CASE REPORT

Dietary Supplementation With Cyplexinol For Amelioration of Osteoporosis: A Case Study

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ABSTRACT

A 50-y-old male in otherwise good health was diagnosed with severe osteoporosis with a lumbar spinal T-score of -3.8. Further testing revealed no underlying causes other than a family history of the disease. He was placed on a trial regimen of 450 mg Cyplexinol twice daily for four months. Repeat DEXA scans after four months of this therapy showed an improved lumbar spinal T-score of -3.3, the first time that improvement in T-scores has been demonstrated in this short amount of time. Cyplexinol, the first orally consumable demineralized bone matrix (DBM) consisting of a naturally-derived bone morphogenetic protein complex (BMP-complex), may be a beneficial alternative to conventional treatments for osteoporosis with an ability to reverse bone mineral density loss in as little as 4 months. (*Altern Ther Health Med.* 2018;25(2):12-16.)

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INTRODUCTION

Osteoporosis is a degenerative skeletal disease marked by a decrease in bone mineral density (BMD) and an increased risk of fractures. The condition is typically progressive with age, and once bone tissue is lost it is difficult to replace. Conventional therapies for osteoporosis consist of pharmaceuticals, such as bisphosphonates, which prevent further bone degradation and can improve T-scores to some degree when used for long enough; however, these drugs can lead to some negative effects when used long-term.[1] Various physical interventions have been trialed but to date none have proven to be effective.[2] Here we present a case where a patient with severe osteoporosis was able to improve the T-score in his lumbar spine by 9.3% over a period of four months by supplementation with Cyplexinol, a naturally-derived BMP complex. This report was written following the CARE guidelines for clinical case reporting.[3]

Patient Narrative

A 50-y-old Caucasian male came into an arthritic care clinic to request a screening for osteoporosis. The patient was in excellent physical health, with no recent illnesses, no medical history of inflammatory conditions or musculoskeletal issues or bone fractures, and at the time was not taking any medications. At the time he was exercising regularly, did not smoke, and had consumed a Mediterranean-style diet of anti-inflammatory foods for most of his life with occasional alcohol consumption. Aside from possible genetics and being thin, the patient had no lifestyle or illness-related risk factors for osteoporosis. His mother had been diagnosed with moderate osteoporosis for the past ten years and had been treated with various therapies, most recently denosumab for multiple years. The patient's father likewise had been diagnosed with severe osteoporosis for the past three years and had been taking teriparatide for the past two years. This family history compelled the patient to seek a bone mineral density scan as a precaution.

DEXA scans of the patient's left and right femoral neck and lumbar spine resulted in T-scores of -2.1, -1.8, and -3.8, respectively (Figure 1). FRAX tool evaluation based on the femoral neck T-score assessed a 10-year risk of major osteoporotic fracture at 4.9%. Accordingly, the patient was diagnosed with severe osteoporosis.

Follow-up labs were run to rule out any underlying conditions (Figure 2). A fasting blood draw showed values within the normal range for vitamin D, thyroid panel, celiac panel, comprehensive metabolic panel (including calcium), parathyroid hormone (PTH), and insulin-like growth factor 1 (IGF-1). Two inflammatory markers, fibrinogen and hs-CRP, were elevated. Since the patient did not have a history of high

Table 1. Timeline of patient medical history, tests, diagnoses, and interventions.

	Relevant Past Medical History and Interventions		
	Excellent physical condition with no recent illnesses or musculoskeletal problems, no history of inflammatory or glycemic conditions, no medications recently. No smoking, occasional alcohol, and lifetime of Mediterranean-style diet. Mother diagnosed with moderate osteoporosis and father diagnosed with severe osteoporosis.		
	Summaries from Initial and Follow-up Visits	**Diagnostic Testing**	**Interventions**
Nov. 2017	Due to family history, patient chooses to be screened for OP.	DEXA scan shows severe OP with lumbar T-score of -3.8.	
Dec. 2017	Labs performed to check for underlying conditions.	Bloodwork results normal for Vit. D, celiac panel, blood sugar, thyroid panel, CMP (calcium), IGF-1, osteocalcin. Elevated hs-CRP and fibrinogen from acute transient stress.	
Jan. 2018	Labs performed to check for underlying conditions.	NTX and hs-CRP levels normal.	Patient placed on trial of 450mg Ostinol twice daily.
May 2018	Repeat OP check.	DEXA scan showed lumbar T-score had improved to -3.3.	Continue regimen of 450mg Ostinol twice daily.

Figure 1. DEXA scans of patients left femoral neck (left), right femoral neck (center), and lumbar vertebrae (right) at baseline.

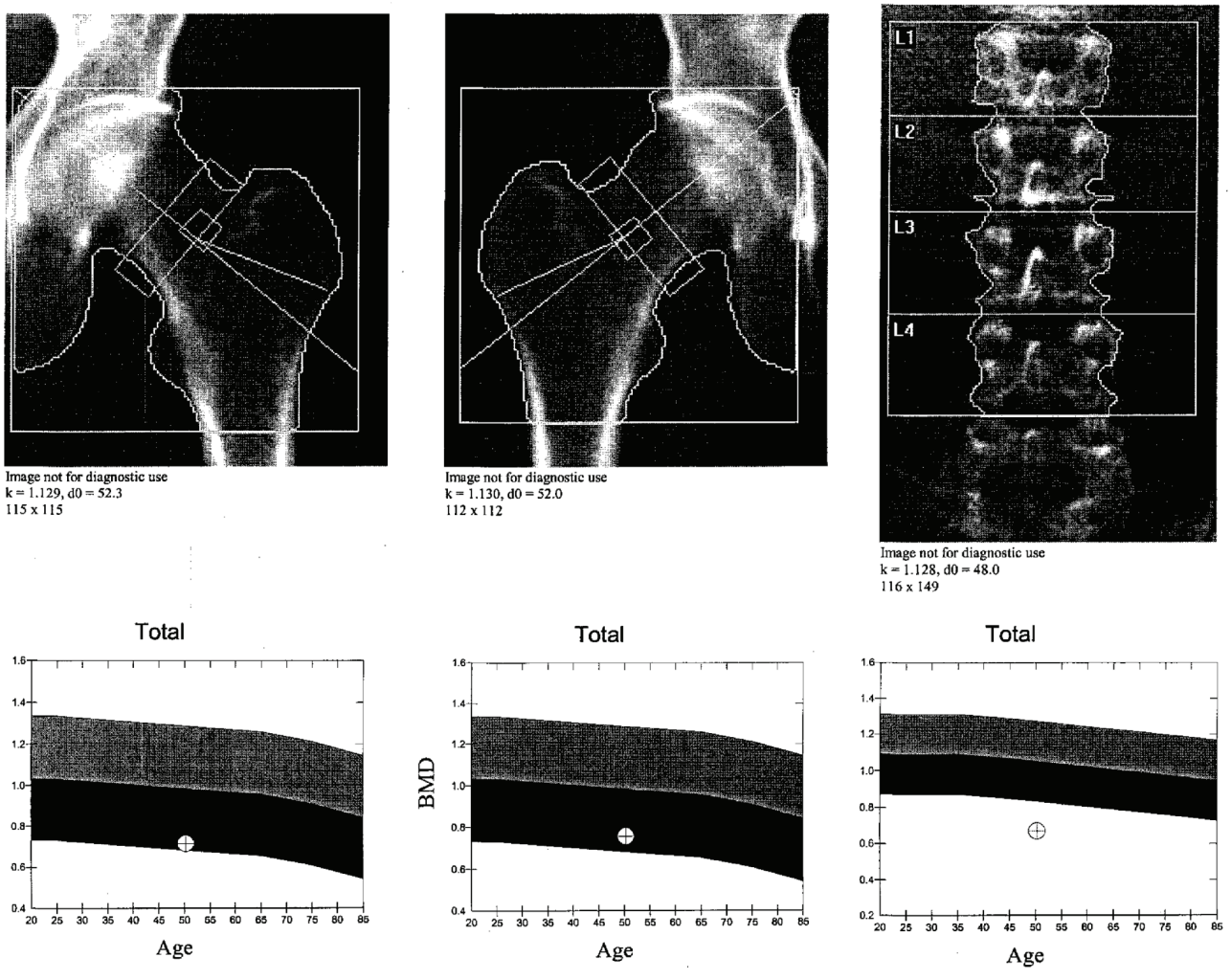


Figure 2. Fasting blood draw laboratory results at baseline, indicating no underlying causes for the patient's osteoporosis.

	Laboratory Test	Notes	High Risk	Intermediate Risk	Optimal	High Risk Range	Intermediate Risk Range	Optimal Range	Previous Results 2/9/2015
Metabolic	25-hydroxy-Vitamin D (ng/mL)					≤ 14	15 - 29	30 - 100	45
	25-hydroxy-Vitamin D (ng/mL)				50	< 20	20 - 29	30 - 100	
	Uric Acid (mg/dL)				2.9	≥ 8.0	7.0 - 7.9	2.0 - 6.9	3.4
	TSH (µIU/mL)				2.61	< 0.27 or > 4.20		0.27 - 4.20	2.05
	Homocysteine (µmol/L)				7	> 13	11 - 13	< 11	8
Renal	Cystatin C (mg/L)				0.70	≥ 1.04	0.96 - 1.03	≤ 0.95	0.94
	Estimated Glomerular Filtration Rate (eGFR, mL/min/1.73m2)					< 60	60 - 89	> 89	93
	Creatinine, serum (mg/dL)				0.8	> 1.2		0.7 - 1.2	0.9
Glycemic Control	Glucose (mg/dL)				86	> 125	100-125	70 - 99	95
	HbA1c (%)				5.4	≥ 6.5	5.7 - 6.4	≤ 5.6	5.2
	Estimated Average Glucose (mg/dL) (calculated)				108.3	≥ 139.9	116.9 - 139.8	≤ 116.8	102.5
	Fructosamine (µmol/L)					> 346	302 - 346	< 302	331
	Glycation Gap					> 0.77	0.45 - 0.77	< 0.45	-2.21
	Postprandial Glucose Index					> 7.9	6.0 - 7.9	< 6.0	9.9
Insulin Resistance	Leptin (ng/mL)					> 43	20 - 43	< 20	< 2
	Leptin:BMI Ratio					> 1.17	0.66 - 1.17	< 0.66	0.09
	Adiponectin (µg/mL)					< 10	10 - 14	> 14	10
	Free Fatty Acid (mmol/L)					> 0.70	0.60 - 0.70	< 0.60	0.46
	Ferritin (ng/mL)**					> 252	147 - 252	< 147	85
	α-hydroxybutyrate (µg/mL)					> 5.7	4.5 - 5.7	< 4.5	3.8
	Oleic Acid (µg/mL)					> 79	60 - 79	< 60	35
	Linoleoyl-GPC (µg/mL)					< 10.5	10.5 - 13.0	> 13.0	29.0
	HOMA-IR (calculated)				0.9	> 4.2	2.6 - 4.2	< 2.6	0.8
Beta Cell Function	Insulin (µU/mL)				4	≥ 12	10 - 11	3 - 9	4
	Proinsulin (pmol/L)				7	> 16	8 - 16	< 8	9
	C-peptide (ng/mL)					> 4.6	3.1 - 4.6	1.0 - 3.0	1.3
	Proinsulin:C-peptide Ratio					> 4.9	3.6 - 4.9	< 3.6	7.0
	Anti-GAD (IU/mL)					> 5 Positive		≤ 5 Negative	< 5
Lipids	Total Cholesterol (mg/dL)				161	≥ 240	200 - 239	< 200	193
	LDL-C Direct (mg/dL)			101		≥ 130 CHD & CHD risk eq. > 100	100 - 129 CHD & CHD risk eq. 70 - 100	< 100 CHD & CHD risk eq. < 70	117
	HDL-C (mg/dL)				53	< 40		≥ 40	63
	Triglycerides (mg/dL)				67	> 199	150 - 199	< 150	67
	Non-HDL-C (mg/dL) (calculated)				109	≥ 160	130 - 159	< 130	130
Lipoprotein Particles and Apolipoproteins	Apo B (mg/dL)				79	≥ 100	81 - 99	≤ 80	90
	LDL-P (nmol/L), by NMR			1355		≥ 1360	1020 - 1359	< 1020	1580
	Small LDL-P (nmol/L), by NMR			737		> 1000	501 - 1000	< 501	746
	sdLDL-C (mg/dL)				20	> 30	21 - 30	< 21	26
	Apo A-I (mg/dL)			130		< 114	114 - 131	> 131	150
	HDL-P (µmol/L), by NMR		33.2			≤ 34.0	34.1 - 38.0	> 38.0	37.4
	HDL2-C (mg/dL)				17	≤ 8	9 - 11	≥ 12	24
	Apo B:Apo A-I Ratio (calculated)					≥ 0.81	0.61 - 0.80	≤ 0.60	0.60
	Lp(a)-P (nmol/L)			80		> 125	75 - 125	< 75	
Inflammation/ Oxidation	Fibrinogen (mg/dL)		809			< 126 or > 517	438 - 517	126 - 437	361
	hs-CRP (mg/L)		17.0			> 2.9	1.0 - 2.9	< 1.0	< 0.3
	Lp-PLA$_2$ (ng/mL)				163	> 383	291 - 383	< 291	
	Myeloperoxidase (pmol/L)			321		≥ 332	256 - 331	≤ 255	
	F_2-Isoprostanes (urine) (ng/mg of creatinine)					≥ 0.33	0.22 - 0.32	≤ 0.21	0.14
	Oxidized LDL (U/L)				39	> 70	60 - 70	< 60	

	Laboratory Test	Notes	Positive	Negative	Positive Range	Negative Range	Previous Results 2/9/2015
Celiac Disease	Deamidated Gliadin Peptide Antibody, IgA (U/mL)			0.4	≥ 15.0	< 15.0	
	Deamidated Gliadin Peptide Antibody, IgG (U/mL)			< 0.4	≥ 15.0	< 15.0	
	Tissue Transglutaminase (tTG) Antibody, IgA (U/mL)			< 0.5	≥ 15.0	< 15.0	
	Tissue Transglutaminase (tTG) Antibody, IgG (U/mL)			< 0.8	≥ 15.0	< 15.0	

CBC with Automated Differential / Platelet	Result	Flag	Reference Interval
WBC (x10^3/µL)	5.4		4.0 - 10.5
RBC (x10^6/µL)	4.4		4.1 - 5.6
Hemoglobin (g/dL)	15.3		12.5 - 17.0
Hematocrit (%)	45		36 - 50
MCV (fL)	102	H	80 - 98
MCH (pg)	35	H	27 - 34
MCHC (g/dL)	34		32 - 36
RDW (%)	12.9		11.7 - 15
Platelets (x10^3/µL)	247		140 - 415
Neutrophils (%)	54		40 - 74
Lymphocytes (%)	26		14 - 46
Monocytes (%)	9		4 - 13
Eosinophils (%)	11	H	0 - 7
Basophils (%)	1		0 - 3
Neutrophils (absolute) (x10^3/µL)	2.9		1.8 - 7.8
Lymphocytes (absolute) (x10^3/µL)	1.4		0.7 - 4.5
Monocytes (absolute) (x10^3/µL)	0.5		0.1 - 1.0
Eosinophils (absolute) (x10^3/µL)	0.6	H	0.0 - 0.4
Basophils (absolute) (x10^3/µL)	0.0		0.0 - 0.2
Immature Granulocytes (absolute) (x10^3/µL)	0.0		0.0 - 0.1

Electrolytes	Result	Flag	Reference Interval
Na+ (mmol/L)	140		133 - 145
K+ (mmol/L)	4.6		3.5 - 5.3
Cl- (mmol/L)	106		98 - 110
CO_2 (mmol/L)	24		19 - 31
Anion Gap (calculated)	9		6 - 18
Calcium (mg/dL)	9.3		8.8 - 10.5
Magnesium (mg/dL)	2.1		1.6 - 2.4
Phosphorus (mg/dL)	3.4		2.7 - 4.5

Liver	Result	Flag	Reference Interval
ALT / GPT (U/L)	15		< 42
AST / GOT (U/L)	17		< 41
ALP (U/L)	72		< 16 years 96 - 410 16 - 20 years 49 - 210 21 - 90 years 35 - 117 > 90 years 38 - 140
Total Bilirubin (mg/dL)	0.4		Up to 1.2

Bone	Result	Flag	Reference Interval
PTH, Intact (pg/mL)	32		15 - 65

Autoimmune	Result	Flag	Reference Interval
hs-CRP (mg/L)	17.0	H	< 5.0

Others	Result	Flag	Reference Interval
Albumin (g/dL)	4.3		3.7 - 5.1
% Albumin (calculated)	58		54 - 71
Globulin (g/dL) (calculated)	3.1		1.9 - 3.5
Albumin:Globulin Ratio (calculated)	1.38		1.15 - 2.50
Total Protein (g/dL)	7.4		6.1 - 8.0

Thyroid	Result	Flag	Reference Interval
TSH (µIU/mL)	2.61		0.27 - 4.20
T4, free (ng/dL)	1.39		0.93 - 1.70
T3, free (pg/mL)	3.0		> 19 yrs - 2.0 – 4.4

Male and Female Hormones	Result	Flag	Reference Interval
Dehydroepiandrosterone sulfate (µg/dL)	146		15 - 19 yrs: 70 - 492 20 - 24 yrs: 211 - 492 25 - 34 yrs: 160 - 449 35 - 44 yrs: 89 - 427 45 - 54 yrs: 44 - 331 55 - 64 yrs: 52 - 295 65 - 74 yrs: 34 - 249 > 74 yrs: 16 - 123
Estradiol (pg/mL)	28.4		25.8 - 60.7
Human sex hormone-binding globulin (nmol/L)	79		10 - 80
Testosterone (ng/dL)	477		< 1 year 12 - 21 1 - 6 years 12 - 32 7 - 12 years 12 - 68 13 - 17 years 28 - 1110 > 17 years 348 - 1197
Free Testosterone (ng/dL) (calculated)	5.30		4.7 - 24.4

levels of either marker this was attributed to acute transient stress from major life changes including job relocation and buying a house. A test the next month showed that hs-CRP levels had returned to the normal range. Osteocalcin levels were normal, indicating adequate vitamin K, and an NTX test indicated no excessive breakdown of bone tissue. With no underlying disorders acting as the cause of the osteoporosis as well as the family history, the patient's condition was likely due to genetics.

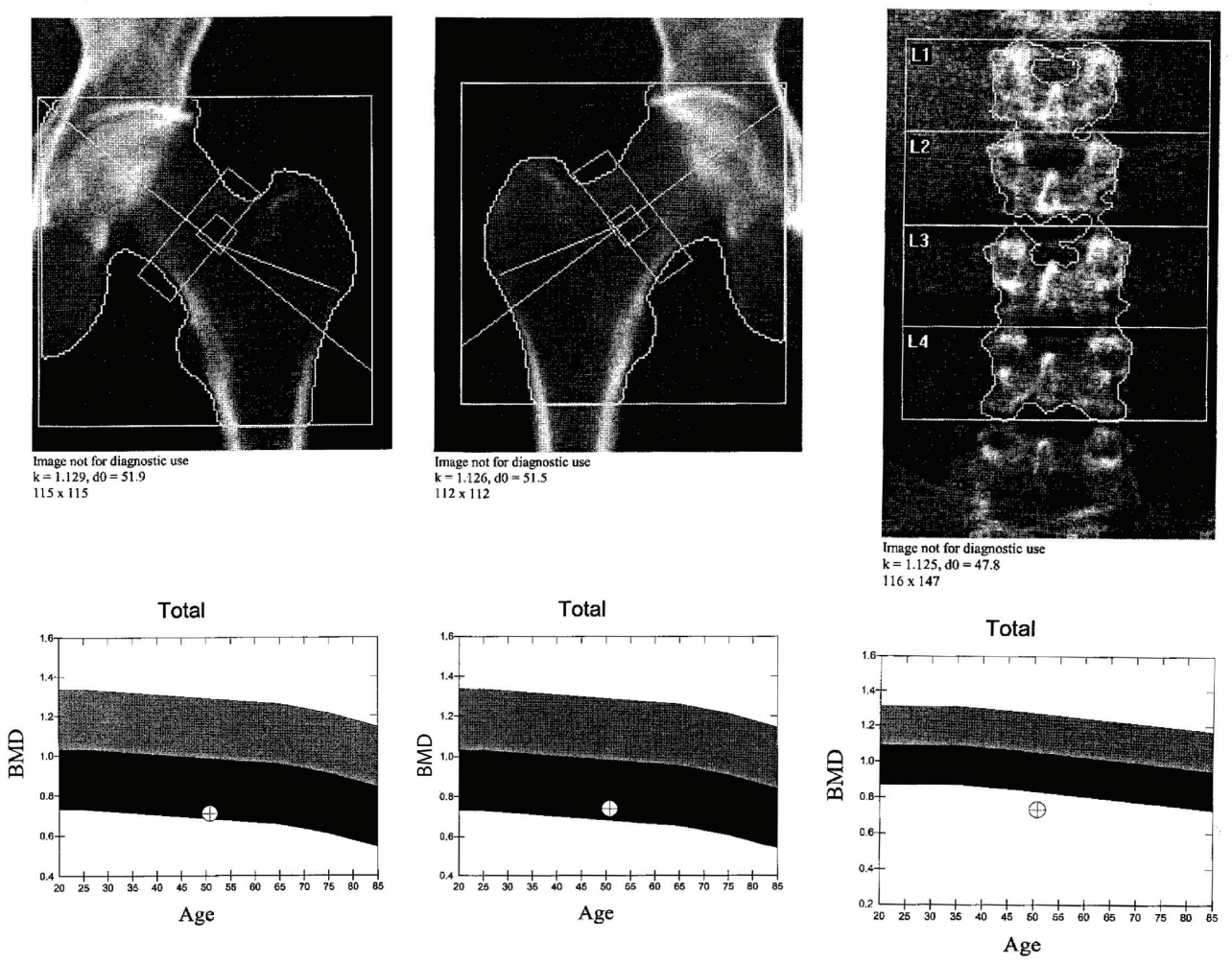
The patient was faced with the choice of whether to undergo aggressive pharmaceutical therapy, likely denosumab, through a rheumatologist. Being a naturopathic doctor, the patient opted instead to begin a trial of a natural dietary supplement. He was placed on a regimen of 450 mg of Cyplexinol twice daily. Cyplexinol (brand name Ostinol™, ZyCal Bioceuticals Healthcare Co., Inc., Toms River, NJ) is the first orally consumable demineralized bone matrix (DBM) consisting of a naturally-derived bone morphogenetic protein complex (BMP-complex). The patient adhered very well to the supplement and continued this course of treatment for four months before returning for repeat scans. No other lifestyle or dietary changes were made.

Repeat DEXA scans were performed on the same bone densitometer from Hologic. After four months of consistently following the Cyplexinol regimen, the T-scores of the left femoral neck, right femoral neck, and lumbar vertebrae were evaluated at -2.1, -1.9, and -3.3, respectively (Figure 3). The lumbar spine T-score increase of 0.5, from -3.8 to -3.3, was a significant improvement over baseline. This correlates with an increase in BMD of 0.062 g/cm2 (from 0.669 g/cm^2 to 0.731 g/cm^2) or 9.3%. Following these initial positive results, the current treatment plan is for the patient to continue his regimen of 450 mg Cyplexinol twice daily.

DISCUSSION

Conventional pharmaceuticals for the treatment of osteoporosis typically act by preventing further degradation of bone mineral density. They do so by blocking the function of osteoclasts, the cells that break down bone tissue as part of the body's natural cycle of bone turnover. Drugs in the bisphosphonate class mimic pyrophosphate and inhibit osteoclastic enzymes, while monoclonal antibodies such as denosumab downregulate the hormone signaling which stimulates osteoclast activity.[4] These drugs do not restore

Figure 3. DEXA scans of patients left femoral neck (left), right femoral neck (center), and lumbar vertebrae (right) following four months of supplementation with Cyplexinol.



bone density,[5] and their long-term use has been associated with serious long-term effects such as osteonecrosis of the jaw and atypical femoral fractures. Therefore, physicians typically do not recommend their use beyond 3-5 years, which may be insufficient for patients with severe osteoporosis or with the highest risk of fracture.[1] Teriparatide, a PTH mimetic, is capable of inducing osteoblast activity and promoting bone tissue anabolism, but is likewise used with reservation due to a link to osteosarcoma.[4]

Cyplexinol, on the other hand, is the first and only orally consumable demineralized bone matrix which is comprised of BMPs and other growth factors bound to a partially hydrolyzed collagen matrix, naturally produced in the bones. In animal studies, Cyplexinol has been found to be osteoinductive, promoting mesenchymal stem cell differentiation into osteoblasts and chondrocytes for *de novo* bone and cartilage tissue production.[6] Two small clinical studies with osteoarthritic patients indicated that short-term supplementation with Cyplexinol is capable of reducing pain intensity and frequency in arthritic joints,[6,7] and one other case series involving four osteopenic and osteoporotic subjects showed an increase in BMD following Cyplexinol® supplementation.[8]

In our current case, a bi-daily schedule of Cyplexinol supplementation was capable of increasing a severely osteoporotic BMD by 0.062 g/cm^2, and the corresponding T-score by 0.5 in as little as four months. This is a significant improvement in a relatively short amount of time, as treatment with conventional therapies can take a year or longer to achieve a similar result, if any is seen.[4] As the vertebrae are comprised predominantly of spongy cancellous bone, the prominent site of bone remodeling,[5] the fact that the lumbar spine began with the lowest T-score and was the only area to demonstrate improvement in this time is not unexpected. The compact, slower-growing cortical bone of the femoral neck will likely require a longer period of treatment to show noticeable improvement.

These results show a promising new approach to osteoporosis which enhances the body's own regenerative capabilities to replenish bone density that has been lost, does

not rely on pharmaceuticals with potentially harmful side effects, and provides hope for treating cases of osteoporosis where BMD loss is already substantial. The obvious limitations here are the length and scope of the study-although the patient did not demonstrate any negative consequences to initiating this therapy, the timing was not sufficient to witness any long-term effects of the supplement. Further studies with larger cohorts are needed to fully evaluate the effects of Cyplexinol on both skeletal and general health.

CONCLUSION

Supplementation with 450mg Cyplexinol twice daily was able to improve the lower spinal T-score of a patient with severe osteoporosis from -3.8 to -3.3 after only four months on the regimen. Cyplexinol offers a promising alternative to conventional treatments for osteoporosis, possibly with fewer health risks, and can provide greater benefits than current pharmaceutical interventions by rebuilding bone tissue after it has already been significantly degraded.

REFERENCES

1. Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2016;31(1):16-35.
2. Charmetant C, Phaner V, Condemine A, Calmels P. Diagnosis and treatment of osteoporosis in spinal cord injury patients: A literature review. *Annals of physical and rehabilitation medicine.* 2010;53(10):655-668.
3. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development. *Global advances in health and medicine.* 2013;2(5):38-43.
4. Das S, Crockett JC. Osteoporosis - a current view of pharmacological prevention and treatment. *Drug design, development and therapy.* 2013;7:435-448.
5. Langdahl B, Ferrari S, Dempster DW. Bone modeling and remodeling: potential as therapeutic targets for the treatment of osteoporosis. *Therapeutic advances in musculoskeletal disease.* 2016;8(6):225-235.
6. Spinks K, Scaffidi JJ. In Vivo Osteoinduction: Evaluating 2-Beta Coxatene as an Immunoinductive Compound and Novel Ingredient for Joint Support. *Integrative medicine (Encinitas, Calif).* 2016;15(5):34-44.
7. Spinks K, Walker M, Scaffidi J. Clinical Assessment of Low-dose Osteoinductive Protein as a Stand-alone Regimen in Self-reported Osteoarthritis. *Integrative medicine (Encinitas, Calif).* 2015;14(2):23-32.
8. Tripodi D. Osteoinductive Effects of Cyplexinol in the Management of Osteoporosis: A Case Series. *Alternative therapies in health and medicine.* 2017;23(6):42-47.