The Effect of Vitamin D Replacement on Musculoskeletal Pain in Hypothyroid Patients with Vitamin D Deficiency

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Abstract—Hashimoto's thyroiditis [HT] is the most common chronic autoimmune thyroid disorder that can cause hypothyroidism. Environmental and genetic factors are playing role in its etiology. The role of vitamin D as an immune modulator has been emphasized in recent years. The goal of present study is to assess whether vitamin D supplements can reduce the musculoskeletal pain of HT patients who had vitamin D deficiency.

This is a single arm clinical trial that included 42 cases who have HT with musculoskeletal pain after becoming euthyroid. 25-hydroxy vitamin D was less than 32 nmol/L. We measured calcium, phosphorus, parathyroid hormone (PTH), thyroid stimulating hormone (TSH), 25-hydroxy vitamin D and severity of body pain at the beginning of the study and after 8 weeks of treatment with vitamin D (cholecalciferol 50,000 weekly). We used SPSS software version 16 to analyze data.

Vitamin D supplementation, after 8 weeks, improved musculoskeletal pain, and increased mean serum calcium, phosphorus, and 25-OH-Vitamin D levels significantly. There were no significant changes in mean TSH levels.

Vitamin D supplements can potentially helpful in reducing musculoskeletal pain of HT patients who also have vitamin D deficiency. High prevalent area of vitamin D deficiency should consider concomitant treatment of vitamin D deficiency in HT patient.

KEY WORDS: Hashimoto's thyroiditis, vitamin D deficiency, musculoskeletal pain, Vitamin D replacement.

INTRODUCTION

Vitamin D deficiency is a public health challenges that outside of the bone system has possible relationship with cardiovascular disease, insulin resistance, infectious diseases, cancers, and autoimmune disorders such as rheumatoid arthritis and autoimmune thyroid disease (1-5). Vitamin D is a steroid hormone which plays an important role in regulating many genes. It also employs different effects on cellular proliferation, differentiation, apoptosis, angiogenesis, and inflammation (3-6). The role of calcitriol as a key hormone in the regulation of the musculoskeletal system is well described. However, after finding vitamin D receptor (VDR) in extra skeletal tissues, VDR was introduced as a transcriptional factor that carries various biological effects (7, 8), and contributes to orchestration of inflammatory processes in autoimmune diseases (9, 10). VDR probably has immunosuppressive, regulatory, and tolerogenic effects in autoimmune processes (11, 12).

Autoimmune thyroid disease (Hashimoto's thyroiditis) and vitamin D insufficiency are linked together. TSH has negative correlation with serum vitamin D (13, 14). In addition, calcidiol (25- hydroxyvitamin D, 25VD) concentration has positive correlation with thyroid volume, and negative correlation with anti-TPO (thyroid peroxidase) and anti-TG (thyroglobulin) antibody levels (15, 16). Vitamin D supplementation may improve autoimmunity in patient with autoimmune thyroid disease (AITD) by reducing anti TPO- Ab levels (5).

Vitamin D deficiency and hypothyroidism are often associated with signs and symptoms of nociceptive pain and musculoskeletal discomfort (17, 18). Levothyroxine therapy can improve musculoskeletal symptoms of hypothyroidism (19). However, in accordance with vitamin D deficiency, musculoskeletal pain can potentially stay in euthyroid states, and may increase the risk of medication non-compliance. To

the best of our knowledge, in the setting of vitamin D deficiency and Hashimoto's hypothyroidism, nobody tested effect of vitamin D supplementation on musculoskeletal pain of hypothyroid patients.

We hypothesized that vitamin D supplementation in euthyroid patients with Hashimoto's hypothyroidism (on levothyroxine with TSH < 4) can improve musculoskeletal symptoms and probably their compliance with medication.

MATERIALS AND METHODS:

This study is a single-arm clinical trial to investigate the effects of vitamin D supplementation on musculoskeletal pain in the patients with Hashimoto's hypothyroidism (HT). Participants singed informed consent after having a broad explanation about the study course, interventions and benefit and side effects of prescribed medications (levothyroxine and cholecalciferol).

Our endocrinologist selected the enrollees between patients who came to Faculty Group Practice (FGP) clinic (Abolfazl clinic in Bushehr, Iran) from April to September 2010.

All participants had Hashimoto's hypothyroidism (TSH > 10 with positive anti-TPO antibody).

All patients with HT and musculoskeletal pain were treated with levothyroxine. Continued musculoskeletal pain after achieving normal TSH (TSH < 4) was considered for further investigation. HT with normal TSH (on levothyroxine), 25 VD less than 32 ng/ml and continued musculoskeletal pain were criteria to be joined.

25-hydroxy Vitamin D, calcium, phosphorous serum level and body pain severity assessed before and after prescription of 8 weeks 50,000 IU in euthyroid HT patient with low vitamin D.

Our data analyzed with SPSS software version 16 and paired t-test and Wilcoxon test used for descriptive statistics and Kolmogrov and Simonov test was done for evaluation of normality of data distribution. Cases had normal distribution and data analyzed using necessary tests.

Musculoskeletal pain scored per visual analogue scale (VAS) or 0-10 numeric pain rating scale.

TSH, total T4, total T3 and anti-TPO-Ab were measured by using Monobite kit (ELISA method).

Calbiotec PHASC (Pharm avaran e sabz co.) was used to check serum levels of 25VD (ELISA method).

Serum calcium and phosphorus were measured by using Pars azmoon kit (enzymatic method).

Ethics committee of Bushehr University of Medical Sciences approved the study.

We excluded patients with history of concomitant autoimmune or rheumatologic disease (such as rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia syndrome), major systemic illness (included parathyroid disease, adrenal disease, diabetes mellitus, chronic renal failure, liver disease, or ischemic heart disease), hypertension or hyperlipidemia on medication, elevated liver enzymes (AST and ALT) and muscle enzyme (CK).

RESULTS

Out of 70 patients with Hashimoto's thyroiditis and musculoskeletal pain, 63 patients who were complaining of musculoskeletal pain after receiving levothyroxine and having normal TSH (TSH 0.5 - 4) joined the study. During 3 months follow up, 21 patients had lost follow up assessment and 42 patients completed end of study questionnaire.

Our enrollee included 22 women (52.4%) and 20 man (47.6 %). Age distribution ranged between 15 and 70 with mean age of 40.88±15.77.

Vitamin D supplementation increased mean serum calcium (from baseline value 8.58 ± 0.23 to 9.04 ± 0.34), phosphorus (form starting value 2.3 ± 0.29 to 3.65 ± 0.55) and 25-OH-Vitamin D levels significantly. There were no significant changes in mean TSH levels during vitamin D supplementation (mean baseline values 3.46 ± 1.13, and end of study levels 3.3 ± 1.35) (Table 1).

Pain of 38 cases (90 %) improved significantly after vitamin D replacement (P-value < 0.0001).

Table 1

Biochemical results before & after treatment

Patient's data	Before treatment	After treatment	P-Value
25(OH) vitamin D, nmol/L or ng /ml	17.9	55.59	.000
Calcium mg/dl	8.58	9.04	.000
Phosphorus mg/dl	2.3	3.65	.000
TSH mIU/L or µIU/ml	3.46	3.3	.5

DISCUSSION

In this single arm trial involving patients with history of Hashimoto's thyroiditis, on levothyroxine, who had THS < 4, 25-hydorxy vitamin D < 32, and musculoskeletal pain; vitamin D supplementation (cholecalciferol 50,000 weekly) improved musculoskeletal discomfort.

Hashimoto's thyroiditis often causes musculoskeletal symptoms including joint pain, muscle weakness, cramps, and myalgias. On the other hand, vitamin D deficiency which is associated with autoimmune diseases such as HT, is a prevalent condition in different age groups from young children to middle-aged adults (2, 20).

Literature presents controversies around improvement of musculoskeletal pain after vitamin D supplementation in patients with low vitamin D (25-OD vitamin D < 20 ng/mL) with or without underlying diseases (21-23). However, vitamin D supplementation has some beneficial effects on musculoskeletal pain and fatigue, probably by increasing serum level of 25 OH vitamin D (24).

Higher prevalence of vitamin D deficiency in HT (25), may play a role in musculoskeletal pain, and thus medication noncompliance of these patients. Musculoskeletal pain of our patients (HT with vitamin D deficiency) improved after vitamin D supplementation. No change in TSH level, and increase in serum levels of calcium, phosphorus and 25 OH vitamin D after vitamin D supplementation may explain

independent beneficial role of vitamin D supplementation in musculoskeletal pain of HT patients. Without measuring TPO and PTH after treatment, role of vitamin D supplementation as an immune modulator or regulator of calcium homeostasis in muscle is not completely explainable. Effects of Vitamin D on size, strength and function of muscle (6) may partially explain current improvement of musculoskeletal pain of HT. however, other possible mechanisms such as modulation of autoimmunity, increase efficacy of thyroid hormones, improvement of bone quality cannot be excluded.

CONCLUSION

Vitamin D deficiency should be considered as a possible cause of musculoskeletal pain in HT patients. Vitamin D supplementation may improve their musculoskeletal pain and possibly medication compliances.

REFERENCES

[1] Metwalley KA, Farghaly HS, Sherief T, Hussein A. Vitamin D status in children and adolescents with autoimmune thyroiditis. J Endocrinol Invest. 2016 Jul; 39 (7): 793-7.

[2] Ittyachen AM, Vijayan A, Kottam P, Jose A. Aches, pains and headache: an unusual combination of hypothyroidism, vitamin D deficiency, cervical radiculopathy and cortical vein sinus thrombosis. BMJ Case Rep. 2015 Jul 8; 2015.

[3] Vondra K, Stárka L, Hampl R. Vitamin D and thyroid diseases. Physiol Res. 2015; 64 Suppl 2: S95-S100.

[4] Ishikawa LL, Colavite PM, Fraga-Silva TF, Mimura LA, França TG, Zorzella-Pezavento SF, Chiuso-Minicucci F, Marcolino LD, Penitenti M, Ikoma MR, Sartori A. Vitamin D Deficiency and Rheumatoid Arthritis. Clin Rev Allergy Immunol. 2016 Aug 2.

[5] Chaudhary S, Dutta D, Kumar M, Saha S, Mondal SA, Kumar A, Mukhopadhyay S. Vitamin D supplementation reduces thyroid peroxidase antibody levels in patients with autoimmune thyroid disease: An open-labeled randomized controlled trial. Indian J Endocrinol Metab. 2016 May-Jun; 20 (3): 391-8.

[6] Wintermeyer E, Ihle C, Ehnert S, Stöckle U, Ochs G, de Zwart P, Flesch I, Bahrs C, Nussler AK. Crucial Role of Vitamin D in the Musculoskeletal System. Nutrients. 2016 Jun 1; 8 (6).pii: E319.

[7] Stocklin E, Eggersdorfer M. Vitamin D, an essential nutrient with versatile functions in nearly all organs. Int J Vitam Nutr Res. 2013; 83 (2): 92-100.

[8] Wacker M, Holick MF. Sunlight and Vitamin D: A global perspective for health. Dermatoendocrinol. 2013 Jan 1; 5 (1): 51-108.

[9] Griffin MD, Xing N, Kumar R: Vitamin D and its analogs as regulators of immune activation and antigen presentation. Annu Rev Nutr. 2003; 23: 117-45.

[10] Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. Am J Physiol Renal Physiol. 2005 Jul; 289 (1): F8-28.

[11] Adorini L. Immunmodulatory effect of vitamin D receptor ligands in autoimmune diseases. Int Immunopharmacol. 2002 Jun; 2 (7): 1017-28.

[12] Cantorna MT, Mahon BD. Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. Exp Biol Med (Maywood). 2004 Dec; 229 (11): 1136-42.

[13] Mackawy AM, Al-Ayed BM, Al-Rashidi BM. Vitamin d deficiency and its association with thyroid disease. Int J Health Sci (Qassim). 2013 Nov; 7 (3): 267-75.

[14] Kim D. Low vitamin D status is associated with hypothyroid Hashimoto's thyroiditis. Hormones (Athens). 2016 Jul; 15 (3): 385-393.

[15] Bozkurt NC, Karbek B, Ucan B et al. The association between severity of vitamin D deficiency and Hashimoto's thyroiditis. Endocr Pract. 2013 May-Jun; 19 (3): 479-84.

[16] Camurdan OM, Doger E, Bideci A, et al. Vitamin D status in children with Hashimoto thyroiditis. J Pediatr Endocrinol Metab. 2012; 25 (5-6): 467-70.

[17] Holick MF. Vitamin D and sunlight: Strategies for cancer prevention and other health benefits. Clin J Am Soc Nephrol. 2008 Sep; 3 (5): 1548-54.

[18] Jacobs-Kosmin D, DeHoratius RJ. Musculoskeletal manifestations of endocrine disorders. Curr Opin Rheumatol. 2005 Jan; 17 (1): 64-9. Review.

[19] Kumar KV, Manoj S. Visual vignette. Hypothyroidism-associated myopathy. Endocr Pract. 2012 Mar-Apr; 18 (2): 295.

[20] Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med. 2008 Aug 11; 168 (15): 1629-37.

[21] Al Faraj S, Al Mutairi K. Vitamin D deficiency and chronic low back pain in Saudi Arabia. Spine (Phila Pa 1976). 2003 Jan 15; 28 (2): 177-9.

[22] Ruiz-Irastorza G, Egurbide MV, Olivares N, Martinez-Berriotxoa A, Aguirre C. Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences. Rheumatology (Oxford). 2008 Jun; 47 (6): 920-3.

[23] Warner AE, Arnspiger SA. Diffuse musculoskeletal pain is not associated with low vitamin D levels or improved by treatment with vitamin D. J Clin Rheumatol. 2008 Feb; 14 (1): 12-6.

[24] Khan QJ, Reddy PS, Kimler BF, Sharma P, Baxa SE, O'Dea AP, Klemp JR, Fabian CJ. Effect of vitamin D supplementation on serum 25-hydroxy vitamin D levels, joint pain, and fatigue in women starting adjuvant letrozole treatment for breast cancer. Breast Cancer Res Treat. 2010 Jan; 119 (1): 111-8.

[25] Tamer G, Arik S, Tamer I, Coksert D. Relative vitamin D insufficiency in Hashimoto's thyroiditis. Thyroid. 2011 Aug; 21 (8): 891-6.