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Pathogenic and Therapeutic Role of Vitamin D in Antiphospholipid Syndrome Patients

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Abstract

In this chapter, the novel findings on interrelationship between vitamin D status and two well-known prothrombotic states, antiphospholipid syndrome, particularly its thrombotic phenotype, and metabolic syndrome will be reviewed. We shall present the results obtained from patients included in Serbian National Antiphospholipid Syndrome Registry, 68 patients with primary antiphospholipid syndrome (PAPS) and 69 patients with antiphospholipid syndrome associated with certain autoimmune rheumatic disease (sAPS), as well as 50 patients with pure metabolic syndrome (MetS). These results will be analysed and compared with the novel literature data. Prevalence of MetS in APS is high, with the atherogenic dyslipidaemia as its most prevalent characteristic. Prevalence of thrombotic events was significantly higher in APS patients with coexisting MetS, compared with those without MetS. Among APS patients, prevalence of VitD deficiency was significantly higher than in patients with pure MetS. VitD level was also significantly lower in APS patients with coexisting MetS or previous thrombotic events than in those without them. Elucidating interrelationships between VitD deficiency, MetS and thrombotic events in APS patients open up the possibility of distinguishing those subjects with the particularly high cardiovascular risk and ensuing need for the strict control of modifiable risk factors and VitD supplementation.

Keywords: vitamin D, antiphospholipid syndrome, metabolic syndrome, classification criteria, thrombosis

1. Introduction

The antiphospholipid syndrome (APS), primary or associated with certain autoimmune rheumatic diseases, especially systemic lupus erythematosus, represents prothrombotic state. Coexistence of metabolic syndrome (MetS) and autoimmune rheumatic diseases is already recognized [1, 2], while clinical significance of MetS in patients with APS has not been systematically studied [3]. Recent recognition of certain pleiotropic functions of vitamin D (VitD) has enabled us to hypothesize on its role in the pathogenesis of obesity, MetS, APS, autoimmunity and thrombosis. Therefore, the aim of this review will be: (1) to clarify the possible linking role of VitD between APS and MetS, (2) to critically assess the need for estimation of VitD status in APS patients, depending on the coexistence of MetS and (3) to explore the potential therapeutic role which VitD, as an immunomodulator and anti-thrombotic agent, could have in these patients.

2. Basic definitions

Metabolic syndrome (MetS) and antiphospholipid syndrome (APS) are among most prevalent and still highly controversial syndromes. While clinical relevance of antiphospholipid antibodies (aPL) was recognized more than 30 years ago, definite classification criteria for antiphospholipid syndrome were given at the International Workshop in Sapporo, Japan 1998 [4] and revised 2006 in Sidney, Australia [5]. Very interesting proposal of APS criteria based on biological mechanisms is presented lately aiming at simplicity and greater accuracy and, at the same time, avoiding non-specific formulations [6] (**Table 1**). Recent investigations have also shown that, beside characteristic thrombotic or obstetric symptoms, there is growing number of systemic non-criteria manifestations (for example, thrombocytopenia, livedo reticularis, skin ulcerations, pseudovasculitis, migraine and epilepsy) correlating with certain type of aPL and with important predictive role [7, 8]. It is likely that a prominent place among these manifestations belongs to components of MetS, but it is still to be proved. The prevalence of APS in the general population is estimated to be around 2–4%.

Initial Reaven's postulate in 1988, which draw attention to the causal association between insulin resistance with ensuing hyperinsulinemia and cardiovascular diseases [9], was followed by numerous definitions of MetS. Three of them, i.e. definitions given by World Health Organization (WHO) [10], the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [11] and International Diabetes Federation (IDF) [12], were most frequently used and still neither of them is obsolete. While all three definitions share central obesity, atherogenic dyslipidaemia and arterial hypertension as common criteria, WHO definition put the insulin resistance in focus of metabolic syndrome while an obligatory criterion requested by IDF definition is elevated waist circumference (WC) with population- and country-specific cut-offs (**Table 2**). All of these three definitions are very similar but different enough, especially when used for the assessment of prevalence of MetS in some other entities, in this case, among patients with APS. Even the latest joint attempt of several major

professional organizations (the IDF Task Force on Epidemiology and Prevention, National Heart, Lung and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society and International Association for the Study of Obesity) to unify interconnected cardio-metabolic risk factors into a universal definition of metabolic syndrome did not seem to be final [13].

Sapporo criteria[4]	Sidney criteria[5]	Newly proposed minimalistic criteria[6]	
Clinical criteria *(at least one)* **1. Vascular thrombosis:** ≥ 1 clinical episodes of arterial, venous or small vessel thrombosis, confirmed in any tissue or organ by appropriate imaging studies or histopathology, but without significant inflammation in the vessel wall.		**Thrombotic APS** see Sapporo/Sidney criteria.	aβ2GP1-domain I IgG β2GP1-dependent LA LA aβ2GP1-independent LA aFII (aFII/PS) IgG aA5 IgG
2. Pregnancy morbidity (a) ≥ 1 unexplained early pregnancy loss at or beyond the 10th week with normal fetal morphology documented by ultrasound or direct fetal examination; (b) placenta-mediated late pregnancy complications (before 34 weeks) causing ≥ 1 fetal death; (c) ≥ 3 unexplained early pregnancy loss without maternal anatomic and hormonal abnormalities as well as without maternal and paternal chromosomal abnormalities.			
3. Laboratory criteria *(at least one)*		**Obstetric APS** 1. Unexplained early pregnancy loss (at or beyond 10th week)	
Detected on ≥ 2 occasions, at least 6 weeks apart: β2-glycoprotein I–dependent aCL IgG and/or IgM isotype antibodies, in medium or high titer; LA detected according to the guidelines of the International Society on Thrombosis and Hemostasis.	Detected on ≥ 2 occasions, at least 12 weeks apart: LA detected according to the guidelines of the International Society on Thrombosis and Hemostasis; aCL antibody of IgG and/or IgM isotype; anti- β2-glycoprotein I antibody of IgG and/or IgM isotype.	Placenta-mediated late pregnancy complications (before 34 weeks) with fetal death	aβ2GP1-domain I IgG β2GP1-dependent LA LA

Table 1. Antiphospholipid syndrome definitions.

Similar ambiguity exists concerning the definition of adequate circulating VitD level, as well as of its deficiency and insufficiency. Earlier definition of VitD insufficiency by its blood level of <20 ng/mL (50 nmol/L), given by the World Health Organization (WHO) [14], has been recently accepted by most researchers as a definition of the deficiency of this vitamin [15, 16]. Its insufficiency is defined as a VitD concentration between 20 and 30 ng/mL (50 and 75 nmol/L), while its concentrations >30 ng/mL (75 nmol/L) are regarded as sufficient [17, 18].
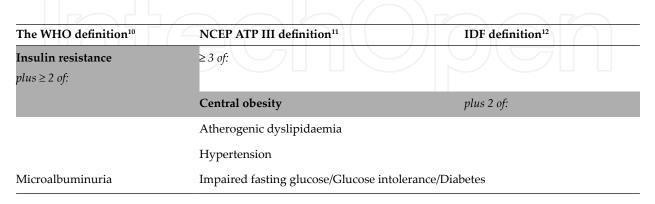
The WHO definition[10]	NCEP ATP III definition[11]	IDF definition[12]
Insulin resistance _plus ≥ 2 of:_	_≥ 3 of:_	
	Central obesity	_plus 2 of:_
	Atherogenic dyslipidaemia	
	Hypertension	
Microalbuminuria	Impaired fasting glucose/Glucose intolerance/Diabetes	

Table 2. Metabolic syndrome definitions—similar but different enough.

3. Experience from Serbian National APS Registry

3.1. Patients and methods

Study included a total of 137 APS patients, attending outpatient clinic of the University Medical Center Bezanijska kosa, all Caucasians, who were previously enrolled in Serbian National APS Registry. These patients represented only the part of those so far included in this Registry, which is still growing and is still unable to appraise the prevalence of APS among general population in Serbia. Among studied patients, 68 were PAPS patients (59 females, nine males, mean age 43.51+10.58 years) and 69 sAPS patients (61 females, eight males; mean age 47.83+15.67 years). All studied APS patients have met 2006 updated Sydney criteria [5] which requested the presence of at least one clinical criteria (i.e. vascular thrombosis or multiple and recurrent foetal losses) and at least one of antiphospholipid antibodies (aPL), i.e. lupus anticoagulant (LA), anticardiolipin (aCL) and/or anti-β2-glycoprotein 1 (β2GP1) antibodies. Most of our sAPS patients had APS associated with systemic lupus erythematosus (SLE) (n=60; 87%), while the rest had Sjögren's syndrome (n=8; 11.5%) and ankylosing spondylitis (n=1; 1.5%). Mean duration of these rheumatic diseases in sAPS patients was 5.69+2.87 years, ranging from 1 to 13 years.

Characteristics of two subgroups of APS patients were compared with 50 MetS patients (35 females, 15 males; mean age 47.68+11.66 years). The presence of metabolic syndrome among studied patients was determined according to the International Diabetes Federation (IDF) clinical definition [12]. An obligatory criterion for MetS requested by this definition is abdominal obesity defined by elevated waist circumference (WC) with gender- and ethnic-specific cut-offs, meaning 94 cm for males, and 80 cm for females belonging to European population. Besides abdominal obesity, two or more of the four additional criteria (a) hyper-

triglyceridemia >150 mg/L, confirmed or already treated; (b) high density lipoprotein (HDL) cholesterol <40 mg/dL in males or <50 mg/dL in females; (c) blood pressure >130/85 mmHg, newly diagnosed or already treated; (d) impaired fasting glycaemia, >100 mg/dL or previously diagnosed diabetes) are necessary for the diagnosis.

For every participant, clinical data concerning thrombotic events, their appearance, management and follow-up were obtained from medical charts review. As thrombotic events, the following were recorded: superficial and deep venous thrombosis, pulmonary embolism, peripheral arterial occlusion, cerebral vascular accident and myocardial infarction.

After an overnight fast, height (m), weight (kg) and waist circumference (cm) were measured in every participant with underwear and without shoes. Waist circumference (WC) was measured at the level of the umbilicus while the participant was standing and breathing normally. Body mass index (BMI) was calculated according to the widely accepted formula dividing body weight by the square of individual's height. Morning samples of venous blood (3–5 mL) were withdrawn from every participant for the analysis of serum glucose and lipids. Serum vitamin D levels were determined in every participant .

The study was approved by the Institutional Ethics Committee. All examinations were conducted according to the most recent amendment of Declaration of Helsinki (Edinburgh, 2000), only after obtaining an informed consent for participation in the study from every subject.

Statistical analysis was performed using the STATISTICA 10 software program. Descriptive statistics was used. Prevalence of MetS as well as of its individual components, within studied groups of patients was expressed as percentage. Testing significance of their differences, the Student's t-test and Fisher's exact test were used, considering p value <0.05 statistically significant.

3.2. Results

3.2.1. Prevalence of MetS among patients with APS

Metabolic syndrome was observed in high percentage of patients with APS. Its prevalence did not differ significantly between PAPS (36.76%) and sAPS (42.03%) patients (p=0.53).

Anthropometric and metabolic syndrome characteristics among studied groups are given in **Table 3**. Borderline statistical significance of the difference in WC value was observed when two subgroups of APS patients were compared with MetS patients (F=2.77, p=0.065), while BMI has differed highly significantly between these groups (F=9.765, p=0.0001). In spite of slightly lower BMI and slightly higher WC in PAPS patients, neither BMI (p=0.434) nor WC (p=0.275) did differ significantly between two subgroups of APS patients.

Atherogenic dyslipidaemia, represented by hypertriglyceridemia and low HDL cholesterol, was the most prevalent characteristic of metabolic syndrome among PAPS patients. In spite of this, prevalence of low HDL cholesterol among PAPS patients were significantly lower than in MetS patients (48.3% vs. 70%, p=0.02). Prevalence of hypertriglyceridemia (45.59% vs.

42.03%, p=0.67) and low HDL cholesterol (48.53% vs. 53.62%, p=0.55) did not differ significantly between PAPS and sAPS patients. Hypertension was significantly less prevalent among these patients compared with MetS (23.53% vs. 58%, p=0.0002) and even with sAPS (23.53% vs. 52.17%, p=0.0007) patients. The least prevalent characteristic of metabolic syndrome among patients with APS was hyperglycaemic disorder. Compared with MetS patients in whom impaired fasting glycaemia, glucose intolerance or diabetes were present in as much as 36%, these disorders were observed in only 5.88% of PAPS patients (p=0.0001) and 4.35% of sAPS patients (p<0.0001).

	MetS	PAPS	sAPS
BMI (kg/m^2)	32.09+6.14	27.81+5.98	28.54+4.22
WC (cm)	93.67+14.36	90.73+9.18	88.53+11.91
TG > 150 mg/dL (%)	58	45.59	42.03
HDL < 40/50 mg/dL (%)	70	48.53*[*]	53.62
Hypertension (%)	58	23.53**[**]	52.17§[§]
IFG, IGT, DM (%)	36#[#]	5.88**[**]	4.35

*p < 0.05, PAPS vs. MetS.
**p < 0.01, PAPS vs. MetS.
#p < 0.01, sAPS vs. MetS.
§p < 0.01, PAPS vs. sAPS.

Table 3. Anthropometric and metabolic syndrome characteristics among studied groups.

3.2.2. Prevalence of thrombotic events among APS patients with or without MetS

Compared with patients with metabolic syndrome, prevalence of thrombotic events was significantly higher among patients with PAPS (52.94% vs. 22%, p=0.0009) and sAPS (56.52% vs. 22%, p=0.0003). Thrombotic events were reported with similar prevalence in PAPS and sAPS patients (p=0.674).

When compared with APS patients without characteristics of MetS, thrombotic events were significantly more frequent among MetS positive patients with sAPS (75.86% vs. 42.5%, p=0.0075).

Although higher among MetS positive, compared with MetS negative patients with PAPS, difference of prevalence of thrombotic events among these two subgroups of PAPS patients did not reach statistical significance (68% vs. 44.19%, p=0.0622).

3.2.3. Vitamin D status among APS patients depending on MetS and/or thrombotic events

Low VitD status (insufficiency or deficiency) was highly prevalent among PAPS (insufficiency in 27.94% and deficiency in 36.76%) and sAPS patients (insufficiency in 30.43% and deficiency in 40.58%), as well as among patients with pure MetS (insufficiency in 20% and deficiency in 32%).

In comparison with patients with pure MetS (28.58+14.32 ng/mL), VitD concentrations were lower in PAPS (25.76+12.18 ng/mL) and sAPS patients (23.81+11.22 ng/mL), but with statistically significant difference only between these concentrations in sAPS patients and patients only with MetS (p=0.04).

Significantly lower VitD level was observed in those with coexisting MetS (MetS +), compared with those without it (MetS -) both in PAPS (MetS +: 22.0+8.52 vs. MetS -: 27.0+13.49 ng/mL, p=0.05) and sAPS patients (MetS +: 18.83+9.16 vs. MetS -: 27.42+11.28 ng/mL, p=0.0012).

Also, significantly lower VitD level was observed in APS patients with thrombotic events (TE+), compared with those without these events (TE -), both in PAPS (TE +: 20.61+12.18 vs. TE -: 31.56+12.72 ng/mL, p=0.0001) and sAPS patients (TE +: 20.67+10.43 vs. TE -: 27.9+11.04 ng/mL, p=0.007).

In 11 (22%) of patients with MetS, but without APS, some thrombotic event was confirmed. In those patients, VitD levels were also significantly lower than in those without these events (TE +: 18.45+10.66 vs. TE -: 31.43+13.63 ng/mL, p=0.003).

However, both in PAPS and sAPS patients, with coexisting MetS, previous thrombotic events did not influence serum VitD levels (PAPS: p=0.12; SAPS: p=0.93).

4. Relationship between antiphospholipid syndrome and metabolic syndrome

Estimation of prevalence of MetS in general population seems to depend to a substantial degree on the used definition, at least in certain countries or in certain ethnic groups [19–22]. Its prevalence varies between <10% in China and as much as 60% among women of Samoa [23]. Different prevalences of MetS, ranging between 18 and 48%, were also recorded among populations of different European countries and regions [20–22, 24–26]. It is interesting to emphasize that even in populations in which comparable prevalence of MetS was found using each of three already mentioned definitions, level of agreement between them was not good. As could be expected, worse agreement was found between WHO-NCEP ATP III and WHO-IDF than between NCEP ATP III-IDF definitions because of the central obesity as common denominator of the last two definitions [20, 21, 23]. This observation raised the possibility that in fact different individuals were identified as having MetS by different definitions of this syndrome [23].

In a search for factors that contribute to the manifestations of APS, MetS came into a focus surprisingly late. Data on coexistence of these two syndromes are still relatively scarce, particularly considering that of MetS and primary APS (PAPS).

4.1. Metabolic syndrome in primary antiphospholipid syndrome patients

Recently, prevalence of MetS among PAPS patients has been assessed by Medina et al. [3] and Rodrigues et al. [27]. Both surveys were performed in Hispanics among whom MetS has the

highest prevalence [28]. Defined by the IDF criteria, the prevalence of MetS among 71 Brazilian PAPS patients was 33.8% [27]. Comparable prevalences of MetS were recorded among 58 Mexican PAPS patients, using NCEP ATP III (34.5%) or IDF definitions (37.9%), while it was only 17.2% when WHO definition was applied [3]. It has been hypothesized that these cases, identified by WHO definition, were insulin resistant and with more severe forms of MetS [3, 29]. However, in investigation conducted by Medina et al., prevalence of MetS among PAPS patients was higher than in corresponding general population (17.2% vs. 13.6%) when WHO definition was used [3]. Same as in general population without APS [20, 21, 23], among PAPS patients agreement between WHO and NCEP ATP III definitions of MetS was low (κ value 0.394), moderate between WHO and IDF definitions (κ value 0.427), while only between NCEP ATP III and IDF definitions agreement was good (κ value 0.851) [3].

Regarding individual components of MetS, atherogenic dyslipidaemia was most prevalent among Mexican PAPS patients, being present in approximately half of them [3]. Significantly higher mean triglyceride levels and significantly lower mean HDL levels were previously reported among PAPS patients in comparison with controls [30–33]. Some specific autoantibodies could influence lipoprotein levels and effects in these patients. These antibodies may interfere with paraoxonase (PON) activity of HDL and, indirectly, beta-2-glycoprotein I (beta-2-GPI) [32, 33], thus promoting LDL oxidation. Relationships between lipid profile, certain anti-lipoprotein antibodies, inflammatory markers and clinical manifestations of PAPS were meticulously investigated [31–33], but on relatively small number of patients and with inconsistent results. Delgado Aves et al. have not demonstrated any correlation between the observed decrease in PON activity and either aPL nor antibodies against HDL (anti-HDL) in PAPS patients [33]. However, pro-inflammatory and prothrombotic roles were proposed for anti-HDL, being present in higher titre among asymptomatic persistently aPL positive subjects, as well as in PAPS patients with thrombotic events, when compared with patients with inherited thrombophilia and healthy controls [32]. It has been also hypothesized that hypertriglyceridemia could be the result of decreased degradation as a consequence of an inhibition of lipoprotein lipase (LPL) by aPL [3]. Currently, there are only scarce data on prevalence of antibodies against LPL (anti-LPL) in PAPS patients, speaking against their existence and influence [31].

Different authors have observed similar prevalences of hypertension among PAPS patients (22.4 and 26.3%) [3, 31], not differing significantly from that in controls (20%). Nevertheless, among PAPS patients, hypertension was significantly more frequent in those with arterial thrombosis, with which it was independently associated [31]. It is interesting that in spite of highly prevalent insulin resistance (32.8%), hyperglycaemic disorders were present in only 5% of PAPS patients [3].

4.2. Metabolic syndrome in patients with antiphospholipid syndrome associated with autoimmune rheumatic diseases.

The literature data on coexistence of MetS and numerous rheumatic diseases (i.e. systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, ankylosing spondylitis, osteoarthritis, gout) are fairly extensive [1, 34–42]. The prevalence of MetS among patients with

these disorders ranges between 14 and 62.8% [1, 3]. Qualifier "antiphospholipid syndrome associated with certain autoimmune rheumatic disease" (sAPS), which replace currently obsolete term "secondary APS", refers mainly to the systemic lupus erythematosus (SLE) despite the still unscrambled puzzle of their relations [5].

It has been speculated that high prevalence of MetS among these patients might be the consequence of certain pharmacologic interventions, particularly of chronic corticosteroid therapy [43]. However, the presence of MetS in as much as 16% of 1494 young (35.2+13.4 years) SLE patients with rather short disease duration (24.1+18.0 weeks) seems to be enough to reject this relationship as causal [2]. Nevertheless, it should be kept in mind that duration and magnitude of corticosteroid exposure could aggravate well-known cardiovascular risk factors clustering as characteristics of MetS.

On the other hand, other pharmacological interventions, primarily methotrexate (MTX) use in patients with rheumatoid arthritis, have been depicted as independent factors for reduced prevalence of MetS in these patients, especially those older than 60 years [44, 45]. This beneficial effect of MTX was attributed to its anti-inflammatory, as well as to some still unclear drug-specific effects, i.e. affecting adenosine levels and, concomitantly, glucose and lipid metabolism, or decreasing homocysteine levels as an indirect effect of simultaneous use of folic acid [44]. However, other authors reported somewhat conflicting results not being able to confirm decreasing prevalence of MetS in subjects treated with MTX, among total of 353 patients with rheumatoid arthritis [46].

5. Vitamin D and thrombosis

Prothrombotic state is one of the well-known characteristics of both antiphospholipid and metabolic syndrome. It has rather complex pathogenesis in which VitD status has an important role affecting primarily immune-mediated thrombosis. Indirect proofs for this relationship are as follows: (a) existence of nuclear VitD receptors in vascular smooth muscle cells, endothelial cells, cardiomyocytes, platelets, as well as in most types of the immune cells [47–51], and (b) expression of cytochrome P450 enzyme, CYP27B1 activity by the same cell types, enabling local synthesis of biologically active form of VitD, 1,25(OH)2D [52].

There is substantial experimental data indicating that VitD plays significant role in maintenance of physiological balance between thrombosis and haemostasis [47]. It has been demonstrated that VitD exerts following actions:

- in monocytes, expression of tissue factor (TF) is downregulated, while the expression of thrombomodulin (TM) is upregulated [53];

- in vascular smooth muscle cells, the expression of TM is upregulated, but there is also downregulation of plasminogen activator inhibitor-1 (PAI-1) and thrombospondin-1 (THSP-1) [54];

- in endothelial cells, platelet activation is attenuated as well as the expression of vascular cell adhesion molecule-1 (VCAM-1) [55].

Net result of numerous effects of this vitamin on different haemostatic factors is its antithrombotic role. Prothrombotic state that exists in VitD receptor knockout animal models proves the importance of these extra-skeletal effects of VitD as well as the observation that all of them are VitD receptor-mediated [47, 56].

However, there are still relatively few indirect and even less direct clinical evidences for the association between VitD status and thrombotic events in humans. First of them came from the epidemiological studies in which have been observed that cardiovascular morbidity and mortality depended on season of the year and latitude [47, 57, 58]. Seasonal variations were also demonstrated for tissue plasminogen activator (tPA) antigen, fibrinogen, D-dimer and von Willebrand factor (vWF) concentrations in 6538 British subjects without significant cardiovascular disorders, aged 45 years [59]. In this population, negative correlation between VitD level and tPA, fibrinogen and D-dimer concentrations was observed indicating that at least some of the seasonal variations of these thrombotic markers could be attributed to the VitD status. More direct proof for the association between VitD status and thrombosis came from the research conducted in huge population of 18 791 subjects from general population of Copenhagen [60]. Authors have observed that every quartile of a decrease in VitD concentrations was accompanied by an increase in risk of venous thromboembolism (VTE), resulting in a 37% increased VTE risk between subjects with the VitD concentrations, in the lowest quartile and those in highest quartile.

Recent publication which retested the seasonality of different cardiovascular events in regard to VitD levels, in the Scottish Heart Health Extended Cohort (SHHEC), brings a dose of confusion in previously proposed relations. Namely, it failed to prove that seasonal appearance of cardiovascular events resembled seasonal variations in serum VitD concentrations nor that these events expressed more pronounced seasonality in those with lower VitD concentrations, compared with those with its higher concentrations [61]. But, during follow-up, significant correlations were observed between lower baseline concentrations of VitD and subsequent incident cardiovascular morbidity and incident cardiovascular and all-cause mortality [61].

Results of recent trials assessing the effects of VitD supplementation on the risk of thromboembolism were inconclusive [62–64]. In the Multiple Environmental and Genetic Assessment (MEGA) case-control study which included 2506 patients with venous thrombosis, thrombotic risk was 37% lower in those supplemented with various vitamins including VitD [62]. However, in a large cohort of postmenopausal women (n=36282) from the Women's Health Initiative, daily supplementation with calcium and VitD failed to reduce the overall risk of thromboembolism [63]. Even when high doses (300,000 IU) of VitD were given intramuscularly, in a small group of patients with proven deep vein thrombosis and pulmonary embolism, observed reduction in plasma concentrations of P-selectin and high-sensitive C-reactive protein (hs-CRP) did not reached statistical significance [64]. Additional information could be expected from the ongoing Vitamin D and OmegA-3 Trial (VITAL) and that is why the results of this investigation are eagerly awaited [65].

6. Role of vitamin D in metabolic syndrome

Currently, increasing prevalence and co-existence of obesity, MetS and hypovitaminosis D represent serious public health concern [66, 67]. New data have considerably changed hierarchy of MetS components, with the shift of the focus from obesity and insulin resistance, firstly toward fatty liver and now toward VitD deficiency [68].

It is still questionable if relationship between VitD status and obesity is unidirectional or bidirectional, with the accumulating evidence favouring the influence of VitD on body composition and not vice versa. Namely, few years ago tempting hypothesis on essential role of VitD in evolvement of obesity has been postulated [68]. It started from a situation that is completely opposite to the "thrifty genotype hypothesis" proposed long ago [69] and gave the feasible explanation not only for obesity and MetS epidemic in adults but also for their growing prevalence among children [70]. According to this hypothesis, we are living in "obesogenic" environment, loaded with energy resources and unsuitable for efficient metabolism. It has been proposed that VitD as an ultraviolet (UV)-B radiation sensor (i.e. decline in its concentrations) could induce shift toward "winter metabolism", characteristic for MetS [68]. If this is true, then it could be expected that VitD supplementation may be efficient in prevention and treatment of obesity and MetS. Significant decrease in body fat mass after 12 week of VitD repletion (25 μg of cholecalciferol daily), compared to placebo (−2.7+2.0 kg vs. −0.4+2.0 kg, p<0.001), could be the proof for this presumption [71]. It was also speculated that VitD deficiency during pregnancy could lead to the epigenetic changes predisposing, in that manner, new-born children to obesity and MetS later in life [68, 70]. Experimental support for these assumptions is the expression of VitD receptors on adipocytes and its involvement in adipogenesis which is regulated by the intracellular concentrations of VitD [72], as well as inhibition of lipid accumulation in adipocytes and their atrophy achieved by the knock-down of VitD receptors [72, 73].

Nowadays, VitD deficiency is common even in general population (49%), but significantly more prevalent (p=0.006) and quite similar in overweight/obese patients with MetS (72%) and without MetS (69%) [74]. Premise that exaggerated adiposity could lead to VitD insufficiency or deficiency by its seclusion within adipose tissue could not be confirmed. It has been shown that VitD concentrations varied considerably (range 4–2470 ng/g) in the subcutaneous abdominal fat of 17 severely obese patients (BMI=48.7+8.1 kg/m2) undergoing bariatric surgery [75]. In spite of the average weight loss of 54.8 kg after one year and continuous VitD supplementation with more than 2500 IU/day, mean serum VitD concentrations did not change significantly during this period (23.1+12.6 vs. 26.2+5.36, p=0.58) [75].

Most of the studies have confirmed that serum VitD concentrations significantly inversely correlated with obesity parameters, BMI (r=-0.159, p=0.007) [74], or waist circumference (p<0.001) [76] as well as with serum triglycerides (r=-0.149, p=0.012) [76]. In the lowest quartiles of VitD concentrations corresponding to its severe deficiency, odds ratio (OR) for hypertriglyceridemia was 2.74 (95% CI: 1.64–4.57) [77]. This association between serum concentrations of VitD and triglycerides could be explained by the activation of lipoprotein lipase by VitD in adipocytes [76]. No significant relation could be demonstrated between VitD status and total-

(r=-0.044, p=0.461) [74], low density lipoprotein (LDL)- (r=-0.005, p=0.932) and high density lipoprotein (HDL)-cholesterol (r=0.065, p=0.276) [74]. Interestingly, hypothesis was proposed ten years ago stating the possibility that statins could be the analogues of VitD, acting via same receptors, particularly when we are talking about their mutual effect of enhancement of immune competence [78]. So, it seems that this absence of association between VitD status and parameters of cholesterol metabolism made this hypothesis shaky to some extent.

Another component of MetS for which association with VitD status has not been unequivocally confirmed is hypertension. Variability of blood pressure driven by the seasons or latitude speaks for the existence of this association, as well as the results of experimental studies pointing to VitD as an inhibitor of the renin-angiotensin-aldosterone axis [79, 80]. Negative correlation between VitD concentrations and blood pressure was demonstrated in most but not all of the surveys. This negative association was stronger in subjects younger than 50 years [81–83], while the absence of any relationship between VitD status and hypertension was also registered in some of the trials [74, 76, 84, 85], particularly those conducted in older subjects [84, 85]. However, in postmenopausal women with the VitD concentrations in the lowest quartiles corresponding to its severe deficiency, odds ratio (OR) for hypertension was 1.81 (95% CI: 1.15–2.85) [77].

7. Role of vitamin D in antiphospholipid syndrome

Although APS represents acquired, autoimmune condition, its pathophysiology and, especially pathophysiology of thrombosis in APS is highly heterogeneous, involving different genes and acquired factors [86], VitD insufficiency/deficiency being among them.

Same as for relationship between MetS and APS, much more is known about the impact of VitD status on antiphospholipid syndrome, associated with autoimmune rheumatic diseases, than on primary antiphospholipid syndrome. Patients with PAPS represent the population of particular interest for the investigation of interrelations with components of MetS and/or VitD status since these patients, unlike those with sAPS, were not treated with drugs (i.e. cortico-steroids, immunosuppressants) which may affect expression of most of the MetS characteristics as well as VitD level.

One of the first announcements on the prevalence of VitD insufficiency or deficiency in PAPS and their impact on its manifestations dated from 2010 [87]. This letter to the editor presented the results of research conducted by Brazilian investigators in the group of forty-six PAPS patients, younger than 60 years, in whom the VitD levels were assessed in the autumn, when it was expected to be highest. VitD deficiency was found in 11% and insufficiency in 74% of these PAPS patients, resembling the findings of Italian authors [88] which have reported the prevalence of VitD deficiency in 17% and insufficiency in 60% of PAPS patients. It is interesting that Brazilian authors have noticed that VitD insufficient PAPS patients tended to be more overweighed than those with adequate VitD level [87]. Also, it seems that thrombotic APS is characterized with significantly lower concentrations of VitD than purely obstetric clinical syndrome (20.8 vs. 33.3 ng/ml, p<0.01) [88] highlighting once again the role of this vitamin in

thrombosis. High prevalence of VitD deficiency among patients with APS (49.5%) and its significant correlation with thrombotic events were confirmed by Israeli authors [68]. In vitro, they have also demonstrated VitD ability to inhibit anti-β2-glycoprotein I autoantibody (anti-β2-GPI Ab)-mediated TF expression [89].

Seasonal variations in VitD concentrations were demonstrated in PAPS patients same as in healthy controls, with preserved differences in its level between these two groups through all seasons [88, 90]. These differences were most pronounced during summer, while they were not statistically significant only during the spring. This observation was somewhat surprising, given the lack of banning from sun exposure in these patients. That sun avoidance is not a cause of highly prevalent VitD deficiency and insufficiency in PAPS patients was indirectly demonstrated in previous Italian studies [88, 90] by observed absence of any difference in VitD levels between antinuclear antibodies (ANA)-positive and negative PAPS patients.

Until now, there is no valid explanation for the probable cause-and-effect relationship between insufficient VitD level, on one side, and PAPS or sAPS, on the other. There are only assumptions, and even they are much better clarified for sAPS [91–93], especially that accompanying SLE [91, 94, 95]. It is obvious that low levels of vitamin D in sAPS could not be attributed purely to banning of sun exposure or the use of certain medication in these patients. In an Israeli and European cohort of patients with SLE, significant negative correlation (r=-0.12, p=0.018) was demonstrated between the serum VitD concentrations and disease activity, assessed by SLE disease activity-2000 (SLEDAI-2K) and European Consensus Lupus Activity Measurement (ECLAM), which were converted into standardized z-value [94]. Severe VitD deficiency was found in 17.89% of 123 SLE patients with short disease duration, while the presence of renal disease (OR 13.3, 95% CI 2.3–76.7, p<0.01) and photosensitivity (OR 12.9, 95% CI 2.2–75.5, p<0.01) were its strongest predictors [95]. Investigation conducted in a small group of young women with newly diagnosed SLE, from one of the sunny places in Iran, gave very interesting results. VitD deficiency was highly prevalent among these patients, mild in 12.5%, moderate in 62.5% and severe in 17.5% of them [96]. It was much more pronounced in them than in general population of the similar age in that region, in whom mild VitD was present in 15.5%, moderate in 47.1% and severe in 7.1%. Very interesting was also an observation that serum VitD concentrations showed significant negative correlation with another disease activity score, the British Isles Lupus Assessment Group (BILAG) (r=-0.486, p=0.001), in spite of the short duration of disease [97]. Hypothetical explanation for the low serum concentrations of VitD in SLE patients by the existence of inhibiting anti-VitD antibodies in circulation could not be confirmed by the literature data [97, 98]. Their existence could be proven in 4–6% of patients with SLE and 3.5% of APS patients. Its association with anti-dsDNA (p=0.0004) could point to its potential role in this condition, but being only one of 116 different antibodies present in SLE patients characterized by the polyclonal B lymphocyte activation, it is still uncertain if it is pathogenic [97]. It seems that their presence did not affect VitD levels in these patients [97, 98], and it was speculated that they could be the consequence of high-dose VitD consumption rather than the cause of this vitamin deficiency [99].

Once again, it is important to emphasize that VitD deficiency is more pronounced in more severe APS phenotypes, i.e. thrombotic APS [88]. It could be speculated that supplementation

of this vitamin in these very patients may have certain beneficial effects [88, 99], but there is still no prospective studies proving them. Hypothesis of statins as VitD analogues has not still been tested in well-designed, randomized prospective trials [78]. However, since its proposal, there have been many experimental and small clinical studies confirming statins therapeutic value in APS patients, particularly in those with its thrombotic form [99–103]. So, future studies are badly needed to determine all the aspects of VitD repletion in APS prevention/therapy (choice between VitD precursors, its active form or VitD analogues, their dosage and treatment goals).

8. Key messages

• Prevalence of metabolic syndrome in APS, primary or associated with certain rheumatic diseases, is high.

• Atherogenic dyslipidaemia is the most prevalent characteristic of metabolic syndrome in APS patients.

• Prevalence of thrombotic events was significantly higher in APS patients with coexisting metabolic syndrome, compared with APS patients without metabolic syndrome characteristics.

• Among APS patients, prevalence of vitamin D deficiency was significantly higher in patients with coexisting metabolic syndrome, compared with those without it.

• Among APS patients, vitamin D level was also significantly lower in patients with previous thrombotic events than in those without them.

• In the contemporary literature, there are much more data in favour of pathogenic than therapeutic role of vitamin D in thrombotic events characterizing APS and/or metabolic syndrome. So, prospective studies designed to test all the aspects of VitD repletion in prevention and/or therapy of thrombotic events in APS and/or metabolic syndrome are badly needed.

9. Conclusions

Elucidating interrelationships between vitamin D deficiency, metabolic syndrome phenotype and thrombotic events in APS patients open up the possibility of distinguishing those subjects with the particularly high cardiovascular risk and ensuing need for the strict control of modifiable risk factors and vitamin D supplementation.

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