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ASSOCIATION OF SERUM VITAMIN D AND CALCIUM IN PATIENTS WITH CARDIAC ARRHYTHMIA

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ABSTRACT

Present study was designed for investigating the serum levels of vitamin-D and calcium and their association in male subjects with/ without palpitations (P), premature atrial contractions (PACs) and premature ventricular contractions (PVCs) and to understand the pathophysiological significance of serum variations in patients with cardiac arrhythmia. Male subjects with palpitations (n: 30), premature atrial contractions (n: 30), and premature ventricular contractions (n: 31) were studied using ECG, Holter monitors recordings, echocardiography, vitamin D (ng/mL) and calcium (mg/dL) levels. The data was collected from out-patients Department of Cardiology, International Medical Center (IMC), Jeddah, Kingdom of Saudi Arabia (KSA). Vitamin-D status was determined by measuring the serum 25-hydroxyvitamin-D-(25 [OH] D levels, and serum calcium was determined by standard kit method. Serum levels of vitamin D and calcium in healthy male controls (C; n: 32) were assessed for comparison purposes. Comparison of serum vitamin D for all mentioned four groups showed significant variation among groups (Fs: 2.928; P = 0.037). However, individual comparisons indicated significant variations for PACs vs C (P = 0.0088) and PVCs vs C (P = 0.0388), though P vs PACs was close to significance (P = 0.0598). The other comparisons for P vs C, P vs PVCs and PVCs vs PACs showed non-significant variations. Comparison of serum calcium for all mentioned four groups showed highly significant variation among groups (F: 8.424; p = 0.00004). Whereas, the individual comparisons showed significant variations for the comparisons P vs C (P = 0.0014), PACs vs C (P < 0.0001), and PVCs vs C (P = 0002). The P vs PACs (P = 0.0748) was found not significant. The remaining two comparisons P vs PVCs and PVCs vs PACs gave non-significant variations. Association of vitamin D and calcium levels in normal healthy male subjects, and in patients with PACs and PVCs were found highly significant. The present studies suggest that serum vitamin D and calcium levels and their correlation in patients with cardiac arrhythmia have significant pathophysiological importance.

Keywords: Cardiac arrhythmia, serum vitamin D, serum calcium, palpitations, premature atrial contractions, premature ventricular contractions.

INTRODUCTION

It is known that arrhythmias occur due to electrical conduction problems in the heart. However, details of the factors causing various types of arrhythmias and the underlying pathophysiology are quite complicated and controversial. Role of vitamin D and calcium and their association might be quite interesting in understanding the occurrence of arrhythmias. Vitamin D is recognized as a significant factor for cardiovascular health and vitamin D deficiency as a potential risk factor for a variety of cardiovascular disease processes. However, there is a need to establish well controlled and organized studies to confirm the significance of vitamin D in cardiovascular disease processes (Reddy Vanga *et al.*, 2010). It was found that serum 25-hydroxyvitamin D3 (25-OHD) ≤ 20 ng/mL in patients with primary fibromyalgia syndrome (PFMS) showed 67.9 % palpitations compared to those having >20 ng/mL and showing 36.4% palpitations (Olama *et al.*, 2013).

Decreased 25(OH)D serum levels were found associated significantly with left atrial (LA) fibrosis in patients with paroxysmal atrial fibrillation (AF) and were considered as involved in the recurrence of AF post-cryoablation (Canpolat *et al.*, 2017). It was found that decreased levels of plasma vitamin D had strong association with AF in chronic HF (heart failure) patients (Belen *et al.*, 2016). Low vitamin D was found associated with AF (atrial fibrillation), and it was suggested for its possible involvement in the process of the AF development (Chen *et al.*, 2014).

Deficiency of vitamin D was noted associated with new onset atrial fibrillation (AF) post-CABG (coronary artery bypass grafting) surgery (Emren *at al.*, 2016). The patients with Vit. D deficiency showed increase in left intra- and inter-AEMD (atrial electromechanical delay) and P-wave dispersion (PWd) (Canpolat *et al.*, 2015).

The serum levels of 25(OH) D were found as an independent predictor for AEMD (atrial electromechanical delay) in patients with Vit. D deficiency; and a significant decrease were observed in inter-AEMD after vit. D replacement therapy (Canpolat *et al.*, 2015). Studies with longer follow-up are needed to investigate whether vit. D-

deficient patients with prolonged AEMD (atrial electromechanical delay) develop clinical arrhythmia and vit. D replacement decreases the risk of atrial arrhythmias (Canpolat *et al.,* 2015).

Low level of serum 25(OH)D was not found associated with atrial fibrillation (AF) and it was suggested for further studies for the clarification of the association between circulating 25-hydroxyvitamin D [25(OH)D] and the risk of atrial fibrillation (AF) (Alonso *et al*., 2016). A study for investigating the association of vitamin D and risk of atrial fibrillation did not support any association of vitamin D with atrial fibrillation (Vitezova *et al.,* 2015).

Vitamin D levels were found similar to much extent in both of the groups (with & without atrial fibrillation following CABG (coronary artery bypass grafting) surgery) and no statistically significant difference between the groups found, though there was a non-significant decrease in plasma levels of vitamin D in a group with atrial fibrillation (Shadvar *et al.,* 2016).

A variety of the reports document the decreased levels of vitamin D associated with the occurrence of arrhythmias (Reddy Vanga *et al.,* 2010; Chen *et al.,* 2014; Canpolat *et al.,* 2015; Belen *et al.,* 2016; Emren *at al.,* 2016; Canpolat et al., 2017), and other reports show/ suggest either no possible change (Vitezova *et al.,* 2015; Alonso *et al.,* 2016) or no significant change in vitamin D serum levels (Shadvar et al., 2016) or debatable/controversial (Carvalho and Sposito, 2015). Hence, further large-scale studies are essentially required to elucidate the exact role/ significance of vitamin D deficiency.

It has been suggested that though vitamin D supplementation is recommended for the prevention of osteoporosis, and enough in vivo and in vitro information is available explaining the significance of vitamin D in cardiovascular health and disease, no clear evidence is available for considering or ruling out the significance of vitamin D and understanding the association of vitamin D with cardiovascular events (Carvalho and Sposito, 2015).

If long-standing hyperparathyroidism (with clinic and biochemical features of hypocalcemia) left untreated, life-threatening disorders like cardiac arrhythmias may occur (Cecchi *et al.,* 2015). Hypocalcemia may lead to life-threatening ventricular arrhythmias (Cecchi *et al.,* 2015). Another report showed that arrhythmia occurred in 11 neonates with hypocalcemia (Wang and Chen, 2009).

Chronic hypocalcaemia in a case manifesting prolonged QT-interval was found to be associated with AA (atrial arrhythmia) (Nijjer *et al.,* 2010). Low serum level of calcium in low yielding Holstein cows lead to more frequent dysrhythmias (including sinus arrhythmia, wandering pacemaker, bradycardia, tachycardia, atrial premature beat, sinoatrial block, atrial fibrillation, and atrial tachycardia) (Jafari Dehkordi *et al*., 2014).

In view of controversial reports, it has been attempted in the present investigation to study the involvement of the serum levels of vitamin D and calcium and their association in subjects with/ without palpitations, premature atrial contractions (PACs) and premature ventricular contractions (PVCs).

MATERIALS AND METHODS

The present study was designed to evaluate serum vitamin D and calcium in male subjects with arrhythmia. Healthy male participants (C, n: 32) were included as control subjects. Detailed information about the subjects, discomforts/ medications, familial history, smoking, diet, vitamin use/ allergies etc, and clinical, behavioral, biochemical, and physiological profile was recorded in the Questionnaire.

Subjects with palpitations (P, n: 30), premature atrial contractions (PACs, n: 30), and premature ventricular contractions (PVCs, n: 31) were studied in the present investigation. The ECG, Holter monitor recordings, echocardiography and vitamin D/ calcium level were recorded on a data sheet. Vitamin-D status was determined by measuring the serum 25-hydroxyvitamin-D-(25[OH] D) level, and serum calcium was determined by standard kit method.

The data was collected from out-patients Department of Cardiology, International Medical Center (IMC), Jeddah, Kingdom of Saudi Arabia (KSA). Data sheets were filled up by the research students with a supervision of a cardiologist. All questions relating to descriptive measures (e.g. age, weight, height etc) were recorded. Blood samples were analyzed in the Department of Clinical Biochemistry IMC, according to the Department's standards. The data was analyzed statistically employing unpaired 't' test for analyzing two-tailed P value; one-way analysis of variance (ANOVA) for analyzing the values of Fs and p; Tukey-Kramer post-hoc test for each pair of means and polynomial/ linear regression. Ethical approval was obtained from Umm Al-Qura University Faculty of Medicine, International Medical Center (IMC) as well as from the Ethical Committee at King Abdul-Aziz University, KSA.

RESULTS

Serum vitamin D (ng/mL) and calcium (mg/dL) levels were analyzed for male controls and male subjects having arrhythmia. Comparison was done among and compared among healthy controls (C, n: 32), subjects with

palpitations (P, n:30), subjects with premature atrial contractions (PACs, n: 30), and subjects with premature ventricular contractions (PVCs, n: 31).

Serum levels of Vitamin D (mean ± SE) in C, P, PACs and PVCs were found respectively as 31.44 ± 1.71, 29.61 ± 1.79, 24.74±1.79 and 25.68 ± 2.14 (Fig.1). Whereas, serum calcium levels (mean ± SE) in C, P, PACs and PVCs were as 9.29 ± 0.20, 8.37 ± 0.18, 7.80 ± 0.26 and 7.83 ± 0.30, respectively (Fig.2).

Comparison of serum Vitamin D (ng/ml) for all mentioned four groups showed significant variation among groups (Fs: 2.928; P = 0.037). Individual comparisons (Fig.1) indicated significant variations for PACs vs C (t = 2.7074 (df = 60), P = 0.0088) and PVCs vs C (t = 2.1114 (df = 61), P=0.0388), though P vs PACs was close to significance (t = 1.9197 (df = 58), P = 0.0598). The other comparisons showed non-significant variations for P vs C (t = 0.7391 (df = 60), P = 0.4627), P vs PVCs (t = 1.4030 (df = 59), P = 0.1659) and PVCs vs PACs (t = 0.3357 (df = 59), P = 0.7383).

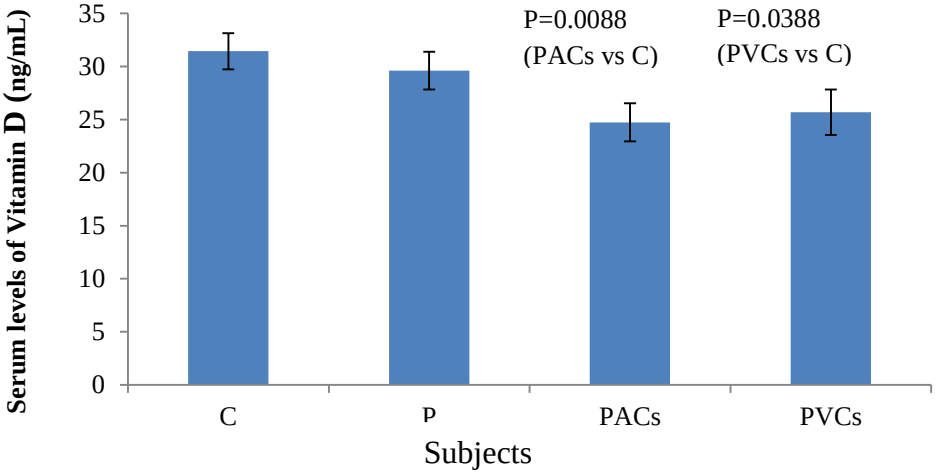

Fig.1. Serum vitamin D in normal healthy subjects and patients with cardiac arrhythmia.

P vs C: subjects with palpitations vs healthy controls (P=0.4627), P vs PACs: subjects with palpitations vs subjects with premature atrial contractions (P = 0.0598), P vs PVCs: subjects with palpitations vs subjects with premature ventricular contractions (P=0.1659), PACs vs C: subjects with premature atrial contractions vs healthy controls (P = 0.0088), PVCs vs C: subjects with premature ventricular contractions vs healthy controls (P = 0.0388), PVCs vs PACs: subjects with premature ventricular contractions vs subjects with premature atrial contractions (P=0.7383), values are in mean± SE.

Comparison of serum calcium (mg/dL) for all mentioned four groups showed highly significant variation among groups (Fs: 8.424; P = 0.00004). Whereas, the individual comparisons (Fig.2) showed significant variations for the comparisons P vs C (t = 3.3517 (df = 60), P = 0.0014), PACs vs C (t = 4.5914 (df = 60), P < 0.0001) , and PVCs vs C (t = 4.0202 (df = 61), P = 0.0002). P vs PACs (t = 1.8146 (df = 58), P = 0.0748) was found not quite significant. The remaining two comparisons P vs PVCs (t = 1.5123 (df = 59), P = 0.1358) and PVCs vs PACs (t = 0.0754 (df = 59), P = 0.9402) gave non-significant variations.

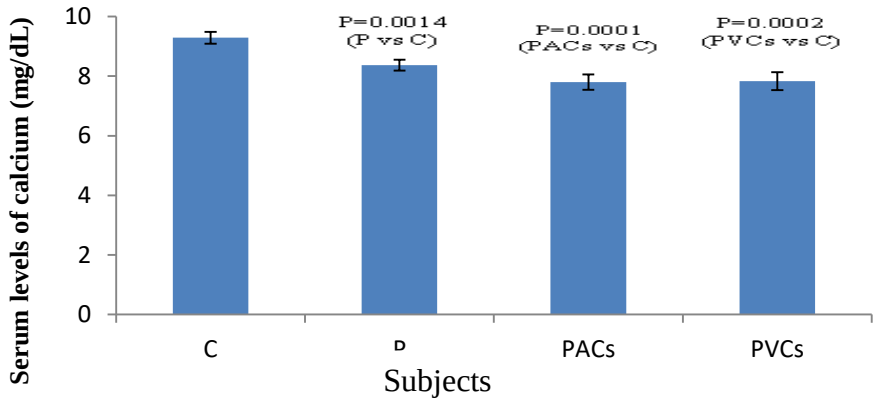

Fig. 2. Serum calcium in normal healthy subjects and patients with cardiac arrhythmia.

P vs C: subjects with palpitations vs healthy controls (P = 0.0014), P vs PACs: subjects with palpitations vs subjects with premature atrial contractions (P = 0.0748), P vs PVCs: subjects with palpitations vs subjects with premature ventricular contractions (P = 0.1358), PACs vs C: subjects with premature atrial contractions vs healthy controls (P < 0.0001), PVCs vs C: subjects with premature ventricular contractions vs healthy controls (P = 0.0002), PVCs vs PACs: subjects with premature ventricular contractions vs subjects with premature atrial contractions (P = 0.9402), values are in mean ± SE.

Relationship of serum vitamin D with calcium levels was analyzed employing polynomial regression in normal healthy male subjects (C, n: 32, Fig. 3), subjects with palpitations (P, n:30, Fig. 4), premature atrial contractions (PACs, n: 30, Fig. 5), and premature ventricular contractions (PVCs, n: 31, Fig. 6).

Relationship of vitamin D and calcium levels in normal healthy male subjects (Fig.3) showed highly significant correlation (r^2:0.7015; P-value of quadratic P< 0.0001).

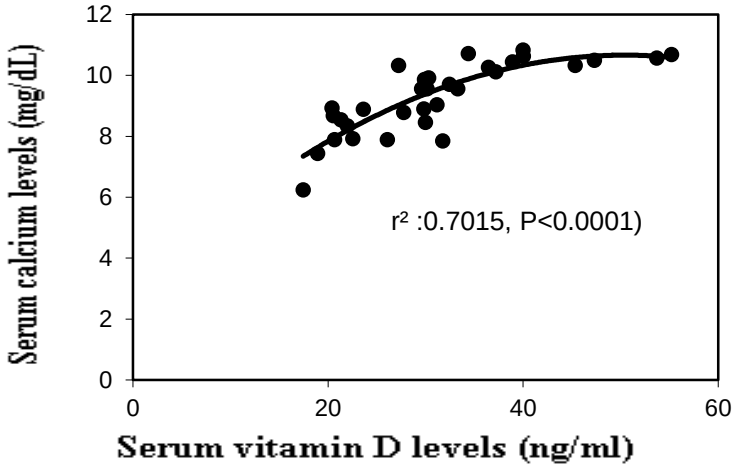

Fig. 3. Relationship of Vitamin D and calcium levels in normal healthy male subjects
(Quadratic (polynomial regression) equation: $y = -0.0031x^2 + 0.3082x + 2.8962$, $r^2 = 0.7015$,
degrees of freedom: 29)

Relationship of vitamin D and calcium levels in male patients with palpitations (Fig.4) showed non-significant correlation (r^2: 0.1218; P-value of quadratic: 0.1732).

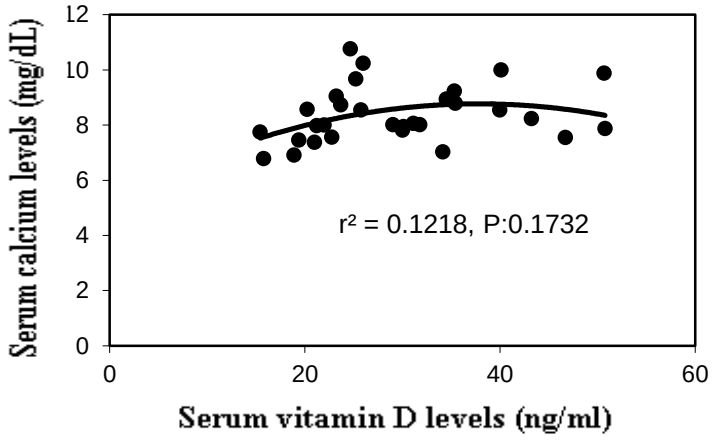

Fig. 4. Relationship of Vitamin D and calcium levels in male patients with palpitations.

Relationship of vitamin D and calcium levels in male patients with PACs (Fig.5) showed highly significant correlation (r^2: 0.7081; P-value < 0.0001).

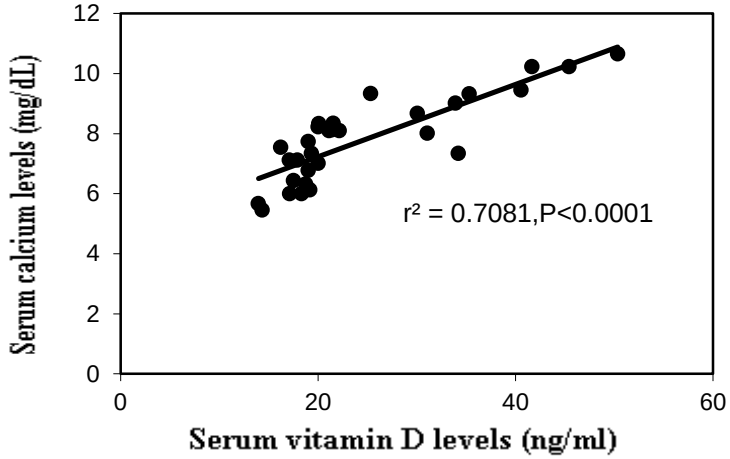

Fig. 5. Relationship of Vitamin D and calcium levels in male patients with PACs.
(Linear regression equation: y = 0.1203x + 4.8277, r^2 = 0.7081, degrees of freedom: 28)

Relationship of vitamin D and calcium levels in male patients with PVCs (Fig.6) showed highly significant correlation (r^2: 0.8257; P<0.0001).

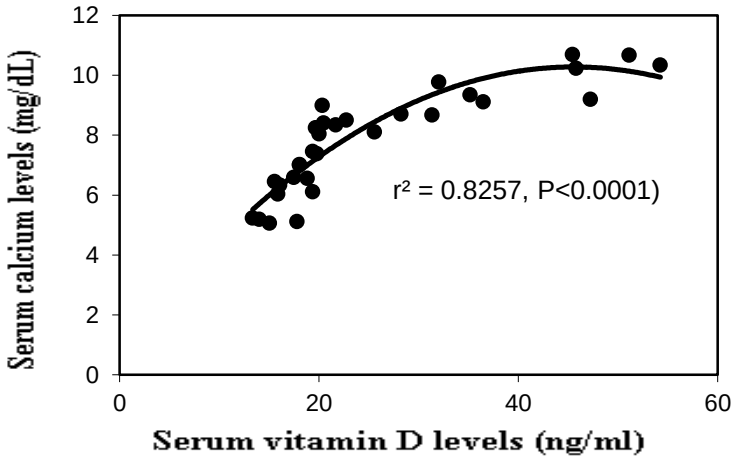

Fig. 6. Relationship of Vitamin D and calcium levels in male patients with PVCs.
(Quadratic (polynomial regression) equation: $y = -0.0046x^2 + 0.4179x + 0.7552$, r^2: 0.8257, degrees of freedom: 28)

DISCUSSION

Results showing low serum levels of vitamin D in subjects with arrhythmia (PACs and PVCs) as well as those with palpitations as compared to control subjects are quite similar to a report (Shadvar *et al.,* 2016) where decrease in plasma levels of vitamin D was found in arrhythmia as compared to that in controls.

The present study investigating significant variations in serum calcium for all studied groups having arrhythmia is similar to most of the studies performed by other workers (Wang and Chen, 2009; Nijjer *et al.,* 2010; Jafari-Dehkordi *et al*., 2014; Cecchi *et al.,* 2015; John and Suthar, 2016). Hence, reduced levels of serum calcium and hypocalcemic levels may lead to arrhythmias.

The present findings of the highly significant correlation between vitamin D and calcium levels in normal healthy male subjects are quite interesting physiologically. Whereas, highly significant correlation between vitamin D and calcium levels in male patients with PACs and PVCs but not with palpitations seems clinically quite valuable for understanding the interactive role of both factors in the development of arrhythmias and other related cardiovascular processes/ events in disordered conditions. Association between serum vitamin D and calcium in

subjects with arrhythmias and other cardiovascular disease phenotypes for finding the pathophysiological interpretation of such association have rarely been studied. However, an interesting study (Thiele *et al.,* 2015) points out the occurrence of arrhythmia in calcium/ vitamin D supplement users though the clear underlying mechanisms are unknown. The mentioned study (Thiele *et al.,* 2015) seems helpful in interpreting our present investigations showing highly significant correlation between vitamin D and calcium levels in male patients with PACs and PVCs.

CONCLUSION

The present study suggests that serum vitamin D and calcium levels and their correlation in patients with cardiac arrhythmia have significant pathophysiological importance.

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