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Vitamin D replacement therapy in patients with cardiac syndrome X

A Andishmand, Z Ansari, MH Soltani, H Mirshamsi and S Raafat

Abstract

Aims: The aim of present study was to assess whether vitamin D, with proven beneficial effects on the cardiovascular system, has any effect on angina and exercise-induced ischemia in patients with cardiac syndrome X and low serum vitamin D.

Methods: Patients with cardiac syndrome X and low serum vitamin D3 were studied before and after treatment with an intramuscular injection of vitamin D3 (300,000 units, every other week for 2 months). We determined the angina episode (per day) and several indices of exercise capacity.

Results: At the end of the treatment course (75±6 day), a significant increase of serum vitamin D3 occurred and was within the normal range (45±8 ng/ml) and the frequency of angina improved significantly (p=0.003). Exercise duration and maximal work capacity increased significantly (p<0.001). Maximal ST-segment depression (mm) decreased significantly (p=0.001). The calculated Duck treadmill score improved significantly (p=0.001).

Conclusions: Our findings show that vitamin D replacement therapy in patients with cardiac syndrome X and vitamin D deficiency dramatically improves symptoms and signs of ischemia.

Keywords

cardiac syndrome X; vitamin D; replacement therapy; vitamin D deficiency; ischemia

Introduction

Cardiac syndrome X (CSX), or stable primary microvascular angina (MVA), includes patients who have typical stable angina, findings compatible with myocardial ischemia, normal (or near normal) coronary arteries on angiography and the absence of any other specific cardiac disease (e.g., variant angina, cardiomyopathy, valvular disease).[1] Coronary microcirculation endothelial dysfunction has been proposed as the pathophysiological mechanism of angina.[2–4] On the other hand, studies in the general population show an inverse relationship between 25-OH D levels and the incidence of cardiovascular (CV) diseases. The Framingham Offspring Study showed participants without prior cardiovascular disease and 25-dihydroxyvitamin D (25-OH D) <15 ng/ml had an increased risk of developing the first CV event during the mean 5.4 years of observation compared with those with 25-OH D >15 ng/ml.[5] Studies have also shown that replacement of vitamin D has favorable effects on endothelial function.[6,7] The findings that the syndrome of microvascular angina is associated with endothelial dysfunction and that vitamin D may have a beneficial effect on endothelial function stimulated us to examine the effects of vitamin D replacement therapy on the symptom and exercise response of patients with cardiac syndrome X.

Patients and Methods

Study population

This study was approved on July 2011 by the Review Board and Ethics Committee of Shahid Sadouqi Medical

Cardiovascular Research Center, Afshar Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Corresponding author:
Hamide Mirshamsi
Cardiovascular Department
Afshar Hospital, Jomhoori Blvd
Yazd, 8917945556
Iran.
Email: mirshamsih@yahoo.com

University of Yazd. The study was conducted between October 2011 and December 2012 in Yazd, Iran. A total of 184 patients with chest pain were evaluated to assess whether they met the desired characteristics for study enrollment. Inclusion criteria were as follows: typical chest pain on effort, normal 12-lead ECG at rest, diagnostic criteria of ischemia during exercise stress test (horizontal or downsloping ST-segment depression ≥0.1 mV), normal left ventricular ejection fraction (LVEF), absence of valvular heart disease and myocardial hypertrophy, and normal coronary angiograms and level of serum vitamin D ≤20 ng/ml. They were excluded if they had malignancy, kidney or liver failure or systemic inflammatory diseases and inability to perform the treadmill exercise test. All patients gave their written informed consent to the study. None of the women were receiving estrogen replacement therapy. Among all the screened subjects, the diagnosis of CSX was made in 35 (19%) of patients, of whom 16 (45.7%) subjects had normal serum vitamin D levels and were not included. Therefore, a total of 19 patients were enrolled in the study.

Study protocol

After angiography, from the 35 patients with a diagnosis of CSX, a total of 19 patients met the inclusion criteria. Anti-anginal medications were discontinued one week before enrolment and the patients performed a baseline exercise stress test; then intramuscular injections of vitamin D3 (300,000 unit) were given every other week (a total of 5 injections/patient). The patients were instructed to take no anti-anginal drugs except sublingual nitroglycerin during the follow-up period. Frequency of angina per day and quality of life and functional capacity were reported by themselves. After two months' treatment, venous blood samples for the measurement of serum vitamin D3 and other lab tests (Electrochemiluminescence, Roche Diagnostics Co., Ltd., Mannheim, Germany) was repeated and, if the level of serum vitamin D was normalized, a repeat exercise test was performed.

Exercise testing

All patients underwent treadmill exercise tests before and after two months of treatment (Biomedical Systems Inc., St Louis, MO, USA), according to the standard Bruce protocol. Resting heart rate, blood pressure and 12-lead ECG were recorded before exercise. The exercise testing was performed in all patients to the end points of severe physical exhaustion, moderate to severe angina, serious arrhythmia or ≥2 mm ST-segment depression. During exercise, three ECG leads were continuously monitored. A 12-lead ECG was recorded every minute at peak exercise and every 2 min and 6 min of recovery. Maximum ST–segment depression (mm) was defined as the greatest exercise-induced ST depression 80 ms after the J point, which was horizontal or downsloping in leads with or without baseline ST-segment depression. The treadmill angina index was determined as 0 for no angina, 1 if typical angina occurred during exercise and 2 if angina was the reason for stopping the exercise. Exercise time (min) was defined as the duration of the exercise. The Duke treadmill score was calculated as;

Exercise time – (5 × maximum ST deviation) – (4 × angina index).

Maximum work capacity was defined as MET. (MET is defined as the resting metabolic rate, i.e., the amount of oxygen consumed at rest, sitting quietly in a chair; approximately 3.5 ml O_2/kg/min for a 70 kg person). Mean duration of treatment was 75±6 days.

Statistical analysis

SPSS for Windows Version 16 (SPSS Inc., Chicago, IL) was used for all statistical analysis. Data are presented as mean value ± SD for continuous variables. A paired t-tests was carried out to compare results before and after treatment. A p-value <0.05 was considered significant.

Results

We studied 19 patients with CSX (16 female and 3 male, mean age 51.4±6.5 years) before and after treatment with vitamin D. Ages ranged between 39 and 69 years. Table 1 outlines the demographic characteristics of the patients. All enrolled patients completed the protocol. After the treatment course, 75±6 day, serum vitamin D level increased significantly from baseline (13±5.2 versus 45±8 ng/ml, p<0.001). Also, the daily frequency of angina decreased significantly (0.85±0.29 versus 0.61±0.36, p=0.003); other clinical and paraclinical

Table 1. Baseline characteristics.

Age (mean±SD)	51.4 ± 6.5
Gender	
Female	16 (84%)
Male	3 (16%)
CAD Risk factors	
Diabetes	4 (21%)
Hypertension	7 (37%)
Hyperlipidemia	2 (11%)
BMI ≥30	2 (11%)

BMI: body mass index.

Table 2. Comparison of clinical and paraclinical parameters before and after vitamin D administration.

	Before (mean ±SD)	After (mean ±SD)	Change	p-value
Chest pain episode (f/day)	0.85±0.29	0.61±0.36	−0.24±0.14	0.003
Heart rate (bpm)	75±12	73±15	−2±0.1	0.314
BMI (kg/m^2)	25.3±4	25.2±3	−0.1±0.8	0.433
Systolic BP (mmHg)	130±10	126±8	−4±0.6	0.111
Diastolic BP (mmHg)	78±10	76±8	−2±0.5	0.140
LDL-C (mg/dl)	134±23	131±18	−3±0.23	0.260
HDL-C (mg/dl)	43±5	43.2±7	+0.2±0.03	0.345
Triglyceride (mg/dl)	183±24	179±21	−4±1.66	0.100
Total cholesterol (mg/dl)	223±26	218±31	−5±3.2	0.100
Fasting blood glucose (mg/dl)	92±35	89±28	−3±1.8	0.230
Serum vitamin D (ng/ml)	13±5.2	45 ± 8	+32±6.8	<0.001

f: frequency; BPM: beats per minute; BMI: body mass index; BP: blood pressure; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

Table 3. Comparison of exercise parameters before and after vitamin D administration.

	Before (mean±SD)	After (mean±SD)	p-value
Total exercise time (min)	6.9 ± 2.1	9 ± 1.9	<0.001
Maximal work capacity (MET)	9.3 ± 2.6	11.9 ± 2.5	0.001
Maximal ST-segment depression (mm)	1.57 ± 0.59	0.97 ± 0.43	0.001
Duck Treadmill score	−4 ± 4.4	0.6 ± 4.5	0.001

parameters did not change (Table 2). Exercise test findings are also presented in Table 3. Exercise duration was prolonged significantly (6.9± 2.1 versus 9±1.9 min, p<0.001) and maximal ST-segment depression (mm) decreased (1.57±0.57 versus 0.97±0.43 mm, p=0.001).

Maximum work capacity was significantly increased (9.3±2.6 versus 11.9±2.5 MET, p=0.001) and calculated Duck treadmill score improved significantly after treatment (-4 ±4.4 versus 0.6±4.5, p=0.001).

Discussion

To our knowledge, this study is the first to investigate the impact of vitamin D replacement therapy on patients with cardiac syndrome X. The present study shows that short-term therapy with vitamin D improves exercise capacity, the threshold of ischemia and the daily life symptoms of patients with CSX. Clear evidence supports the role of endothelial dysfunction in patients with CSX and various treatments have addressed this issue.[2–4] Impaired endothelial function is a common pathway of different causes leading to chest pain in patients with normal coronary angiograms. On the other hand, growing evidence indicates the benefits of vitamin D may be related to its favorable effects on endothelial function. Tarcin and colleagues demonstrated that 25(OH)D deficiency is associated with endothelial dysfunction and increased lipid peroxidation and replacement of vitamin D have favorable effects on endothelial function.[7] Investigations have suggested the inactivation of nitric oxide due to increased superoxide anion causes oxidative stress which may induce leukocyte activation and the release of vasoconstrictor mediators. These factors may adversely affect the coronary flow and result in chest pain or ischemia during non-invasive testing in these patients.[8,9] Also, studies have revealed selective vitamin D receptor (VDR) activation influences the renin–angiotensin system (RAS). In this regard, several studies have demonstrated angiontensin-converting enzyme (ACE) inhibitors may have a benefit on the coronary vascular bed. Pizzi et al. have shown six months of therapy with atorvastatin and ramipril improves endothelial function and the quality of life of patients with CSX.[10] There is evidence to indicate that renin–angiotensin system inhibition is associated with reduced free radical concentration and ACE inhibitors improve coronary flow reserve by bradykinin-mediated and nitric oxide-dependent mechanisms.[11–14] Kaski et al. have also found plasma endothelin is raised in patients with angina and normal coronary arteriograms.[15] On the other hand, some studies have shown that some beneficial effects of vitamin D on the cardiovascular system is mediated via suppression of endothelin-1.[16,17] Consequently, impaired endothelial function is postulated to provide a pathophysiological mechanism which causes ischemia in patients with cardiac syn-

drome X and vitamin D may improve endothelial function by modulation of the renin-angiotensin system and suppression of endothelin.

Study limitations

One important limitation of the current study was the relatively small number of participants who were included; therefore, further studies with larger sample sizes are warranted to confirm our findings. A double-blinded study of a before-and-after design and without a control group would have been preferable to use, but we did not have ethical approval. Also, we selected a group of patients with CSX with low serum vitamin D. We did not measure markers of endothelial function. The self-response questionnaire format used during this study may be identified as another limiting factor.

Conclusions

Our findings suggest that vitamin D replacement therapy could provide a novel way of reducing angina symptoms and exercise capacity in patients with CSX. Given the small and limited nature of this study, further research is needed to test the reproducibility of these findings and define the optimum dose and the physiological effects of this new treatment on endothelial function.

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Declaration of conflicting interest

The authors declare that they have no conflicts of interest.

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References

1. Lanza GA, Crea F. Primary coronary microvascular dysfunction: clinical presentation, pathophysiology, and management. *Circulation* 2010; 121: 2317–2325.
2. Piatti P, Fragasso G, Monti LD, et al. Endothelial and metabolic characteristics of patients with angina and angiographically normal coronary arteries: comparison with subjects with insulin resistance syndrome and normal controls. *J Am Coll Cardiol* 1999; 34: 1452–1460.
3. Quyyumi AA, Cannon RO 3rd, Panza JA, Diodati JG, Epstein SE. Endothelial dysfunction in patients with chest pain and normal coronary arteries. *Circulation* 1992; 86: 1864–1871.
4. Motz W, Vogt M, Rabenau O, Scheler S, Luckhoff A, Strauer BE. Evidence of endothelial dysfunction in coronary resistance vessels in patients with angina pectoris and normal coronary angiograms. *Am J Cardiol* 1991; 68: 996–1003.
5. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008; 117: 503–511.
6. Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels. *Diabet Med* 2008; 25: 320–325.
7. Tarcin O, Yavuz DG, Ozben B, et al. Effect of vitamin D deficiency and replacement on endothelial function in asymptomatic subjects. *J Clin Endocrinol Metab* 2009; 94: 4023–4030.
8. Vane JR, Anggard EE, Botting RM. Regulatory functions of the vascular endothelium. *N Engl J Med* 1990; 323: 27–36.
9. Gewaltig MT, Kojda G. Vasoprotection by nitric oxide: mechanisms and therapeutic potential. *Cardiovasc Res* 2002; 55: 250–260.
10. Pizzi C, Manfrini O, Fontana F, Bugiardini R. Angiotensin-converting enzyme inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A reductase in cardiac Syndrome X: role of superoxide dismutase activity. *Circulation* 2004; 109: 53–58.
11. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest* 2002; 110: 229–238.
12. Griendling KK, Minieri CA, Ollerenshaw JD, Alexander RW. Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. *Circ Res* 1994; 74: 1141–1148.
13. Nikolaidis LA, Doverspike A, Huerbin R, Hentosz T, Shannon RP. Angiotensin-converting enzyme inhibitors improve coronary flow reserve in dilated cardiomyopathy by a bradykinin-mediated, nitric oxide-dependent mechanism. *Circulation* 2002; 105: 2785–2790.
14. Chen JW, Hsu NW, Wu TC, Lin SJ, Chang MS. Long-term angiotensin-converting enzyme inhibition reduces plasma asymmetric dimethylarginine and improves endothelial nitric oxide bioavailability and coronary microvascular function in patients with syndrome X. *Am J Cardiol* 2002; 90: 974–982.
15. Kaski JC, Elliott PM, Salomone O, et al. Concentration of circulating plasma endothelin in patients with angina and normal coronary angiograms. *Br Heart J* 1995; 74: 620–624.
16. Wu-Wong JR, Nakane M, Ma J, Ruan X, Kroeger PE. Effects of Vitamin D analogs on gene expression profiling in human coronary artery smooth muscle cells. *Atherosclerosis* 2006; 186: 20–28.
17. Chen S, Law CS, Gardner DG. Vitamin D-dependent suppression of endothelin-induced vascular smooth muscle cell proliferation through inhibition of CDK2 activity. *J Steroid Biochem Mol Biol* 2010; 118: 135–141.