European Journal of Preventive Cardiology

Original scientific paper

European Journal of Preventive Cardiology
2015, Vol. 22(4) 535–542

DOI: 10.1177/2047487313518473
ejpc.sagepub.com

Severely vitamin D-deficient athletes present smaller hearts than sufficient athletes

Richard J Allison[1,2], Graeme L Close[2], Abdulaziz Farooq[3], Nathan R Riding[2,3], Othman Salah[4], Bruce Hamilton[5] and Mathew G Wilson[4]

Abstract

Background: Vitamin D (25(OH)D) deficiency has associations with bowl/colon cancer, arthritis, diabetes, and cardiovascular disease. Many athletes are vitamin D deficient, yet no studies have examined the association between 25(OH)D status and cardiac structure and function in healthy athletes.

Design: A total of 506 national-level athletes [football (50%), handball (23%), volleyball (16%), and basketball (11%)] and 244 control participants presented for precompetition medical assessment. Controls were healthy individuals registered with a sporting federation undertaking <2 h of exercise per week.

Methods: All individuals undertook a physical examination, 12-lead electrocardiogram, echocardiogram, and serum 25(OH)D evaluation.

Results: From 506 athletes and 244 controls, 23 and 12.3% demonstrated 25(OH)D sufficiency (>30 ng/ml), 30 and 23.4% insufficiency (20–30 ng/ml), 37.2 and 48.8% deficiency (10–20 ng/ml), and 11 and 15.6% severe deficiency (<10 ng/ml). Severely 25(OH)D-deficient athletes present significantly ($p < 0.05$) smaller aortic root and left atria diameters, intraventricular septum diameter (IVSd), left ventricular diameter during diastole (LVIDd), left ventricular mass (LVM), left ventricular volume during diastole (LVvolD), and right atrial (RA) area than insufficient and sufficient athletes. Furthermore, following logarithmic transformation adjusting 25(OH)D for age, body surface area, ethnicity, and athletic participation, positive associations were observed between 25(OH)D and IVSd, LVIDd, posterior wall thickness during diastole, LVM, and LVvolD in athletes but not in the control participants.

Conclusions: Severely 25(OH)D-deficient athletes present significantly smaller cardiac structural parameters than insufficient and sufficient athletes. Future research should investigate the precise mechanism(s) causing cardiac hypertrophy with increases in serum 25(OH)D in healthy athletes.

Keywords

Athlete's heart, cardiac structure and function, vitamin D deficiency

Received 23 July 2013; accepted 8 December 2013

Introduction

Vitamin D (25(OH)D) is a secosteroid hormone that is either generated de novo by the basal layers of the epidermis via ultraviolet-B radiation or is consumed within the diet. The bioactive metabolite, 1,25-dihydroxyvitamin D exerts its biological activity by binding to and activating the vitamin D receptor, to regulate numerous downstream signalling pathways in various cells and tissues.[1] The effects of this hormone extend well beyond the mineralization of bone and calcium regulation, with important roles in the maintenance of skeletal, renal, metabolic, immune, and

[1]National Sports Medicine Program, ASPETAR, Qatar Orthopaedic and Sports Medicine Hospital, Qatar
[2]Research Institute for Sport and Exercise Science, Liverpool John Moores University, Liverpool, Merseyside, UK
[3]Athlete Health and Performance Research Centre, ASPETAR, Qatar Orthopaedic and Sports Medicine Hospital Qatar
[4]Department of Sports Medicine, ASPETAR, Qatar Orthopaedic and Sports Medicine Hospital, Qatar
[5]High Performance Sport New Zealand, Auckland, New Zealand

Corresponding author:
Richard Allison, ASPETAR – Qatar Orthopaedic and Sports Medicine Hospital, PO Box 29222, Doha, Qatar.
Email: richard.allison@aspetar.com

cardiovascular function. Indeed, it is well known that 25(OH)D deficiency may have significant adverse long-term health impacts, including recognized associations with bowl and colonic cancer, arthritis, diabetes, and cardiovascular disease.[2–5]

Ever since Weishaar et al.[6] observed an association between 25(OH)D and cardiovascular function using 25(OH)D-deficient rats 25 years ago, several research groups have established associations between 25(OH)D and cardiac structure and function (in both human and animal models). Yet the majority of these studies have only examined pathological conditions such as chronic kidney disease,[7] thalassaemia major,[8] hypertension,[9] peripheral arterial disease,[10] and congestive heart failure (CHF).[11]

It is known that the vitamin D receptor and the associated apparatus for 1,25-dihydroxyvitamin D production are present throughout the heart and vascular system, with the vitamin D receptor specifically located in cardiac myocytes and fibroblasts.[12] Further, 25(OH)D deficiency is known to adversely affect cardiac contractility, vascular tone, cardiac collagen content, and cardiac tissue maturation.[13] Histological analysis of 25(OH)D-deficient rats demonstrate significantly smaller ventricular myofibrils and increases in extracellular matrix proteins compared to 25(OH)D-sufficient rats.[14]

Regular participation in intensive physical exercise is associated with several structural and electrophysiological cardiac adaptations that enhance diastolic filling and facilitate a sustained increase in cardiac output that is fundamental to athletic excellence. Such cardiac adaptations are collectively referred as the 'athlete's heart' and are frequently reflected on the 12-lead electrocardiogram (ECG) and imaging studies.[15] Numerous factors affect the adaptations of the athletes heart, including sporting modality, duration and intensity, age, ethnicity, sex, anthropometry, and performance-enhancing substance abuse. However, it is also well recognized that many professional athletes are vitamin D deficient[16] and no studies have examined the association between 25(OH)D status and cardiac structure and function in healthy athletes.

Accordingly, the present study aimed to examine the relationship between 25(OH)D status and cardiac structure and function within a large cohort of healthy athletes compared to a control population presenting for precompetition medical assessment at our institution.

Methods

Following ethical approval from Shafallah Medical Genetics Centre, all athletes and control participants completed informed consent in either Arabic or English.

Participants

Between November 2010 and June 2012, 521 male national level athletes exercising $\geq$6 h/week presented at our institution for precompetition medical assessment [football ($n=269$, 51%), handball ($n=115$, 22%), volleyball ($n=82$, 16%), and basketball ($n=55$, 11%)]. A further 244 individuals registered with a Qatari sporting federation (such as sailing, archery, shooting, bowling) but exercising $\leq$2 h/week were used as a control population. Arabs ($n=427$) came from seven Gulf states and Five Middle-Eastern countries; Black Africans ($n=207$) came from nine African countries; Caucasians ($n=116$) came from six European/North American countries.

Preparticipation cardiovascular screening

All individuals were screened using a precompetition medical assessment form, examining family history of cardiovascular disease and personal symptoms, with a physical examination undertaken by a sports medicine physician. A standard 12-lead ECG was obtained using a GE Mac 5500 (New York, USA) after a 5-min rest in the supine position.

Echocardiographic examination was performed using a commercially available ultrasound system (Philips, USA) by an experienced sports cardiologist. Images of the heart were obtained in the standard planes, using previously published criteria.[17]

Athlete exclusion and further evaluation

Fifteen athletes demonstrated ECG and/or echocardiographic abnormalities suspicious of a disease associated with sudden cardiac death and were excluded from further analysis.

Vitamin D status assessment

The remaining 506 athletes and 244 control participants undertook serum 25(OH)D evaluation via chemiluminescent immunoassay technology (LiaisonR 25-OH Vitamin D Total Assay; Diasorin, Saluggia, Italy). Sensitivity for 25(OH)D was 7 ng/ml, below which levels were recorded as <7 ng/ml. The intra and inter-assay CV was 7.6–9.4 and 9.8–13.4%, respectively. In addition, all individuals completed a vitamin D questionnaire that addressed specific areas relevant to vitamin D status. This included ethnicity, exposure time to daily sunlight, type of skin exposure, and use of sunscreen. Based upon the serum 25(OH)D results, athletes and control participants were subsequently split into four 25(OH)D categories based upon their status; severely deficient (<10 ng/ml), deficient (10–20 ng/ml), insufficient (20–30 ng/ml), and sufficient (>30 ng/ml).

Statistical analysis

Data were coded and analysed using SPSS version 21.0. Two way analysis of variance (ANOVA) was used to compare physical and lifestyle habits and cardiac structure and function parameters between the four serum 25(OH)D concentration groups within and between the subject groups (athletes vs. controls). Post-hoc Bonferroni adjustments were performed where appropriate. Mean, standard deviation, and ranges were reported for the continuous variables. The Chi-squared test was used to test the association between lifestyle habits and serum 25(OH)D groups. Multiple linear regression was used to determine the association of ECG and echocardiographic parameters against serum 25(OH)D. Natural log transformations were applied to serum 25(OH)D concentrations to remove positive skewness, adjusting for age, ethnicity, body surface area, and athletic participation (athlete vs. controls). A p-value <0.05 was considered statistically significant.

Results

Of the 506 athletes, 23% demonstrated 25(OH)D sufficiency, 30% insufficiency, 37.2% deficiency, and 11% severe deficiency. Of the controls, 12.3% demonstrated 25(OH)D sufficiency, 23.4% insufficiency, 48.8% deficiency, and 15.6% severe deficiency (Table 1). Athletes were significantly ($p < 0.05$) taller, heavier, and had a larger body surface area than all controls in their respective 25(OH)D groups. Athletes severely deficient in 25(OH)D were significantly ($p < 0.05$) shorter and lighter compared to insufficient and sufficient athletes. The incidence of severe 25(OH)D deficiency or deficiency in Caucasian athletes was significantly lower compared to Arabic and Black African athletes, while significantly

Table 1. Physical characteristics of individuals severely deficient, deficient, insufficient, and sufficient in vitamin D

	Vitamin D (ng/ml)				
Variable	<10	10–20	20–30	>30	p-value
Number and percentage					
Athletes	55 (11)	186 (37.2)	150 (30)	115 (23)	–
Controls	38 (15.6)	119 (48.8)	57 (23.4)	30 (12.3)	–
Age (years)					
Athletes	21.7 ± 4.8	22.3 ± 5.2	24.0 ± 5.5*,a,b	23.3 ± 5.3	0.008
Controls	21.7 ± 6.5	23.7 ± 7.3	26.5 ± 10.1[a]	27.0 ± 9.0	0.013
Height (cm)					
Athletes	177.0 ± 13.7*	181.7 ± 11.8*	184.8 ± 11.6*,a	184.4 ± 11.1*,a	<0.001
Controls	172.1 ± 6.5	173.0 ± 6.6	172.7 ± 9.1	172.0 ± 6.4	0.880
Body mass (kg)					
Athletes	75.3 ± 20.8*	80.7 ± 17.2*	84.2 ± 14.5*,a	81.9 ± 13.5*,a	0.005
Controls	68.2 ± 15.6	71.6 ± 14.7	73.3 ± 16.0	68.9 ± 11.7	0.312
Body surface area (m^2)					
Athletes	1.9 ± 0.3*	2.0 ± 0.3*	2.1 ± 0.2*,a	2.0 ± 0.2*	<0.001
Controls	1.8 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	0.403
Resting systolic BP (mmHg)					
Athletes	122.7 ± 10.6	125.7 ± 9.9*	125.2 ± 11.7*	126.8 ± 8.8	0.255
Controls	118.0 ± 9.6	122.4 ± 13.0	120.0 ± 11.1	122.3 ± 9.1	0.403
Ethnicity (%)					
Athletes					
Arabic	13.4	44.6	28.1	13.8	<0.001
Black African	12.3	36.9	29.6	21.2	
Caucasian	2.9	19.4	33.0	44.7	
Controls					
Arabic	14.8	52.7	22.7	9.9	<0.001
Black African	28.6	39.3	28.6	3.6	
Caucasian	0	7.7	23.1	69.2	

Values are mean ± SD or %.; *Significant difference between athletes vs. controls in their respective 25(OH)D groups.; [a]Significant difference compared to the <10 ng/ml cohort.; [b]Significant difference compared to the 10–20 ng/ml cohort.

more Caucasian athletes were 25(OH)D sufficient compared to Arabic and Black African athletes.

Of both athletes and controls, 48% did not expose themselves to sunlight, and 17 and 18%, respectively, exposed themselves to >2 h of sunlight per week (Table 2). Of those individuals that received no UVB radiation, 16.9 and 9.4%, respectively, were sufficient in 25(OH)D, and of those that received >2 h of sunlight per week, 5.8 and 6.8%, respectively, were severely deficient in 25(OH)D. For those individuals that exposed themselves to sunlight, 86 and 69.3%, respectively, uncovered more than their hands and face. Finally, 8.2 and 5.3%, respectively, used sunscreen.

Cardiac structure

All athletes and control participants presented with cardiac morphological parameters within clinically accepted limits. Deficient, insufficient, and sufficient athletes had significantly ($p < 0.05$) greater absolute aortic root (Ao) diameter, left atrium (LA) diameter, intraventricular septum during diastole (IVSd), left ventricular diameter during diastole (LVIDd), left ventricular mass (LVM), left ventricular volume during diastole (LVvolD), and right atrial (RA) area than their respective 25(OH)D control participants (Table 3).

However, severely deficient athletes had significantly ($p < 0.05$) smaller Ao diameter, IVSd, LVIDd, LVM, LVvolD, and RA area than insufficient and sufficient athletes. Furthermore, LVvolD and LVM were significantly ($p < 0.05$) smaller in deficient athletes compared to insufficient and sufficient athletes. LVIDd and LVM were significantly ($p < 0.05$) smaller in severely deficient controls compared to insufficient and sufficient control participants, with no further cardiac structural

Table 2. Lifestyle characteristics of individuals severely deficient, deficient, insufficient, and sufficient in vitamin D

	Vitamin D (ng/ml)					
Variable	<10	10–20	20–30	>30	Total	*p*-value
Exposure time to sunlight (min)						
Athletes						
No sunlight	27 (11.2)	99 (40.9)	75 (31.0)	41 (16.9)	242	0.004
30–60 min	10 (10.5)	43 (45.3)	22 (23.2)	20 (21.1)	95	
60–120 min	13 (15.7)	21 (25.3)	23 (27.7)	26 (31.3)	83	
>120 min	5 (5.8)	23 (26.7)	30 (34.9)	28 (32.6)	86	
Controls						
No sunlight	21 (17.9)	57 (48.7)	28 (23.9)	11 (9.4)	117	0.568
30–60 min	11 (20.8)	22 (41.5)	12 (22.6)	8 (15.1)	53	
60–120 min	3 (10.0)	17 (56.7)	7 (23.3)	3 (10.0)	30	
>120 min	3 (6.8)	23 (52.3)	10 (22.7)	8 (18.2)	44	
Skin exposure to the sun						
Athletes						
None	1 (25.0)	1 (25.0)	2 (50.0)	0 (0.0)	4	0.012
Hands and feet only	14 (19.4)	34 (47.2)	13 (18.1)	11 (15.3)	72	
More than hands and feet	40 (9.3)	151 (35.1)	135 (31.4)	104 (24.2)	430	
Controls						
None	0 (0.0)	2 (40.0)	3 (60.0)	0 (0.0)	5	0.091
Hands and feet only	12 (17.1)	37 (52.9)	18 (25.7)	3 (4.3)	70	
More than hands and feet	26 (15.4)	80 (47.3)	36 (21.3)	27 (16.0)	169	
Use of sunscreen						
Athletes						
Yes	0 (0.0)	8 (19.5)	10 (24.4)	23 (56.1)	41	<0.001
No	55 (11.8)	178 (38.3)	140 (30.1)	92 (19.8)	465	
Controls						
Yes	0 (0.0)	4 (30.8)	5 (38.5)	4 (30.8)	13	0.038
No	38 (16.5)	115 (49.8)	52 (22.5)	26 (11.3)	231	

Values are *n* (%) or *n*.

Table 3. Cardiac structure of individuals severely deficient, deficient, insufficient, and sufficient in vitamin D

	Vitamin D (ng/ml)				
Variable	<10	10–20	20–30	>30	*p*-value
Ao (mm)					
Athletes	26.3 ± 3.1 (20–33)*	27.3 ± 3.0 (19–35)*	28.0 ± 2. 6 (21–34)*,[a]	27.7 ± 2.4 (22–34)*,[a]	0.001
Controls	24.9 ± 2.6 (21–30)	26.4 ± 2.5 (21–33)	26.3 ± 3.2 (21–34)	26.2 ± 2.0 (22–29)	0.145
LA (mm)					
Athletes	32.9 ± 5.1 (22–47)*	33.9 ± 3.9 (22–43)*	34.8 ± 3.6 (26–48)*,[a]	33.8 ± 3.6 (24–45)*	0.013
Controls	30.6 ± 4.0 (24–39)	32.3 ± 4.1 (21–43)	32.7 ± 4.8 (18–43)	32.0 ± 3.4 (24–39)	0.109
IVSd (mm)					
Athletes	8.6 ± 1.4 (6–11)	8.9 ± 1.2 (6–14)*	9.1 ± 1.0 (6–13)*,[a]	9.1 ± 1.1 (6–13)*,[a]	0.014
Controls	8.1 ± 1.1 (6–10)	8.5 ± 1.1 (6–12)	8.3 ± 1.1 (6–11)	8.5 ± 1.0 (6–11)	0.172
LVIDd (mm)					
Athletes	51.2 ± 5.5 (39–61)*	53.5 ± 4.7 (40–62)*	54.5 ± 5.7 (45–64)*,[a]	54.6 ± 4.2 (42–65)*,[a]	<0.001
Controls	48.6 ± 3.7 (41–57)	49.8 ± 4.0 (42–59)	51.3 ± 5.1[a] (41–60)	51.5 ± 4.4[a] (42–58)	0.006
PWTd (mm)					
Athletes	8.0 ± 1.2 (6–10)	8.3 ± 1.1 (6–13)	8.7 ± 2.9 (6–13)	8.6 ± 2.2 (6–10)	0.072
Controls	7.7 ± 0.9 (6–9)	8.4 ± 4.4 (6–14)	8.1 ± 0.8 (6–10)	8.2 ± 0.9 (6–10)	0.607
LVM (g)					
Athletes	157.7 ± 52.7 (63–285)*	173.9 ± 42.6 (65–291)*	184.8 ± 36.3 (80–271)*,[a,b]	184.0 ± 36.2 (82–266)*,[a,b]	<0.001
Controls	131.9 ± 27.8 (81–205)	147.2 ± 34.9 (75–286)	152.7 ± 38.0[a] (68–237)	157.3 ± 34.1[a] (79–218)	0.011
LVvolD (ml)					
Athletes	117.1 ± 34.1 (54–195)	131.8 ± 29.9 (55–212)*,[a]	142.7 ± 27.3 (70–245)*,[a,b]	140.3 ± 30.9 (58–271)*,[a,b]	<0.001
Controls	106.2 ± 26.8 (64–159)	108.0 ± 21.3 (53–176)	112.5 ± 25.0 (63–175)	110.2 ± 23.2 (66–161)	0.540
LA area (mm^2)					
Athletes	17.3 ± 4.5 (9–27)	17.7 ± 3.8 (8–29)	18.5 ± 3.5 (11–31)	18.1 ± 3.6 (8–33)	0.113
Controls	15.6 ± 3.3 (10–24)	15.4 ± 3.1 (9–23)	19.1 ± 22.3 (10–183)	16.4 ± 3.3 (11–25)	0.223
RA area (mm^2)					
Athletes	15.0 ± 4.6 (7–28)	16.5 ± 3.6 (8–28)*	17.3 ± 3.1 (11–29)*,[a]	16.7 ± 3.1 (7–24)*,[a]	0.001
Controls	13.6 ± 2.8 (9–19)	14.9 ± 7.0 (8–21)	14.7 ± 3.1 (9–22)	14.9 ± 3.5 (8–23)	0.643

Values are mean ± SD (range).; *Significant difference between athletes vs. controls in their respective 25(OH)D groups.; [a]Significant difference compared to the <10 ng/ml cohort.; [b]Significant difference compared to the 10–20 ng/ml cohort.; Ao, aortic root diameter; IVSd, intraventricular septum during diastole; LA area, left atrial area; LA, left atrial diameter; LVIDd, left ventricular internal diameter during diastole; LVM, left ventricular mass; LVvolD, left ventricular volume in diastole; PWTd, posterior wall thickness in diastole; RA area, right atrial area.

parameter different between the respective 25(OH)D control participants.

Logarithmic transformation

Following logarithmic transformation adjusting 25(OH)D for age, body surface area, and ethnicity (Table 4), athletes had significantly larger LA, IVSd, LVIDd, LVM, and LVvolD compared to control participants. When athletes and controls were grouped together, there were positive associations between 25(OH)D and LVIDd, PWTd, LVM, and LVvolD. However, after further adjustment for athletic participation, positive associations between 25(OH)D and IVSd, LVIDd, PWTd, LVM, and LVvolD were observed in athletes, that was not maintained in the control participants.

Cardiac function

Regardless of serum 25(OH)D status, all athletes and control participants displayed normal cardiac functional parameters. There was no significant difference in any cardiac functional parameter between athletes and control participants, or within athletes or control 25(OH)D participants.

Discussion

It is well recognized that 25(OH)D is necessary for optimal bone health. 25(OH)D-deficient athletes may be at an increased risk for potential problems such as stress fractures, respiratory infections, frequent illness, and muscle injuries. Yet, to our knowledge, this is the first study to investigate the association between 25(OH)D

Table 4. Logarithmic transformation adjusting 25(OH)D against cardiac morphology for age, body surface area, ethnicity and athletic participation in athletes and/or controls

Variable	Athletes vs. controls	Athletes plus controls	Athletes only	Controls only
Ao (mm)	0.3 ± 0.2 (0.148)	0.2 ± 0.2 (0.315)	0.2 ± 0.2 (0.336)	0.0 ± 0.3 (0.976)
LA (mm)	0.8 ± 0.3 (0.010)	0.1 ± 0.2 (0.787)	0.1 ± 0.3 (0.834)	0.1 ± 0.4 (0.790)
IVSd (mm)	0.2 ± 0.1 (0.013)	0.1 ± 0.1 (0.063)	0.1 ± 0.1 (0.011)	–0.1 ± 0.1 (0.536)
LVIDd (mm)	1.6 ± 0.4 (< 0.001)	0.9 ± 0.3 (0.002)	0.9 ± 0.4 (0.016)	0.8 ± 0.5 (0.120)
PWTd (mm)	–0.2 ± 0.2 (0.479)	0.4 ± 0.2 (0.037)	0.4 ± 0.2 (0.016)	0.3 ± 0.4 (0.466)
LVM (g)	11.1 ± 2.6 (<0.001)	6.7 ± 2.1 (0.002)	5.9 ± 2.6 (0.024)	4.8 ± 3.6 (0.185)
LVvolD (ml)	10.6 ± 1.9 (<0.001)	3.8 ± 1.5 (0.013)	5.6 ± 1.9 (0.003)	–0.5 ± 2.7 (0.860)
LA area (mm^2)	0.4 ± 0.6 (0.471)	0.3 ± 0.5 (0.558)	0.2 ± 0.3 (0.464)	0.0 ± 1.6 (0.986)
RA area (mm^2)	0.5 ± 0.3 (0.198)	0.2 ± 0.3 (0.388)	0.3 ± 0.3 (0.239)	0.0 ± 0.7 (0.976)

Values are β ± SE (*p*-value).; Ao, aortic root diameter; IVSd, intraventricular septum during diastole; LA area, left atrial area; LA, left atrial diameter; LVIDd, left ventricular internal diameter during diastole; LVM, left ventricular mass; LVvolD, left ventricular volume in diastole; PWTd, posterior wall thickness in diastole; RA area, right atrial area.

status and cardiac structure and function in young healthy athletes.

The main finding of the study is that severely 25(OH)D-deficient athletes (<10 ng/ml) presented significantly smaller ($p < 0.05$) Ao and LA diameter, IVSd, LVIDd, LVM, LVvolD, and RA area than insufficient (20–30 ng/ml) and sufficient (>30 ng/ml) athletes. Furthermore, following logarithmic transformation adjusting 25(OH)D for age, body surface area, ethnicity, and athletic participation, positive associations were between 25(OH)D and IVSd, LVIDd, PWTd, LVM, and LVvolD in athletes but not in the control participants.

In the present study, 23% of athletes demonstrated 25(OH)D sufficiency, with near half demonstrating either 25(OH)D deficiency (37.2%) or severe deficiency (11%). This high prevalence of deficiency has been noted previously.[18] It is likely that this high deficiency prevalence reflects the cultural tendency to train and compete after sunset in Qatar, due to the high daily temperatures. However, it should be noted 16.9% of athletes and 9.4% of controls who did not expose themselves to sunlight were sufficient in 25(OH)D. The majority of 25(OH)D is generated de novo by the basal layers of the epidermis via ultraviolet-B radiation and/or, to a lesser extent, consumed within the diet. While we did not measure nutritional intake prior to assessment, it is possible for individuals to become 25(OH)D sufficient with appropriate alimentation with foodstuffs as fish, milk, and cereals. Secondly, significantly more Caucasian athletes were 25(OH)D sufficient compared to Arabic and Black African athletes. Consideration for ethnicity and its impact upon 25(OH)D status is important, as a recent study by Powe et al.[19] reported that Black individuals ($n = 1191$) present significantly ($p < 0.001$) lower serum 25(OH)D levels than Caucasians ($n = 904$), despite being comparable in age, sex, body mass index, and menopausal status (15.6 ± 0.2 vs. 25.8 ± 0.4 ng/ml, respectively). A unique feature of this investigation was the examination of vitamin D-binding protein (the primary vitamin D carrier protein). The authors observed a higher prevalence among Black individuals of a polymorphism in the vitamin D-binding protein gene that was associated with low levels of vitamin D-binding protein, resulting in bioavailable 25(OH)D levels similar to Caucasian individuals despite lower levels of total 25(OH)D. The authors suggest that low levels of vitamin D-binding protein in Black individuals may offer protection against the consequences of 25(OH)D deficiency, such as for example, a higher bone mineral density scores in Black individuals compared to Caucasians.[19]

25(OH)D and cardiac structure and function; healthy vs. chronic disease states

Few studies have examined 25(OH)D status in association with cardiac structure and function in the general population without significant comorbidities. In an older female population (mean ± SD age 73.9 ± 4.9 years, 69.7% female), Van Ballegooijen et al.[20] measured serum 25(OH)D together with ECG and echocardiographic parameters in 2312 individuals free of cardiovascular disease at baseline. While mean serum 25(OH)D demonstrated populational insufficiency (25.2 ± 10.2 ng/ml), serum 25(OH)D was not associated with any ECG or echocardiographic parameter.

However, the vast majority of evidence examining 25(OH)D deficiency against cardiac morphology is in individuals with established chronic disease, and suggests that those individuals who are 25(OH)D deficient display significant increases in LV hypertrophy. Ky et al.[21] observed a significant negative interaction

between serum 25(OH)D and LV mass, end-diastolic and end-systolic volumes in 1431 individuals with chronic renal insufficiency. This association between 25(OH)D deficiency and increased LV mass is also observed in paediatric patients with chronic kidney disease[22] and in individuals with essential hypertension,[23] CHF,[24] and dilated cardiomyopathy.[25]

The precise mechanism(s) causing this cardiac hypertrophy (or in our case, lack of hypertrophy) in the 25(OH)D-deficient state remains unclear. What is understood, however, is that the remodelling mechanisms associated with cardiac disease and chronic overloading (such as long-standing mitral insufficiency, essential hypertension, CHF, kidney disease and dilated cardiomyopathy) differ considerably from the physiological adaptations seen in athletes induced though prolonged and intensive exercise. Furthermore, the observation that 25(OH)D deficiency is associated with, for example LVH in diseased individuals, may be a simple reflection of lack UVB exposure due to severe limitations in their functional capacity to exercise; meaning that they do not walk outside and are thus 25(OH)D deficient.

25(OH)D, cardiac structure and function in Murine models

Unlike models using humans with chronic disease, murine models offer information regarding 25(OH)D deficiency and cardiac structure at the cellular and myofibril level in apparently healthy hearts at baseline. However, unlike the present study which observed LV hypertrophy (wall thickness, mass and volumes) in 25(OH)D-sufficient athletes compared to severely deficient athletes, Assalin et al.[26] recently reported that male weaning Wistar rats fed a 25(OH)D-deficient diet for 4 months compared to rats fed a diet with 1,000 IU of vitamin D/kg, demonstrated LV hypertrophy together with lower fractional shortening and ejection fraction. Furthermore, biochemical analyses showed lower beta-hydroxyacyl coenzyme-A dehydrogenase activity and higher lactate dehydrogenase activity in 25(OH)D-deficient rats; with 25(OH)D deficiency significantly related to increased cytokines release, oxidative stress, apoptosis and fibrosis. These observations are supported by Weishaar et al.[14] who found a significant increase in cardiac hypertrophy (an increase in heart to body mass ratio) in rats feed a 25(OH)D-deficient diet after both 9 and 18 weeks.

Yet the precise mechanism(s) causing cardiac hypertrophy in the 25(OH)D-deficient rat is unclear, with murine models demonstrating conflicting results. Histological analysis of Weishaar et al.[14] rats observed significantly smaller ventricular myofibrils and increased extracellular matrix proteins compared to 25(OH)D-sufficient rats. However, Gezmish et al.[27] examined the effects of a 25(OH)D-deficient diet upon the hearts of 4-week-old Sprague Dawley rats whose mothers were feed a 25(OH)D-depleted diet from 6 weeks prior to pregnancy until 4 weeks of lactation. The authors demonstrated that maternal 25(OH)D deficiency leads to an increase in LV volume, accompanied by an increase in both cardiomyocyte hypertrophy and number (proliferation), in the hearts of 4-week-old rats.

To supplement with 25(OH)D or not

No studies have examined the effect of supplementation upon cardiac structure and function in healthy hearts, but a few have examined those with known cardiac comorbidities. Shedeed[28] evaluated the effect of $25(OH)D_3$ supplementation in infants with CHF. In this double-blind placebo-controlled intervention study of 80 infants with CHF, the intervention consisted of either giving vitamin D3 or placebo. After 12 weeks of $25(OH)D_3$ supplementation, significant improvements in LV end-diastolic and systolic diameters, ejection fraction, and myocardial performance index together with significant improvements in serum 25(OH)D status were observed compared to the placebo group. In the current study, none of the athletes were taking vitamin D supplementation at the time of screening. While the aim of this investigation was not to examine whether athletes should supplement with 25(OH)D to augment cardiac structure, future double-blind placebo-controlled studies should look to examine if 25(OH)D supplementation increases cardiac size in healthy athletes, especially in severely deficient and deficient cohorts.

Limitations

While we acknowledge that cardiorespiratory fitness, training volume, and intensity were not recorded, athletes were only included in the study if they competed at national level and trained for more than 6 h/week. It is felt that the logarithmic transformation adjustments of 25(OH)D for age, body surface area, ethnicity, and, importantly, athletic participation were satisfactory to distinguish cardiac morphological differences between and within athletes and controls.

Conclusion

Severely 25(OH)D-deficient athletes (<10 ng/ml) present significantly ($p < 0.05$) smaller Ao diameter, LAd, IVSd, LVIDd, LVM, LVvolD, and RA area than insufficient (20–30 ng/ml) and sufficient (>30 ng/ml) athletes. Furthermore, following logarithmic transformation

adjusting 25(OH)D for age, body surface area, ethnicity, and athletic participation, positive associations between 25(OH)D and IVSd, LVIDd, PWTd, LVM, LVvolD were observed in athletes but not in control participants. Future research should look to identify the precise mechanism(s) causing cardiac hypertrophy with increases in serum 25(OH)D in healthy athletes.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Hamilton B. Vitamin D and human skeletal muscle. *Scand J Med Sci Sports* 2010; 20: 182–190.
2. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357: 266–281.
3. Lappe JM, Travers-Gustafson D, Davies KM, et al. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007; 85: 1586–1591.
4. Pittas AG, Lau J, Hu FB, et al. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. *J Clin Endocrinol Metab* 2007; 92: 2017–2029.
5. Williams DM, Fraser A, Sayers A, et al. Associations of childhood 25-hydroxyvitamin D2 and D3 and cardiovascular risk factors in adolescence: prospective findings from the Avon Longitudinal Study of Parents and Children. *Eur J Prev Cardiol* 2013 (Epub ahead of print).
6. Weishaar RE and Simpson RU. Vitamin D3 and cardiovascular function in rats. *J Clin Invest* 1987; 79: 1706–1712.
7. Thadhani R, Appelbaum E, Pritchett Y, et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. *JAMA* 2012; 307: 674–684.
8. Noetzli LJ, Carson S, Coates TD, et al. Revisiting the relationship between vitamin D deficiency, cardiac iron and cardiac function in thalassemia major. *Eur J Haematol* 2011; 86: 176–177.
9. Kong J, Kim GH, Wei M, et al. Therapeutic effects of vitamin D analogs on cardiac hypertrophy in spontaneously hypertensive rats. *Am J Pathol* 2010; 177: 622–631.
10. Fahrleitner A, Dobnig H, Obernosterer A, et al. Vitamin D deficiency and secondary hyperparathyroidism are common complications in patients with peripheral arterial disease. *J Gen Intern Med* 2002; 17: 663–669.
11. Pilz S, Marz W, Wellnitz B, et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. *J Clin Endocrinol Metab* 2008; 93: 3927–3935.
12. Chen S, Glenn DJ, Ni W, et al. Expression of the vitamin d receptor is increased in the hypertrophic heart. *Hypertension* 2008; 52: 1106–1112.
13. Achinger SG and Ayus JC. The role of vitamin D in left ventricular hypertrophy and cardiac function. *Kidney Int Suppl* 2005; (95): S37S–S42.
14. Weishaar RE, Kim SN, Saunders DE, et al. Involvement of vitamin D3 with cardiovascular function. III. Effects on physical and morphological properties. *Am J Physiol* 1990; 258(1 Pt 1): E134–E142.
15. Chandra N, Bastiaenen R, Papadakis M, et al. Sudden cardiac death in young athletes: practical challenges and diagnostic dilemmas. *J Am Coll Cardiol* 2013; 61: 1027–1040.
16. Close GL, Russell J, Cobley JN, et al. Assessment of vitamin D concentration in non-supplemented professional athletes and healthy adults during the winter months in the UK: implications for skeletal muscle function. *J Sports Sci* 2013; 31: 344–353.
17. Riding NR, Salah O, Sharma S, et al. ECG and morphologic adaptations in Arabic athletes: are the European Society of Cardiology's recommendations for the interpretation of the 12-lead ECG appropriate for this ethnicity? *Br J Sports Med* 2013 (Epub ahead of print).
18. Hamilton B, Whiteley R, Farooq A, et al. Vitamin D concentration in 342 professional football players and association with lower limb isokinetic function. *J Sci Med Sport* 2013 (Epub ahead of print).
19. Powe CE, Evans MK, Wenger J, et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. *N Engl J Med* 2013; 369: 1991–2000.
20. van Ballegooijen AJ, Visser M, Kestenbaum B, et al. Relation of vitamin D and parathyroid hormone to cardiac biomarkers and to left ventricular mass (from the Cardiovascular Health Study). *Am J Cardiol* 2013; 111: 418–424.
21. Ky B, Shults J, Keane MG, et al. FGF23 modifies the relationship between vitamin D and cardiac remodeling. *Circ Heart Fail* 2013; 6: 817–824.
22. Patange AR, Valentini RP, Gothe MP, et al. Vitamin D deficiency is associated with increased left ventricular mass and diastolic dysfunction in children with chronic kidney disease. *Pediatr Cardiol* 2013; 34: 536–542.
23. Kulah E, Dursun A, Aktunc E, et al. Effects of angiotensin-converting enzyme gene polymorphism and serum vitamin D levels on ambulatory blood pressure measurement and left ventricular mass in Turkish hypertensive population. *Blood Press Monit* 2007; 12: 207–213.
24. Bozic B, Loncar G, Prodanovic N, et al. Parathyroid hormone response to vitamin D insufficiency in elderly males with chronic heart failure. *Physiol Res* 2011; 60(Suppl 1): S155–S163.
25. Al Azkawi H and Al Mutair A. Newborn with dilated cardiomyopathy secondary to vitamin D deficiency. *Case Rep Pediatr* 2012; 2012: 945437.
26. Assalin HB, Rafacho BP, Dos Santos PP, et al. Impact of the length of vitamin D deficiency on cardiac remodeling. *Circ Heart Fail* 2013; 6: 806–816.
27. Gezmish O, Tare M, Parkington HC, et al. Maternal vitamin D deficiency leads to cardiac hypertrophy in rat offspring. *Reprod Sci* 2010; 17: 168–176.
28. Shedeed SA. Vitamin D supplementation in infants with chronic congestive heart failure. *Pediatr Cardiol* 2012; 33: 713–719.