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ORIGINAL ARTICLE

Elite athletes as research model: vitamin D insufficiency associates with elevated central blood pressure in professional handball athletes

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Abstract

Purpose Low vitamin D levels have been associated with elevated blood pressure in the general population. Prospective studies, however, have produced conflicting evidence about the blood pressure-lowering effects of vitamin D supplementation. Cardiorespiratory fitness may modulate the vitamin D–blood pressure association. We therefore examined this association in professional athletes, whose high training load serves as a biological control for physical fitness.

Methods 50 male professional handball players (age 26 ± 5 years) were examined. We assessed the central aortic pressure parameters using transfer function-based analysis of oscillometrically obtained peripheral arterial waveforms. Serum 25-OH vitamin D concentrations were determined by chemiluminescent immunoassay. The threshold for insufficiency was set at values of < 30 ng/mL.

Results Central blood pressure (cBP) was 98 ± 7/60 ± 10 mmHg. The aortic pulse wave velocity (PWV) was 6.3 ± 1.0 m/s. Nine athletes (18%) displayed insufficient 25-OH vitamin D levels and had a significantly ($p < 0.01$) higher cBP compared with the 41 (82%) athletes with sufficient 25-OH vitamin D levels (106 ± 5/68 ± 8 vs. 97 ± 7/58 ± 9 mmHg). Central systolic blood pressure (cSBP) in vitamin D-sufficient athletes was significantly lower in comparison to the healthy reference population (97 mmHg vs. 103 mmHg, $p < 0.001$). This significance of difference was lost in vitamin D-insufficient athletes (106 mmHg vs. 103 mmHg, $p = 0.12$).

Conclusion Significantly raised central systolic and diastolic blood pressure in vitamin D-insufficient elite athletes implicates vitamin D as a potential modifier of vascular functional health.

Keywords Vascular function · Elite athletes · Handball · Pulse pressure wave analysis · Vitamin D · Central blood pressure · Central hemodynamics

Abbreviations

Aix	Augmentation index
Aix@75	Augmentation index at heart rate of 75 beats per minute
BMI	Body mass index
cBP	Central blood pressure
cDBP	Central diastolic blood pressure
cSBP	Central systolic blood pressure
CRF	Cardiorespiratory fitness
CLIA	Chemiluminescent immunoassay
ECG	Electrocardiogram
K2EDTA	Dipotassium ethylene diamine tetra-acetic acid
min	Minute
MPO	Maximum power output
PTH	Parathyroid hormone
PWV	Aortic pulse wave velocity
RHR	Resting heart rate
SD	Standard deviation
VO_{2max}	Maximum oxygen uptake

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Introduction

Many observational studies associated vitamin D deficiency with arterial hypertension (Kunutsor et al. 2013), increased cardiovascular events, impaired vascular function (Al Mheid et al. 2011) and mortality (Wang 2016; Anderson et al. 2010). Vitamin D receptors were found on smooth muscle cells (Somjen et al. 2005), myocytes and endothelial cells (Norman 2008). Supplementation of vitamin D in asymptomatic deficient subjects leads to an improved endothelial function (Tarcin et al. 2009). Further, anti-inflammatory effects of vitamin D (Norman 2008) could be shown and a vitamin D-regulated reduction of the activity of the renin–angiotensin–aldosterone system was found (Forman et al. 2010). All of these mechanisms potentially mediate a blood pressure-regulating effect of vitamin D.

Hence, a causal link between 25-OH vitamin D concentrations and cardiovascular function has been hypothesized (Christakos et al. 2013; Anderson et al. 2010; Arora and Wang 2017). The sound physiological rationale for this association finds support in a genetic study (Vimaleswaran et al. 2014) and in a Mendelian randomization study of the association between vitamin D deficiency and all-cause mortality (Aspelund et al. 2019).

However, two meta-analyses have shown that vitamin D supplementation in deficient adults was ineffective in lowering peripheral or central blood pressure (Beveridge et al. 2015; Rodriguez et al. 2016). In contrast, a recently published randomized controlled trial revealed that high dose vitamin D supplementation, given monthly over 1 year, lowered central blood pressure parameters significantly in vitamin D-deficient adults (Sluyter et al. 2017).

This lack of corroborating evidence is unsurprising given that cardiorespiratory fitness (CRF), measured as maximal oxygen uptake, is a dominant predictor of cardiovascular health (Davidson et al. 2018; Lee et al. 2010). In the general population regular exercise, performed at moderate intensity, is a well-known therapeutic tool to prevent cardiovascular events and to lower blood pressure (Laurent et al. 2011; Lee et al. 2012; Yoshikawa et al. 2019). It constitutes a cornerstone of preventive medicine (Lee et al. 2012). In this context, it is easy to see how failure to control for 25-OH vitamin D status and for CRF may yield conflicting results about the benefits of 25-OH vitamin D supplementation on blood pressure. We therefore hypothesize that 25-OH vitamin D status acts as an effect modifier of the CRF–blood pressure association. We suggest to investigate this hypothesis in populations ideally drawn from the highest CRF strata of a given age bracket. Recruiting professional elite athletes from within a specified sports discipline presents such an opportunity. These athletes' maximal training load, designed to elicit maximal fitness and sports performance, constitutes a strategy of effectively controlling for CRF. It is therefore conceivable that studying the correlations between fitness, vitamin D and cardiovascular function in an elite athletic population may yield insights that would not be attainable in non-athletic normal populations whose typically wide range of physical activity behaviors and fitness levels are potential confounders to these correlations.

So far, only few studies addressed the association between 25-OH vitamin D concentration, central hemodynamics and vascular function in professional athletes, a population repeatedly reported to be vitamin D insufficient and deficient (Owens et al. 2015; He et al. 2016; Mehran et al. 2016; Maroon et al. 2015). Our group recently discovered a high prevalence of vitamin D insufficiency (25-OH vitamin D < 30 ng/mL) in professional handball athletes in Germany (Bauer et al. 2018). We conducted this study to evaluate the associations between vitamin D levels and central hemodynamics in elite handball athletes. Handball is a team sport that exposes athletes to a high hemodynamic stress with its many interval sprints. It was classified as a sport with a high dynamic component (> 75% VO_{2max}) and a moderate static component (10–20%) (Levine et al. 2015).

Athletes were studied during summer, when 25-OH vitamin D levels are expected to have reached their peak (Morton et al. 2012; Krzywanski et al. 2016). We focused our investigation on measures of central (aortic) blood pressure (cBP). cBP is more strongly related to vascular disease and outcome (Roman et al. 2007) than peripheral (brachial) blood pressure, and therefore has a greater prognostic value (Cheng et al. 2013; Fan et al. 2016; Herbert et al. 2014; Roman et al. 2007).

Materials and methods

The following criteria for serum 25-OH vitamin D concentrations were chosen according to recently published studies and recommendations (Holick et al. 2012, 2011; Pludowski et al. 2013; Priemel et al. 2010).

Values of < 30 ng/mL were defined as insufficient and values ≥ 30 ng/mL were defined as sufficient 25-OH vitamin D levels.

The study was carried out at the university hospital in Giessen, Germany, which is located near 50°N latitude. It was conducted as a prospective study during the routine pre-season medical monitoring program of the first German handball division in the second half of July 2016 and July 2017 after a 6-week competition-free interval.

Study population

The participants were 50 healthy, injury-free professional handball athletes of varying nationalities playing in the first German handball division. All athletes were Caucasians with white skin and none of them was a regular sunbed user. None took vitamin D supplements or other multivitamin supplements. All individuals were subjected to a physical examination, 12-lead electrocardiogram, cardiopulmonary exercise test, and blood testing. Age, height, weight, body mass index, serum 25-OH vitamin D, calcium, magnesium and parathyroid hormone levels (PTH) were evaluated. Players were then divided into groups according to vitamin D levels as described above, and statistical analyses were performed.

Blood samples were drawn from an antecubital vein in a sitting position. Blood samples for plasma analyses were collected into two 7.5-mL S-Monovette® tubes (Sarstedt AG & Co. KG, Germany), one containing lithium heparin. An additional 2.7 mL sample, with dipotassium ethylene diamine tetra-acetic acid (K2EDTA) as anticoagulant, was acquired (Sarstedt AG & Co. KG, Germany). Within 30 min of drawing, automated analysis was performed in the laboratory of the university hospital Giessen. Serum 25-OH vitamin D concentrations were determined with a Liaison diagnostic system (DiaSorin, Stillwater, MN, USA) by chemiluminescent immunoassay (CLIA). The range of detection is 4–150 ng/mL with a precision of 5.0% CV and an accuracy SD of 1.2. Parathyroid hormone was analyzed using an electrochemiluminescent immunoassay [Elecsys PTH (1–84)®, Roche Diagnostics, Germany], which measures the circulating active parathyroid hormone. The range of detection is 5.5–2300 pg/mL with a precision range of 2.5–3.4% CV. Furthermore, calcium levels, a complete blood cell count and a basic metabolic panel including electrolytes, were assessed and analyzed by a Modular Analytics E 170 module (Roche Diagnostics, Mannheim, Germany).

All participants received a clear explanation of the study and provided their written informed consent. The local ethics committee of the University of Giessen approved the study protocol. The study meets the ethical standards (Harriss et al. 2017).

Exercise testing

A progressive maximal cycling ergometer test with concurrent brachial blood pressure measurement and ECG recording was performed (Schiller AG®, Switzerland). The exercise test protocol started with a load level of 100 W after a 2-min warm-up period, which was conducted with 50 W. Loads were increased by 50 W every 2 min until exhaustion, which was defined as the participants' inability to maintain the load for 2 min. Next, the load was decreased to 25 W for 3 min of active recovery, followed by a cool-down period at rest of 2 min. The test concluded with a final ECG recording and a brachial blood pressure measurement. We assessed the maximum power output (MPO) of the athletes, maximum heart rate, heart rate at rest and after the exercise test, and systolic and diastolic brachial blood pressure at rest, during and after exercise.

Noninvasive assessment of peripheral and central blood pressure and pulse pressure waveforms

We used the noninvasive vascassist2® device (isymed GmbH, Butzbach, Germany) to acquire pulse pressure waveforms by means of oscillometry. The device uses a validated model (Schumacher et al. 2018) of the arterial tree, representing all central and peripheral arterial sections. By modulating the circuits' capacitance, resistance, inductance, and voltage, the system replicates an individual's acquired pulse pressure waves. The system is based on the premise that the parameters used to replicate the pulse pressure waves are a quantitative representation of the functional parameters that gave rise to the pulse pressure wave in the biological original. The vascassist2® system uses genetic algorithms to optimize the fidelity of the pulse pressure wave replication (Schumacher et al. 2018). Fidelity replications of 99.6% or above were included in the analysis.

The noninvasive vascular evaluation was performed before the exercise testing in all athletes. After a 15-min rest, measurements were performed in a supine position using four conventional cuffs adapted to the arm and forearm circumference of the athletes. Radial and brachial pulse pressure waves were acquired on both arms with step-by-step deflation of the cuffs. The measurements took place in a room with a comfortable temperature of 22 °C and a lack of external stress influences. Participants were advised not to move during the acquisition of pulse pressure waves. Two brachial and three radial measurements were performed to guarantee stable and valid results. The total duration of the examination was 15 min. The acquired pulse pressure waves then were analyzed with a validated electronic model of the arterial tree to assess vascular functional parameters. Brachial and radial systolic and diastolic blood pressure, central systolic and diastolic blood pressure, pulse wave velocity (PWV), augmentation index (Aix), augmentation index at a heart rate of 75 bpm (Aix@75), resistance index, and ejection duration were calculated. cBP was determined with a transfer function that was based on the peripheral arterial waveform. Calculation of Aix@75 was also based on the pulse waveform.

Comparison with reference population

We compared central blood pressure values with those published for a reference population of 20- to 29-year-old healthy adults (Herbert et al. 2014). As the authors reported the distribution as percentiles, we used the z-scores that correspond to the 10th and 90th percentiles to extract the standard deviation of the distribution. As these percentiles were located symmetrically around the mean the assumption of normality of the distribution, as a pre-requisite for the z-score transformation, is justified.

Statistical analysis

Data are presented as mean ± standard deviation (SD). The Shapiro–Wilk test was used to determine normal distribution. In case of skewed distribution of the data, all analyses were performed on normalized data. Between-group comparisons were performed using independent-samples t tests. Bivariate relations were analyzed using Pearson's product–moment correlation coefficient.

Statistical significance was set at $p < 0.05$ two-tailed for all measurements. All statistical analyses were performed using Stata Statistical Software: Release 15. (StataCorp. 2017. College Station, TX: StataCorp LLC) for Macintosh.

Results

A total of 50 professional handball athletes were included in the study. They were experienced athletes and had participated in professional training for 9.8 ± 4.5 years (median 8.5, IQR 7–13 years) with a current mean training time of 18.6 ± 3.0 h (median 19, IQR 16.7–20 h) per week (Table 1).

41 athletes (82%) displayed sufficient 25-OH vitamin D levels of ≥ 30 ng/mL and 9 athletes (18%) were found to be vitamin D insufficient (< 30 ng/mL).

There were no significant between-group differences in age and anthropometrics. As expected, the 25-OH vitamin D levels between the sufficient and insufficient groups (41.3 ± 8.7 ng/mL vs 21.1 ± 7.9 ng/mL) were significantly different at $t(48) = 6.37$, $p < 0.001$). Table 2 shows the between-group comparison for all measured parameters.

Of the hemodynamic parameters, all central and peripheral blood pressure values were significantly higher in athletes with insufficient 25-OH vitamin D levels compared to those with sufficient levels. Amplification of systolic pressure was not significantly different between groups (Table 2).

Athletes with sufficient 25-OH vitamin D levels displayed both a significant lower central diastolic (58 ± 9 vs. 68 ± 8 mmHg, $p = 0.002$) and central systolic blood pressure (97 ± 7 vs. 106 ± 5 mmHg, $p < 0.001$) compared to those athletes with insufficient levels. Further, the mean central blood pressure of the group with sufficient 25-OH vitamin D levels was significantly lower (73 ± 8 vs. 83 ± 6.5 mmHg, $p = 0.001$) (Fig. 1).

Calcium, magnesium and PTH concentrations were not significantly different between groups. Lack of power was the probable reason for the lack of between-group differences in PTH. As there exists an inverse relationship between vitamin D and PTH levels, we used Pearson product–moment correlation coefficient to examine the relationships between 25-OH vitamin D and PTH and calcium levels across the entire group. There were moderate negative correlations between 25-OH vitamin D and PTH levels, $r(48) = -0.35$, $p = 0.015$, and between PTH and Calcium, $r(48) = -0.30$, $p < 0.05$.

cSBP in our vitamin D-sufficient athletes was significantly lower than in the healthy reference population [97 mmHg vs. 103 mmHg, $t(919) = -4.36$, $p < 0.001$]. This significance of difference was lost in vitamin D-insufficient athletes with 106 mmHg vs. 103 mmHg [$t(886) = 1.17$, $p = 0.12$]. Detailed data are given in Table 3.

Systolic pressure amplification was significantly higher both in vitamin D sufficient and insufficient athletes compared to the reference population, with 26 mmHg (± 5 mmHg) and 25 mmHg (± 3 mmHg) vs. 15 mmHg (± 7 mmHg) at $t(919) = 9.94$, $p < 0.001$ and $t(886) = 4.04$, $p < 0.001$, respectively.

Also, none of our athletes exceeded the upper normative limit for maximal systolic blood pressure response of 247 mmHg that has been established for Olympic athletes during maximal exercise testing (Caselli et al. 2016).

Table 1 Characteristics of all 50 handball athletes

	Mean	SD
Age (years)	25.7	5
Height (cm)	191.2	6.4
Weight (kg)	94.8	8.9
Body mass index (kg/m^2)	25.9	1.5
History of training (years)	10.2	4.9
Training per week (h)	18.95	2.2

Discussion

To the best of our knowledge, our study is the first to investigate central blood pressure (cBP) of elite handball players in Germany and its correlation to 25-OH vitamin D status.

Our main findings are that there exists a strong correlation between vitamin D insufficiency and elevation of cBP in professional handball athletes with a significantly lower cBP in athletes with sufficient compared to those with

Table 2 Comparison of the different characteristics according to 25-OH vitamin D levels

	25-OH vitamin D levels				
	30 ng/mL		< 30 ng/mL		*p* value
	n = 41		*n* = 9		
	Mean	SD	Mean	SD	
25-OH vitamin D (ng/mL)	41.3	8.7	21.1	7.9	**< 0.001**
Age (years)	25.7	5	27.5	4.6	0.325
Weight (kg)	93.9	9.9	94.3	11.2	0.911
Height (cm)	190.1	5.6	191.9	9.2	0.689
BMI (kg/m^2)	25.7	2.13	25.5	1.3	0.800
Heart rate at rest (bpm)	55.4	9.1	55.7	6.0	0.931
Central systolic blood pressure (mmHg)	97	7.1	105.8	5.4	**< 0.001**
Central diastolic blood pressure (mmHg)	57.9	8.7	67.8	8.1	**0.002**
Central mean arterial blood pressure (mmHg)	73.2	7.8	82.9	6.5	**0.001**
Aortic pulse pressure (mmHg)	39.5	7	38	6.5	0.575
Systolic blood pressure amplification (mmHg)	25.9	5	24.8	3	0.533
Brachial systolic blood pressure (mmHg)	122.9	8.3	130.6	7.2	**0.013**
Brachial diastolic blood pressure (mmHg)	58.6	8.6	67.4	8.4	**0.008**
Mean brachial arterial blood pressure (mmHg)	74.4	8.2	83.7	6.7	**0.003**
Brachial pulse pressure (mmHg)	64.3	10.9	63.2	8.9	0.776
Pulse pressure amplification (mmHg)	24.9	5.3	25.2	3.2	0.863
Aortic pulse wave velocity (m/s)	6.3	1	6.9	0.9	0.105
Augmentation index @75 (%)	-0.2	0.1	-0.2	0.1	0.446
Maximum heart rate (bpm)	175.8	9.2	167.4	17.2	0.079
Maximum systolic brachial blood pressure (mmHg)	189	19.5	191	26.9	0.799
Maximum diastolic brachial blood pressure (mmHg)	87.3	8.7	86.7	7.4	0.842
Parathyroid hormone (pg/mL)	32.2	21	44.9	13	0.107
Calcium (mmol/L)	2.37	0.09	2.36	0.24	0.824
Magnesium (mmol/L)	0.83	0.05	0.79	0.07	0.090

Bold text signifies significant differences. Values are given as means ± standard deviation (SD)

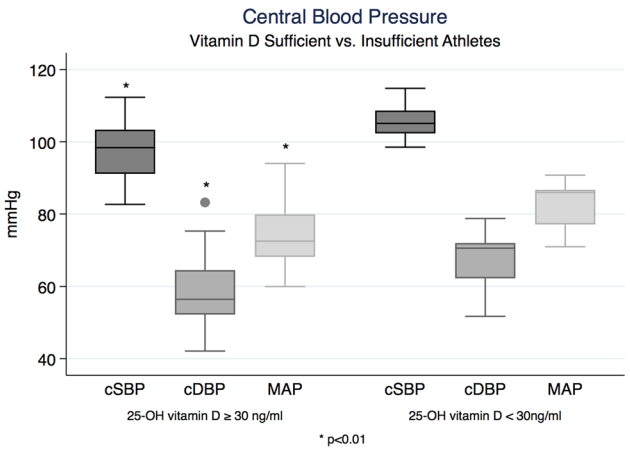

Fig. 1 Central blood pressure according to 25-OH vitamin D levels

insufficient 25-OH vitamin D levels. In addition, athletes with sufficient 25-OH vitamin D concentrations displayed a significantly lower central systolic blood pressure (cSBP) compared with age-matched non-athletic healthy persons, as reported in literature (Herbert et al. 2014). Further, we found that this hemodynamic advantage was lost in the vitamin D-insufficient athletes.

These findings strongly support the acknowledged association between vitamin D insufficiency and markers of impaired vascular function, such as arterial stiffening, endothelial dysfunction (Norman 2008; Tarcin et al. 2009) and up-regulation of the renin–angiotensin–aldosterone system (RAAS) (Forman et al. 2010).

Our focus on cBP rather than peripheral BP has been guided by three considerations. First, as described by Poiseuille's law, pressure is the product of flow and systemic resistance. Second, systemic resistance and vascular compliance are the main regulators of pressure and flow, thereby reflecting the functional integrity of the vascular system. Third, cBP is determined by the complex interaction between aortic compliance and elasticity and the resistance arteries' ability to channel blood flow in accordance with tissue needs (Stephen Hedley and Phelan 2017). Hence,

Table 3 Systolic central blood pressure and amplification of systolic blood pressure of the athletes according to 25-OH vitamin D levels in comparison with the published data of the age-matched healthy reference group (Herbert et al. 2014)

	Athletes according to 25-OH vitamin D levels					
	Reference group		≥ 30 ng/ml		< 30 ng/mL	
	Mean	SD	Mean	SD	Mean	SD
Central systolic blood pressure (mmHg)	103	8.6	**97**	**7.1**	105.8	5.4
Systolic blood pressure amplification (mmHg)	15	7	**25.9**	**5**	**24.8**	**3**

Bold text signifies significant differences compared to values of the reference group. Values are given as means ± standard deviation (SD)

central blood pressure is superior to brachial blood pressure in identifying changes of vascular functional parameters (Hodson et al. 2016) and cardiovascular risk (CVD) (Williams et al. 2006; Roman et al. 2007; Cheng et al. 2013; Fan et al. 2016; Herbert et al. 2014). A loss of distensibility in the central elastic arteries compromises their ability to buffer the ejected blood volume from the left ventricle, leading to an increase in cBP and to compromised coronary flow (Roman et al. 2007; Thijssen et al. 2016). Elevated peripheral resistance resulting from increases in vessel constriction and/or blood viscosity may amplify cBP elevations (Ashor et al. 2014). The impact of aortic stiffness on the development of cardiovascular disease has been documented in several studies (Mitchell 2009; Roman et al. 2007). An early return of the reflected pressure wave contributes to increases in cBP and arterial wall stress (Kaess et al. 2012; Green and Smith 2018), which constitutes an increased risk for cardiovascular and cerebrovascular events (Roman et al. 2007; Fan et al. 2016).

Our observation of significantly raised central systolic and diastolic pressure in vitamin D-insufficient athletes implicates vitamin D as a potential modifier of vascular functional health. As diastolic pressure is largely determined by peripheral resistance, one may speculate that vitamin D possibly affects the vascular tone of resistance vessels. Particularly in young men, cDBP, but not peripheral systolic pressure, is a predictor of cardiovascular risk (Wilkinson et al. 2001). This observation explains why brachial systolic pressure in adults younger than 50 years may be an unsuitable marker for examining the hypothesized association between vitamin D and cardiovascular risk.

Only few studies have been performed about the correlation between central hemodynamic parameters and training status in an athletic population, and none, to the best of our knowledge, has been controlled for vitamin-D status.

One study that has recently been published (Denham et al. 2016) presented evidence about significantly reduced augmentation index (Aix) in endurance-trained athletes vs. healthy untrained controls. In this mixed-gender population, the difference in cSBP between athletes and controls was not significant (106 ± 9 mmHg vs. 110 ± 9 mmHg, $p = 0.07$). The presented cSBP in the athletic population was comparable to our findings in the group of athletes with insufficient 25-OH vitamin D levels, though in our study male athletes with sufficient 25-OH vitamin D levels displayed a lower cSBP. This is consistent with the data of Denham et al. (2016), acknowledging the fact that their cohort was older than our study population. Unfortunately, lack of assessment of 25-OH vitamin D precludes controlling for vitamin-D status and limits the comparison to our results.

In a study investigating arterial stiffness in young professional rowers (mean age 24 years), a cSBP of 107 ± 11 mmHg was reported (Franzen et al. 2016) which is even higher than in our handball athletes with insufficient 25-OH vitamin D levels. This study included female athletes; cBP of healthy women should be lower than those of men (Herbert et al. 2014). Unfortunately, the results are not presented by gender. Therefore, the reported values are assumable lower than those, if only the results of the male athletes would have been presented. Interestingly, the reported PWV in this study cohort was comparable to our own results (6.6 ± 1.2 vs. 6.3 ± 1 m/s) (Franzen et al. 2016). Thus, again, vitamin D status of the professional rowers was not evaluated, which constitutes a major limitation in the comparison of the results, too.

Sotiriou et al. (2019) recently published data investigating arterial adaptations in different sports. They examined male athletes and found a lower cDBP (73 ± 12 vs. 77 ± 10.4 mmHg) and lower cSBP (99 ± 12 vs. 104 ± 14 mmHg) in high- level static sports athletes compared to high-level dynamic sports athletes (Sotiriou et al. 2019). The presented data of highly trained male athletes, performing a dynamic sport, are the most suitable for comparison with our own results. Despite the fact that their cohort was older than ours and vitamin D status was not obtained; cBP was comparable to those of our group with insufficient vitamin D levels.

Another study investigated central hemodynamics in ultra-endurance triathlon athletes (mean age 34) (Knez et al. 2008). The reported cDBP und cSBP are comparable with our results of the 25-OH vitamin-insufficient group (106 ± 8/72 ± 7 mmHg vs. 106 ± 5/68 ± 8 mmHg),

but higher than the results of our 25-OH vitamin-sufficient group (97 ± 7/58 ± 9 mmHg). Again, data about vitamin D status are missing and mixed-gender data are presented. As reported in this study, the influence of physical exercise on cBP was higher than on brachial blood pressure (Knez et al. 2008).

All results of cBP presented in these studies did not exceed the age-matched reference values for the healthy general population (Herbert et al. 2014). Hence, our findings of significantly lower cBP in a homogenous population of healthy, vitamin D-sufficient and well-trained athletes, highlights the potential blood-pressure-modifying influence of vitamin D. In general, a major limitation in comparing our results to those of the mentioned other studies is their lack of control for 25-OH vitamin D status.

Conversely, studies investigating the effects of vitamin D supplementation on central hemodynamics typically lack controlling for training and fitness status, though the blood pressure-lowering effects of exercise are well known, and regular exercise, performed at moderate intensity, is a recommended therapeutic tool in the treatment of arterial hypertension (Laurent et al. 2011; Lee et al. 2012; Yoshikawa et al. 2019). In this context, our study represents the first attempt at disentangling the interaction between central hemodynamics and 25-OH vitamin D status while effectively controlling for training status using elite athletes.

The fact that our athletes with sufficient 25-OH vitamin D levels displayed a significantly lower cBP compared to an age-matched healthy cohort motivates us to hypothesize that even the extreme exercise loads that characterize professional handball training correlate with increased cardiovascular function compared to healthy age-matched reference populations.

While exercise training typically improves markers of arterial function in a dose–response relationship (Green and Smith 2018; Rodriguez et al. 2016; Sluyter et al. 2017; Scragg et al. 2017), one study has found significant elevations of cBP and PWV in endurance-trained marathon runners (Vlachopoulos et al. 2010). Others have reported an unexpectedly high incidence of atherosclerosis in these endurance athletes (Merghani et al. 2017). These findings have stimulated the discussion of sports-related cardiovascular damage in professional athletes, resulting in the "extreme exercise hypothesis", which suggests an upper threshold for exercise. Exceeding this threshold may promote cardiac injury and atherosclerosis (La Gerche and Heidbuchel 2014; La Gerche et al. 2012; Eijsvogels et al. 2018). Our cohort of elite handball athletes had a training amount of nearly 19 h per week, though cBP and PWV in the vitamin D-sufficient athletes were lower than those of age-matched controls, suggesting a better cardiovascular function compared to them. Yet, this advantage was lost in the group with insufficient 25-OH vitamin D levels, as they displayed similar and not statistically different cBP compared to the age-matched reference group. This finding raises the question whether vitamin D may act as a modifier of the association between physical activity and its subsequent cardiovascular benefits.

Contrary to central and peripheral blood pressure, we observed no between-group difference in pulse pressure amplification. There exists a strong inverse linear relationship between pulse pressure amplification and age (Wilkinson et al. 2001). Decreasing pulse pressure amplification therefore is a strong correlate of the age-dependent decline in vascular function, specifically impaired vessel compliance (inverse of vessel stiffness) and increased systemic resistance. Our athletes showed a mean pulse pressure amplification ratio of 1.64 ± 0.1, which corresponds to 64% pulse pressure amplification from central to brachial. This can be considered normal compared to age-matched healthy persons (Wilkinson et al. 2001) and similar results were found in ultra-endurance triathlon athletes with 1.5 ± 0.2 (Knez et al. 2008). We found no significant differences in pulse pressure amplification between vitamin D sufficient and insufficient athletes, despite the fact of significantly different brachial and cBP.

These findings of higher brachial and cBP in vitamin D-insufficient athletes without a difference in pulse pressure amplification might be explainable with vitamin D insufficiency creating a functional environment that necessitates a higher pressure (at rest) for optimal blood supply, without impairment of the vasculature's age-adequate functional abilities. For example, an increase of vascular tone in resistance vessels at rest may be offset by maintained vessel compliance, ensuring the ability of maximal exercise capacity when needed. This would explain why vitamin D supplementation has largely failed as an ergogenic aid. Despite increasing research efforts regarding the effects of vitamin D on vascular cell function, cardiomyocytes and arterial function in different regions of the human vasculature, the exact physiological impact of vitamin D is still unclear (Wang 2016; Tarcin et al. 2009; Somjen et al. 2005; Forman et al. 2010).

Hence, it might be possible that vitamin D and physical activity differentially affect cardiovascular functional health. The exercise load to which our athletes have been routinely exposed may compensate for the deleterious effects of vitamin D insufficiency on the specific markers of vascular function that determine pulse pressure amplification, arterial stiffness and cBP. This potential compensatory effect of exercise highlights its modifying role in the association of vitamin D with cardiovascular risk in the general population.

Limitations

Our study has noteworthy limitations. The number of participants limited its power to uncover potential correlations between 25-OH vitamin D status and markers of cardiac and vascular function other than blood pressure. The focus on elite handball players may limit the results' extrapolation to other sport disciplines. However, as a team sport that exposes athletes to hemodynamic stresses of frequent interval sprints, it represents similar sports with a high dynamic component (> 75% VO_{2max}) and a moderate static component (10–20%) (Levine et al. 2015).

A further limitation is our exclusive focus on male athletes, which precludes the extrapolation of our results to female athletes. We are currently addressing all three issues through extension of our research to include larger numbers of professional male and female athletes from various sports disciplines.

Conclusion

In conclusion, we have shown for the first time that elite handball athletes with insufficient 25-OH vitamin D levels display a significantly higher cBP compared to those with sufficient 25-OH vitamin D levels, implicating vitamin D as a potential modifier of cBP. Further, we demonstrated that cBP was significantly lower in elite athletes with sufficient 25-OH vitamin D levels compared to the age-matched reference group, whereas this advantage was lost in athletes with insufficient 25-OH vitamin D levels.

We suggest that highly trained athletic populations present a unique opportunity to address the modifying effect of CRF on the association of 25-OH vitamin D with cBP and cardiovascular risk markers. Such investigations may offer an effective means to generate hypotheses in a cost- and time-efficient way that may subsequently be tested for their applicability in preventing and treating cardiovascular risk in the general population.

While our group of elite athletes was too small to generate authoritative insights into the complex relationship between fitness, exercise, vitamin D and cardiovascular functions, our results serve to stimulate future investigations into the correlation of vitamin D with parameters of vascular function and their response to vitamin D supplementation in vitamin D insufficient athletes.

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest.

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