table 1. Baseline Characteristics (Mean ± SD).

	Standard (n=34)	Cyclic (n=34)
Age (years)	**65.4 ± 17.8**	**65.0 ± 17.0**
BMI (kg/m^2)	**23.1 ± 2.6**	**23.2 ± 3.03**
Spine BMD (g/cm$^{2)}$)	**0.718 ± 0.091**	**0.761 ± 0.074**
Spine t-score	**-2.92 ± 0.81**	**-2.63 ± 0.65**
Total Hip BMD (g/cm$^{2)}$)	**0.733 ± 0.074**	**0.732 ± 0.091**
Total Hip t-score	**-1.74 ± 0.601**	**-1.72 ± 0.75**
Femoral neck BMD (g/cm2)	**0.591± 0.055**	**0.602+ 0.081**
Femoral neck t-score	**-2.39 ± 0.71**	**-2.25 + 0.71**
Serum CTX (ng/pL)	**485 ± 221**	**436 ± 173**
Serum OC (ng/mL)	**27.4 ± 8.86**	**24.4 ± 6.64**
Serum PINP (ng/mL)	**60.9 ± 22.7**	**59.6 ± 19.1**
Serum 25(OH)D (ng/mL)*	**18.3+ 22.1**	**15.4+21.0**
Serum PTH (pg/mL)	**41.7 + 15.5**	**39.4 + 11.3**
Calcium (mg/dL)	**9.24 ± 0.25**	**9.30 ± 0.32**
History of Non-vertebral fracture ≥age 50 (%)	**20%**	**22%**
Prevalent Vertebral Fractures (%)	**9.4%**	**23.3%**
Prior BP exposure (%)**	**48%**	**52%**

No significant differences between groups except for spine BMD p=0.04

***** All women were treated to bring 25(OH)D to >30 ng/mL before randomization.

****** Exclusions for: use of oral bisphosphonate for > 4 months within the past 2 years or > 5 years total cumulative bisphosphonate use in the past 10 years; use of intravenous ibandronate within the past 18 months; use of intravenous zoledronic acid within the past 4 years

Figure 1. Consort Figure

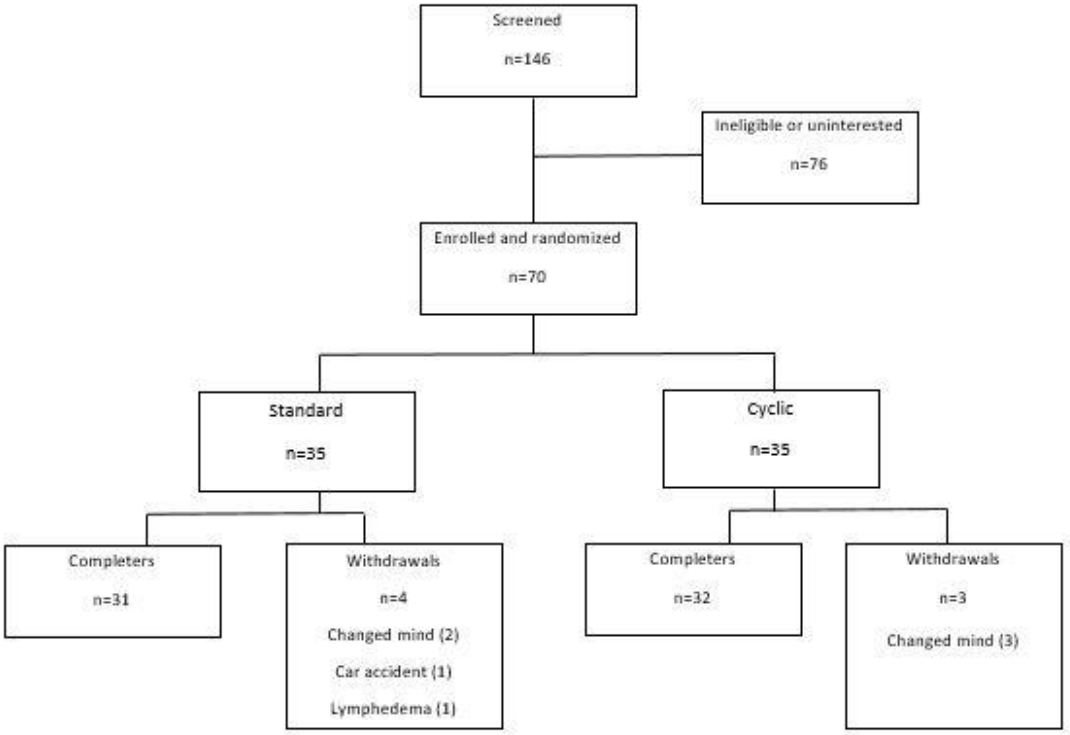

Figure 2.

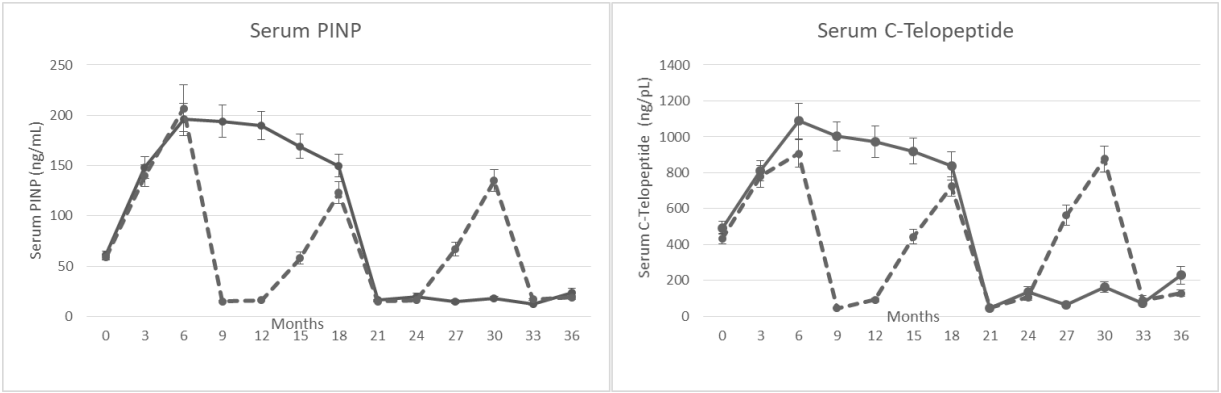

Figure 3.