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Original Scientific Paper

PREVALENCE OF 25-HYDROXYCHOLECALCIFEROL DEFICIENCY AND METABOLIC SYNDROME IN CROATIAN WOMEN WITH NEWLY DIAGNOSED BREAST CANCER

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SUMMARY – The aim of this study was to determine the prevalence of vitamin D deficiency (VDD) and metabolic syndrome (MetS) including individual MetS components in Croatian women with newly diagnosed breast cancer (BC), exploring differences according to menopausal status. This cross-sectional, observational study recruited 203 adult female patients with newly diagnosed BC of any stage from all Croatian regions (median age 59, range 28-87 years), hospitalized consecutively for their first treatment between December 2016 and August 2017. We analyzed pretreatment fasting serum concentrations of 25-hydroxycholecalciferol (25(OH)D), high density lipoprotein, low density lipoprotein, triglycerides, plasma glucose, and measured systolic and diastolic blood pressure, weight and waist circumference; defining VDD as 25(OH)D concentrations <50 nmol/L and MetS according to the 2006 International Diabetes Federation consensus. Consistency of the results was explored according to sampling periods, regions and size of settlements. In total sample, 28.6% of patients presented with concomitant VDD+MetS, whilst VDD was found in 55.1% of women (the finding was consistent by menopausal status), and 48.3% had MetS (65.4% of postmenopausal *vs.* 15.7% of premenopausal women). Concomitant VDD+MetS was more frequent in the inland region (p=0.043), and VDD in inland

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postmenopausal women (p=0.024), whereas in premenopausal women VDD was more frequent during winter period (p=0.038). In conclusion, a high prevalence of VDD and MetS was found in newly diagnosed BC patients, with some regional and seasonal differences.

Key words: *Breast cancer; Vitamin D, 25-hydroxycholecalciferol; Deficiency; Metabolic syndrome; Croatia*

Introduction

Breast cancer (BC) is the most common cancer in Croatian women, with a proportion of 25% in newly diagnosed female cancers in 2016[1] and increasing incidence rates during the past decades[2], aligned with aging of the population[3]. Obesity as one of the environmental risk factors for (postmenopausal) BC[4] shows an increasing trend in Croatian population and worldwide, as well as diabetes and hypertension[5]. It is estimated that metabolic syndrome (MetS), constituting of a combined presence of central obesity plus glucose intolerance, arterial hypertension, and/or (atherogenic) dyslipidemia[6], is present in approximately 39% of Croatian women[7]. The presence of MetS is also showing an increasing trend worldwide[8], and has been associated with an increased risk of BC occurrence[9,10]. Central obesity, the core MetS component, is often accompanied with vitamin D deficiency, thought to be associated with its accumulation in the excessive fat tissue[11,12]. Vitamin D deficiency (VDD) is more frequent in older age and women[12,13], and has been associated with an increased risk of various health conditions and cancers[12], including BC[14,15] for both premenopausal and postmenopausal subpopulations. Previous studies in different populations worldwide have found a higher prevalence of MetS[16,17] and VDD[18-20] in BC and other cancer populations, reporting these conditions separately. To the best of our knowledge, no previous study explored the prevalence of combined presence of VDD and MetS in female BC population in Croatia or worldwide. The presence of MetS and VDD separately has been demonstrated to influence BC survival[21-25], thus their monitoring would be recommended during BC treatment, as it could be induced by treatments[26-29] and persistent despite vitamin D supplementation[19].

The aims of this study were to determine the prevalence of VDD and MetS, including individual MetS components, in Croatian adult women with newly diagnosed BC of any stage from all parts of Croatia and to explore the possible differences in these conditions according to menopausal status.

Patients and Methods

This study had a cross-sectional, observational design with prospective data collection from 203 BC patients, constituting a considerable sample (~8%) of yearly number of new cases in Croatia[1]. This academic study was approved by Ethics Committees of the School of Medicine, University of Zagreb (no. 02/21-LJH) and Sestre milosrdnice University Hospital Center (no. EP-14280/16-22), and conducted in accordance with the principles of Helsinki Declaration. Adult women with previously untreated newly diagnosed BC of any stage and from any Croatian region were consecutively recruited at two surgical oncology departments in University Hospital for Tumors, Sestre milosrdnice University Hospital Center in Zagreb, Croatia, between December 2016 and August 2017. After obtaining patient informed consent, before treatment, morning blood samples were collected in fasting condition for biochemistry analysis of 25-hydroxycholecalciferol (25(OH)D) (nmol/L), high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG) and fasting plasma glucose (FPG) (all as mmol/L). Systolic and diastolic blood pressure (SBP and DBP, mm Hg), weight (kg), height, waist and hip circumferences (cm) were measured once, and blood pressure once after 15 min of sitting. VDD was defined as 25(OH)D serum concentrations <50 nmol/L[30], and MetS according to the 2006 International Diabetes Federation (IDF) consensus for MetS definition[6], using waist cut-off values for European women ≥80 cm, accompanied with two of the following: (a) arterial hypertension ≥130 SBP or ≥85 mm Hg DBP or using antihypertensive; (b) FPG ≥5.6 mmol/L or

known diabetes; and (c) triglycerides ≥1.7 mmol/L or HDL <1.29 mmol/L or using respective therapy.

Although the IDF cut-off points for arterial hypertension in MetS were used when analyzing prevalence of arterial hypertension as an individual MetS component, overestimation of a 'new' hypertension diagnosis was unlikely as the measured borderline values were considered cases only if associated with waist ≥100 cm and/or body mass index (BMI) ≥30 m/kg^2 and/or being on medication with hypotensive effects for different indication (only 4 patients were 'new' hypertension cases and consequently 2 had MetS). Women stating taking vitamin D previously or currently were eligible and categorized as deficient if 25(OH)D was ≤70 nmol/L with normal weight (BMI <25 m/kg^2) or ≤55 nmol/L when overweight (BMI ≥25), as BMI has been shown to be inversely associated with change in serum 25(OH)D concentration during vitamin D supplementation[11].

Medical history data on BC, MetS and VDD risk factors, including current medications, physical activity, alcohol and diet were also collected using a self-reported questionnaire. In addition, size of settlement according to 2011 Croatian Census[31] (urban ≥10,000 inhabitants; or semi-urban/rural[32]) and main country regions according to the Croatian Bureau of Statistics (inland: central Croatia and Slavonia regions; and Mediterranean: Istria and Gorski Kotar, Dalmatia, Lika[33]) of current residence were also determined to explore their influence on MetS and VDD prevalence. Data on age and BMI value (m/kg^2) were determined, and menopausal status (premenopausal/perimenopausal, or postmenopausal) was defined considering perimenopause if women declared to be in a menopause for <1 year. After surgery, pathological BC classification for tumor (pT), nodus (pN) and metastasis (pM) was obtained and BC TNM stage determined according to the American Joint Committee on Cancer (AJCC) 8th Edition Staging Manual[34] which includes other clinical and imaging findings. All measurements, data and blood sample collections were obtained and analyzed before treatment, except for 25(OH)D where serum aliquots were stored at -80 °C in the Hospital Medical Chemistry Unit until enrolment of the last patient. Serum 25(OH)D concentration was analyzed in a single batch after test calibration procedure using the Roche Elecsys diagnostic test on a Cobas e411 analyzer.

Descriptive statistics was used to express patient characteristics including BC, VDD, MetS, individual MetS components, and some of their risk factors in medical history according to their menopausal status. The main statistical comparison was performed between pre-/perimenopausal and postmenopausal groups, while exploratory comparison was undertaken for sampling period, region and size of settlement. Data expressed as n (%) were analyzed using χ^2-test or Fisher exact test (when n ≤5); data expressed as median with range were analyzed using Kruskal-Wallis test with Mann-Whitney *post hoc* test and correction; and means with standard deviation (SD) were analyzed using ANOVA test with Tukey *post hoc* test, all these using MedCalc software version 18.11 (Mariakerke, Belgium).

For contextualization of our findings with Croatian general population, data published on VDD, MetS and its components were searched through the Medline/PubMed and Croatian medical databases (HRČAK, CROSBI), with last update in August 2019, using keywords/MeSH for these conditions with no language or date restrictions, and further reading the reference list of found publications.

Results

We analyzed data on 203 women with newly diagnosed BC (70 pre-/perimenopausal and 133 postmenopausal), age range 28 to 87 (median 59) years. In total sample, 28.6% of patients presented with concomitant VDD+MetS, whilst VDD was found in 55.1% of women, and 48.3% had MetS (Table 1). A significantly higher proportion of postmenopausal (M) compared to premenopausal (PreM) patients had both conditions (39.1% *vs.* 8.6%, respectively) and MetS (65.4% M *vs.* 15.7% PreM), but there was no difference in 25(OH)D deficiency (53.4% M *vs.* 58.5% PreM). VDD+MetS and MetS were expectedly significantly frequent in older age, higher BMI and waist circumference, and postmenopausal status (p<0.001 all). However, analyzing separately 25(OH)D deficiency, only higher BMI (p=0.045) and higher waist circumference (p=0.012) were often co-present. In total sample, the presence of 25(OH)D deficiency was not significantly higher in patients with MetS, and *vice versa* (data not shown in tables).

Table 1. Breast cancer patient population characteristics

Characteristic		Total N (%)	Pre-/peri-menopausal n (%)	Post-menopausal n (%)	p-value	BC *vs.* general population
		Number of patients				
		n=203	n=70	n=133		
Age (years), median (range)		59 (28-87)	44 (28-55)	65 (47-87)	<0.001	58 (mean) *vs.* 44.8[3]
Menopausal status	Premenopause Perimenopause Postmenopause	55 (27.1) 15 (7.4) 133 (65.5)	70 (34.5)	 133 (65.5)	<0.001	-
TNM stage	0 1 2 3 4	16 (7.9) 97 (47.8) 77 (37.9) 12 (5.9) 1 (0.5)	7 (10) 33 (47.1) 28 (40) 2 (2.9) 0	9 (6.8) 64 (48.1) 49 (36.8) 10 (7.5) 1 (0.8)	0.603	-
Central obesity (waist ≥80 cm)	Yes No	163 (80.3) 40 (19.7)	45 (64.3) 25 (35.7)	118 (88.7) 15 (11.3)	<0.001	80.3% *vs.* ~78%[61(approx.)] (PreM 64.3 *vs.* 70.3%[62]; ≥65 y.: 92.8 *vs.* 92.4%[61])
Central obesity (waist ≥88 cm)		120 (59.1)	24 (34.3)	96 (72.2)	<0.001	59.1 *vs.* 51.13%[51] (PreM 34.3 *vs.* 48.6%[62])
Obesity (BMI, kg/m^2)	≥30 ≥25-<30 <25	42 (20.7) 75 (36.9) 86 (42.4)	5 (7.1) 15 (21.4) 50 (71.4)	37 (27.8) 60 (45.1) 36 (27.1)	<0.001	≥30: 20.7 *vs.* 20.1[51] or *vs.* 26.8%[5] (PreM 7.1 *vs.* 27.2%[62]); ≥25: 57.6 *vs.* 33.6[51] or *vs.* 58.4%[5] (PreM 21.4 *vs.* 52.5%[62])
Hip circumference (cm), mean ±SD		105.6 ±10.2	102.1 ±9	107.4 ±10.3	<0.001	-
Waist/hip ratio, mean ±SD		0.87 ±0.08	0.82 ±0.07	0.89 ±0.08	<0.001	-
Waist/height ratio, mean ±SD		0.56 ±0.09	0.49 ±0.06	0.59 ±0.09	<0.001	-
Arterial hypertension*	Yes No New†	88 (43.3) 96 (47.3) 19 (9.4)	10 (14.3) 55 (78.6) 5 (7.1)	78 (58.6) 41 (30.8) 14 (10.5)	<0.001	52.7 *vs.* 44%[53]
Hypertension, or 'new' case with ≥140/≥90 mm Hg or ≥135/≥85‡ mm Hg cut-offs		103 (50.7)	13 (18.6)	90 (67.7)	<0.001	50.7 *vs.* 43%[52]
Diabetes*	Yes No New† In pregnancy	20 (9.9) 106 (52.2) 75 (36.9) 2 (1.0)	1 (1.4) 57 (81.4) 10 (14.3) 2 (2.9)	19 (14.3) 49 (36.8) 65 (48.9) -	<0.001	DM: 9.9 *vs.* 6.9%[54]
*Raised FPG		94 (46.3)	11 (15.7)	83 (62.4)	<0.001	46.3 *vs.* ~45%[48]
Dyslipidemia*	Yes No New†	63 (31.0) 101 (49.8) 39 (19.2)	11 (15.7) 50 (71.4) 9 (12.9)	52 (39.1) 51 (38.3) 30 (22.6)	<0.001	-
*Increased triglycerides or therapy		79 (38.9)	6 (8.6)	73 (54.9)	<0.001	38.9 *vs.* ~44%[48]
*Decreased HDL		47 (23.2)	9 (12.9)	38 (28.6)	0.013	23.2 *vs.* ~19%[48]
Metabolic syndrome*	Yes No	98 (48.3) 105 (51.7)	11 (15.7) 59 (84.3)	87 (65.4) 46 (34.6)	<0.001	48.3 *vs.* 39%[7]; ≥70 y.: 82 *vs.* ~65%[47]
25(OH)D	≥75 nmol/L ≥50-<75 nmol/L ≥25-<50 nmol/L <25 nmol/L	35 (17.3) 56 (27.6) 76 (37.4) 36 (17.7)	10 (14.3) 19 (27.1) 29 (41.4) 12 (17.1)	25 (18.8) 37 (27.8) 47 (35.3) 24 (18.1)	0.8	 <75: 82.7 *vs.* 62.6%[37] <50: 55.1 *vs.* 39.2%[36] <25: 17.7 *vs.* 7%[36]
25(OH)D deficiency§/MetS	None Both	51 (25.1) 58 (28.6)	24 (34.3) 6 (8.6)	27 (20.3) 52 (39.1)	<0.001	-
Only 25(OH)D deficiency; no MetS		54 (26.6)	35 (50)	19 (14.3)	<0.001	
Only MetS; no 25(OH)D deficiency		40 (19.7)	5 (7.1)	35 (26.3)	<0.001	
Vitamin D supplementation	Currently/occasionally No (and not stated)	13 (6.4) 190 (93.6)	1 (1.4) 69 (98.6)	12 (9) 121 (91)	0.037	-

Table 1. ctnd.

Characteristic		Total N (%)	Pre-/peri-menopausal n (%)	Post-menopausal n (%)	p-value	BC *vs.* general population
		Number of patients				
		n=203	n=70	n=133		
Calcium supplementation	Currently/occasionally No (and not stated)	7 (3.4) 196 (96.6)	0 70 (100)	7 (5.3) 126 (94.7)	0.098	-
Osteoporosis/ osteopenia	Yes No**	18 (8.9) 185 (91.1)	0 70 (100)	18 (13.5) 115 (86.5)	<0.001	-
Smoking (previous or current)	Yes No (#6)	105 (51.7) 98 (48.3)	42 (60) 28 (40)	63 (47.4) 70 (52.6)	0.118	-

*IDF definition of cut-off points for MetS components: hypertension ≥130 systolic blood pressure or ≥85 mm Hg diastolic blood pressure, FPG ≥5.6 mmol/L, triglycerides ≥1.7 mmol/L, HDL <1.29 mmol/L, waist circumference ≥80 cm;

†Newly found values exceeding IDF cut-off points;

‡No 'new' patients with this cut-off value;

§25(OH)D serum concentrations <50 nmol/L;

**Including 4 women stating vitamin D intake but not osteoporosis (one 44 and three ≥65 years of age);

#Number of patients with no response to question;

BC = breast cancer; BMI = body mass index; PreM = premenopausal women; DM = diabetes mellitus; IDF = International Diabetes Federation; MetS = metabolic syndrome; FPG = fasting plasma glucose

According to the IDF cut-off values for MetS components within MetS definition, a high prevalence of central obesity was found, i.e., 80.3% for ≥80 cm waist circumference (but 57.6% when defining as BMI ≥25 kg/m^2), along with other components which were present in around half of the women; arterial hypertension in 52.7%, dyslipidemia in 50.2%, and raised FPG/diabetes in 46.8% of patients. However, these findings are driven by the expectedly significantly higher presence of these MetS components in postmenopausal women (p<0.001 all). Considerable proportions of the high prevalence of particular components referred to the previously undiagnosed (not known to patients) MetS components in medical history, yet found at patient examination; 36.9% out of 46.8% prevalence of increased FPG/diabetes pertained to newly diagnosed, as well as 19.2% out of 50.2% for dyslipidemia, but only 9.4% out of 52.7% for hypertension. No differences were observed for tumor stages according to menopausal status.

In total population, VDD+MetS were concomitantly more frequent in the inland region (p=0.043), and VDD was more common in postmenopausal inland women (p=0.024), whilst in premenopausal women VDD was more frequent in winter enrolment period (p=0.038). Some differences were also observed by regions and settlement size for MetS components; diabetes/increased FPG (more frequent in inland total population; p=0.036) and arterial hypertension (more frequent in inland total and M population; p<0.001, and in PreM patients living in semi-urban/rural settlements; p=0.002) (Table 2). Additionally, significantly higher values were found for mean SBP in total and M patients, waist circumference, BMI, and waist-hip ratio values in total and PreM patients living in semi-urban/rural settlements, 25(OH)D serum concentration in PreM in summer period and in Mediterranean M women, and HDL in urban M patients (data not shown in tables).

Table 2. Vitamin D deficiency and MetS according to enrolment period, region and settlement size

Patients characteristics	Enrolment period		p-value	Croatian region[#]		p-value	Settlement size[†]		p-value
	Winter (Dec-Apr)	Summer (May-Aug)		Inland	Mediter-ranean		Urban	Semi-urban/ rural	
Total, N=203 (%)	**131 (64.5)**	**72 (35.5)**	-	**182 (89.7)**	**21 (10.3)**	-	**150 (73.9)**	**53 (26.1)**	-
25(OH)D deficiency, n=112 (%)	72 (64.3)	40 (35.7)	0.935	104 (92.9)	8 (7.1)	0.097	78 (69.6)	34 (30.4)	0.126
MetS, n=98 (%)	61 (62.2)	37 (37.8)	0.511	92 (93.9)	6 (6.1)	0.056	69 (70.4)	29 (29.6)	0.274
Both 25(OH)D deficiency and MetS, n=58 (%)	34 (58.6)	24 (41.4)	0.266	56 (96.6)	2 (3.4)	**0.043**	38 (65.5)	20 (34.5)	0.086
Central obesity*, n=163 (%)	100 (61.3)	63 (38.7)	0.056	146 (89.6)	17 (10.4)	1	116 (71.2)	47 (28.8)	0.074
Arterial hypertension*, n=107 (%)	67 (62.6)	40 (37.4)	0.547	104 (97.2)	3 (2.8)	**<0.001**	77 (72)	30 (28)	0.509
Diabetes/increased FPG*, n=95 (%)	59 (62.1)	36 (37.9)	0.498	90 (94.7)	5 (5.3)	**0.036**	67 (70.5)	28 (29.5)	0.306
Dyslipidemia*, n=102 (%)	66 (64.7)	36 (35.3)	0.959	92 (90.2)	10 (9.8)	0.799	75 (73.5)	27 (26.5)	0.906
Pre-/perimenopausal, n=70 (%)	**46 (65.7)**	**24 (34.3)**	-	**60 (85.7)**	**10 (14.3)**	-	**51 (72.3)**	**19 (27.7)**	-
25(OH)D deficiency, n=41 (%)	31 (75.6)	10 (24.4)	**0.038**	35 (87.5)	6 (12.5)	1	27 (65.6)	14 (34.4)	0.173
MetS, n=11 (%)	8 (72.7)	3 (27.3)	0.737	10 (90.9)	1 (9.1)	1	5 (45.5)	6 (54.5)	0.058
Both 25(OH)D deficiency and MetS, n=6 (%)	5 (83.3)	1 (16.7)	0.657	6 (100)	0	0.584	3 (50)	3 (50)	0.334
Central obesity*, n=45 (%)	27 (60)	18 (40)	0.177	38 (84.4)	7 (15.6)	1	30 (66.7)	15 (33.3)	0.211
Arterial hypertension*, n=15 (%)	11 (73.3)	4 (26.7)	0.554	14 (93.3)	1 (6.7)	0.678	6 (40)	9 (60)	**0.002**
Diabetes/increased FPG*, n=11 (%)	6 (54.5)	5 (45.5)	0.493	10 (90.9)	1 (9.1)	1	7 (63.6)	4 (36.4)	0.474
Dyslipidemia*, n=20 (%)	15 (75)	5 (25)	0.406	16 (80)	4 (20)	0.456	15 (75)	5 (25)	1
Postmenopausal, n=133 (%)	**85 (63.9)**	**48 (36.1)**	-	**122 (91.7)**	**11 (8.3)**	-	**99 (74.4)**	**34 (25.6)**	-
25(OH)D deficiency, n=71 (%)	41 (57.7)	30 (42.3)	0.113	69 (97.2)	2 (2.8)	**0.024**	51 (71.8)	20 (28.2)	0.461
MetS, n=87 (%)	53 (60.9)	34 (39.1)	0.323	82 (94.3)	5 (5.7)	0.188	64 (73.6)	23 (26.4)	0.751
Both 25(OH)D deficiency and MetS, n=52 (%)	29 (55.8)	23 (44.2)	0.117	50 (96.2)	2 (3.8)	0.20	35 (67.3)	17 (32.7)	0.131
Central obesity*, n=118 (%)	73 (61.9)	45 (38.1)	0.254	108 (91.5)	10 (8.5)	1	86 (72.9)	32 (27.1)	0.353
Arterial hypertension*, n=92 (%)	56 (60.9)	36 (39.1)	0.274	90 (97.8)	2 (2.2)	**<0.001**	71 (77.2)	21 (22.8)	0.278
Diabetes/increased FPG*, n=84 (%)	53 (63.1)	31 (36.9)	0.798	80 (95.2)	4 (4.8)	0.098	60 (71.4)	24 (28.6)	0.298
Dyslipidemia*, n=82 (%)	51 (62.2)	31 (37.8)	0.602	76 (92.7)	6 (7.3)	0.748	60 (73.2)	22 (26.8)	0.671

[#]Inland: central Croatia and Slavonia regions; Mediterranean: Istria and Gorski Kotar, Dalmatia, Lika[33]; [†]Urban: settlement >10,000 inhabitants[31,32]; *Cut-off points for MetS components according to IDF definitions;

MetS = metabolic syndrome; FPG = fasting plasma glucose; IDF = International Diabetes Federation

Discussion

At BC diagnosis, we found considerable prevalence of concomitant 25(OH)D deficiency and MetS (28.6%) in total BC population, which was expectedly more pronounced in postmenopausal patients (39.1%) whilst only a small proportion of premenopausal women had both conditions (8.6%). Furthermore, we found a high prevalence of each VDD, MetS, and individual MetS components. Concomitant presence of VDD+MetS could not be compared to general female population in Croatia as no study exploring VDD and MetS together was found. However, in 40.8% of studied women having MetS it was not accompanied by 25(OH)D deficiency, which is consistent with other studies in general population worldwide[35]. In contrast, VDD is not a rare finding in individuals with normal BMI <25 m/kg^2 or without abdominal obesity (half of the women in our study had both) as was also shown in previous studies in general population worldwide[35].

In total BC sample, and consistently in premenopausal and postmenopausal women, we observed a high prevalence of 25(OH)D deficiency <50 nmol/L (55.1%) and severe deficiency <25 nmol/L (17.7%) compared to Croatian healthy adult female population (39.2% and 7%[36]). In addition, the majority (82.7%) of patients were 25(OH)D insufficient having <75 nmol/L. We found only one additional Croatian study exploring 25(OH)D deficiency in healthy women[37], the results of which (32.3% with deficiency and 62.6% with insufficiency) also support our findings. Other Croatian non-cancer studies reporting high VDD prevalence were performed in highly selected populations and included either older women, small number of participants, studied specific comorbidities (osteoporosis and other), and/or sampled blood only in winter, which could explain a higher prevalence of 25(OH)D deficiency[38-41], or have not reported data separately for women and therefore are not suitable for comparison. All these studies included selected populations also considering regional and urban distribution of participants, hampering comparison for the entire country. Although our VDD findings could have been influenced by older age of studied BC population and higher proportion of women sampled in winter period as risk factors for VDD[12], this is generally consistent with findings in some other BC studies worldwide reporting a higher prevalence of VDD at BC diagnosis (e.g., USA[19,42], Chile[18], India[20]) compared to general female population in these countries[13]. Notably, not all BC studies worldwide showed higher VDD prevalence in newly diagnosed BC patients (e.g., Belgium[43], South Korea[44], Brazil[45]) *versus* general population in the corresponding countries[13]. Beside vitamin D supplementation, food intake and sunlight exposure, this may be influenced by differences in coexistence of overweight/obesity, as 25(OH)D concentrations inversely correlate with BMI[46].

Our study revealed MetS to be more prevalent in total BC sample compared to the general Croatian female population (48.3% *vs*. 39%[7]). The observed distribution of MetS by (older) age was expected (65.4% in M *vs*. 15.7% in Pre), as well as of other body/MetS characteristics. Postmenopausal women comprised a higher proportion of study population, and in this BC subpopulation MetS was higher than in the Croatian general older female population aged ≥70 years (82% *vs*. ~65%[47]). In addition, it is known that MetS prevalence varies depending on the Croatia regions, size of settlements[48], criteria for definition of MetS[7,47], and is lower in smokers. This was not observed in our BC study showing no differences of MetS in inland region and rural settlements, in contrast to a previous cardiovascular study[48]. Since we noted some trends, this might be due to different definition of rural area. Furthermore, MetS was not shown to be more frequent in women enrolled in winter period, as some studies pointed[49], but this was the case for VDD in premenopausal women and in line with known seasonal variations[12]. One Croatian study examining BC patients from the inland region treated surgically showed that the majority were overweight/obese, half of the women had hypertension, and 27.2% of hypertensive patients received therapy for endocrinologic disease (defined as diabetes or thyroid disease)[50], which provide some insights into the presence of MetS. Although this seems higher compared to the general female population, the comorbidities could have been influenced by older age.

Data on separate MetS components were also compared to data from the available previous studies on the general Croatian female adult population, including one conducted in a nationally representative sample (2003 Croatian Adult Health Survey, CAHS). In the total BC patient sample, a higher prevalence was

observed for increased waist circumference (59.1% *vs.* 51.13% for ≥88 cm used in CAHS) and overweight (57.6% *vs.* 33.6% in CAHS for BMI ≥25 kg/m^2), but not obesity (20.7% *vs.* 20.1% for BMI ≥30 kg/m^2)[51], although this did not differ from the World Health Organization estimates for the Croatian population (58.4% and 26.8% for BMI ≥25 and ≥30 kg/m^2, respectively)[5]. However, for premenopausal BC patients, a lower prevalence of central obesity was noted compared to CAHS women of childbearing age (Table 1). Arterial hypertension was somewhat more prevalent in our BC sample using both ≥140/≥90 mm Hg cut-off points used in the CAHS population study (50.7% *vs.* 43%[52], respectively) and using IDF ≥130/≥85 mm Hg cut offs (52.7% *vs.* 44%[53]), being consistently more frequent in the inland region[53]. Comparing data in our BC *versus* general Croatian female population, significant difference was found for previously known diabetes (9.9% *vs.* 6.9%[54], respectively), but not for increased FPG (46.3% *vs.* ~45%[48]). Cancer risk including for BC is known to be increased in diabetes patients[55], thus the greater prevalence of previously known diabetes that we observed is in agreement with this. Additionally, in the overall Croatian population of persons with diabetes (CroDiab register; data by sex have not been published), around 40% are obese and up to 85% are overweight, and in diabetic population MetS can be even more frequent depending on the cut-off criteria for MetS components[56]. Therefore, diabetes difference recorded in our study could have contributed to higher MetS findings also through frequently increased weight. There was no significant difference for dyslipidemia in BC women compared to the Croatian general population data available, defined as raised triglycerides or corresponding therapy (38.9% *vs.* ~44%, respectively) or low HDL (23.2% *vs.* ~19%)[48,57]. In general, the high prevalence of newly diagnosed dyslipidemia, (pre)diabetes and (pre)hypertension[48,58] did not exceed the known data for general population.

The effect of MetS risk factors of physical activity, alcohol consumption and diet, known to be inadequate in the Croatian general population[53], could not be interpreted from the questionnaire for BC women due to the high number of non-responded questions. Additionally, beside 25(OH)D deficiency being more frequent in the inland postmenopausal women, no other differences in the prevalence of VDD and/or MetS were shown between urban/rural settlements, or inland/Mediterranean regions, as might be suspected due to possible differences in those lifestyle factors (e.g., diet, outdoor physical activity[53]).

Overall, no firm assumptions could be drawn for the recorded high prevalence of 25(OH)D deficiency and MetS in BC women compared to the general Croatian female population, or their geographical distribution by regions and size of settlement. All differences in the prevalence of developed MetS and individual MetS components observed should be interpreted with caution as they could have been driven by older age of the study BC sample, i.e., epidemiology of BC, also bearing in mind the time elapsed between our and previous studies in the context of the increasing trends of MetS[8], its components, as well as BC[2] and aging of the population worldwide[3].

Since MetS[9,10] and VDD[14,15] have been associated with an increased risk of BC occurrence and BC survival[21-25], and being modifiable risk factors, employing measures to prevent and treat them could contribute to health outcomes related to BC[27,59,60]. Their monitoring would be recommended during BC treatment as they could be induced by treatments[26-29] and persistent despite vitamin D supplementation[19].

Strengths of our study were pretreatment sampling, hence MetS and VDD were not induced by BC treatments, then consecutive inclusion of both premenopausal and postmenopausal women, and sampling in winter and summer periods. Furthermore, the study included homogeneous Croatian population from various country regions and size of settlement, accounting for ~8% of yearly new BC cases; thus it was a representative BC sample, and detailed medical history data allowed description of patient characteristics known to influence both MetS and VDD.

This study had several limitations. We had no healthy control women to directly compare the prevalence of MetS and VDD, however, several reasons substantially hampered enrolment and matching of appropriate controls from such diverse living backgrounds, hence we compared data with the existing previous studies. All patients were enrolled at surgery department, therefore patients at the latest stage of newly diagnosed BC predisposed to receive initial non-surgical medical treatment were somewhat underrepresented. Although blood pressure was measured only

once, overestimation of the new cases is considered to be highly unlikely due to the low proportion of newly found hypertension and above explained measures employed not to ascribe borderline blood pressure values as hypertension. Also, more women were sampled in winter period, and place of current residence is not informative for the length of residence. Medical history data were self-reported[63], so there is a possibility of underreporting of some medications or health conditions, however, this could only result in underestimation of MetS prevalence.

Conclusions

The results of this study showed a high prevalence of VDD and MetS in Croatian women at the time of BC diagnosis. MetS and its simultaneous presence with VDD were expectedly observed in higher proportion of postmenopausal women, whilst half of the premenopausal women had only VDD. Several differences were observed analyzing VDD, MetS and MetS components according to country regions, size of settlement, and period of enrolment.

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Sažetak

UČESTALOST DEFICIJENCIJE 25-HIDROKSIKOLEKALCIFEROLA I METABOLIČKOGA SINDROMA U HRVATSKIH ŽENA S NOVOOTKRIVENIM KARCINOMOM DOJKE

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Cilj ovog istraživanja bio je istražiti učestalost deficijencije vitamina D (DVD) i metaboličkog sindroma (MetS) uključujući pojedinačne komponente MetS-a u žena s novootkrivenim rakom dojke u Hrvatskoj te istražiti razlike prema statusu menopauze. Ova presječna, opservacijska studija uključila je 203 odrasle bolesnice s novootkrivenim rakom dojke bilo kojeg stadija iz svih regija Hrvatske (medijan godina 59, raspon 28-87) uzastopno hospitaliziranih radi prvog liječenja između prosinca 2016. i kolovoza 2017. godine. Analizirali smo serumske koncentracije prije liječenja i natašte 25-hidroksikolekalciferola (25(OH)D), lipoproteina visoke gustoće, lipoproteina niske gustoće, triglicerida, glukoze u plazmi i izmjerili sistolički i dijastolički krvni tlak, težinu i opseg struka, definirajući DVD kao koncentraciju 25(OH)D <50 nmol/L, a MetS prema konsenzusu Međunarodne federacije za dijabetes iz 2006. godine. Dosljednost rezultata istražena je prema razdoblju uzorkovanja, regiji i veličini naselja. U ukupnom uzorku 28,6% bolesnica imalo je istodobno DVD+MetS, dok je DVD nađen u 55,1% žena (nalaz je bio dosljedan u oba statusa menopauze), a 48,3% imalo je MetS (65,4% postmenopauzalnih naspram 15,7% premenopauzalnih žena). Istodobni DVD+MetS bio je češći u kontinentalnoj regiji (p=0,043), a DVD u postmenopauzalnih kontinentalnih žena (p=0,024), dok je u premenopauzalnih žena DVD češće opažen tijekom zimskog razdoblja (p=0,038). Zaključno, nađena je visoka učestalost DVD i MetS u bolesnica s novootkrivenim rakom dojke, uz neke razlike prema regijama i razdoblju uzorkovanja.

Ključne riječi: *Rak dojke; Vitamin D, 25-hidroksikolekalciferol; Deficijencija; Metabolički sindrom; Hrvatska*