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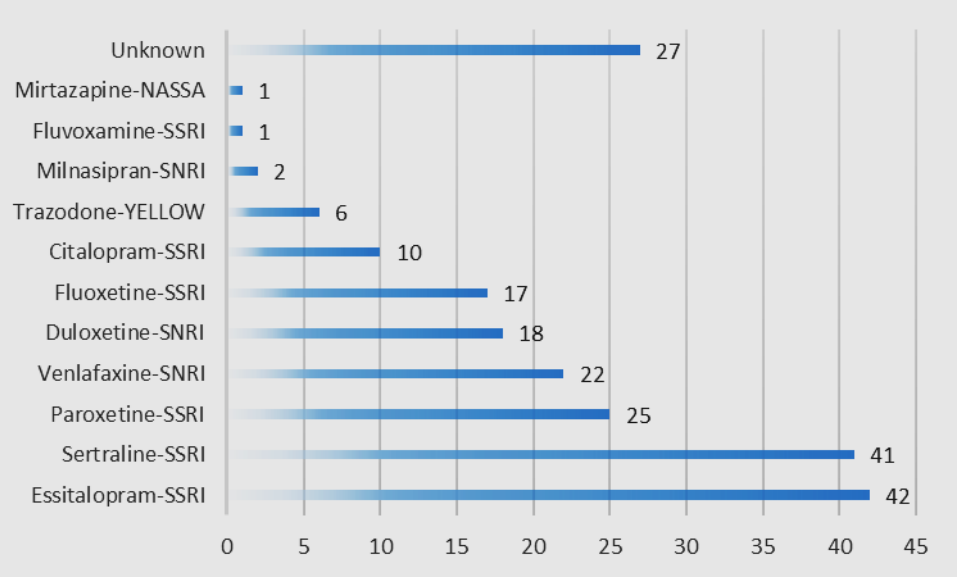

Distribution of active substances of drugs used

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Contents

Research Article

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Relationship between vitamin D levels and hematological parameters

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ABSTRACT

Objective: This study aims to examine the relationship between serum vitamin D levels and hematological parameters, and body mass index.

Material and Methods: It was carried out in the internal medicine outpatient clinic of Ayancık State Hospital between April 2017 and November 2020. Information about the sociodemographic and laboratory values of the patients was obtained from the hospital information system. The patients were divided into two groups as those with vitamin D levels below 20 ng/ml and those with over 30 ng/ml. Vitamin D levels and hematological parameters of all patients were examined.

Results: Of the 343 patients included in the study, 277 were women. When vitamin D levels were evaluated, vitamin D levels were significantly lower in women (82.7%; n:244) according to gender (p=0.023). When vitamin D levels are assessed according to age, It was observed that the vitamin D level of the patients included in the study, especially in the advanced age group, was low. There was no significant difference between vitamin D levels and body mass index (p=0.138). Age, MCV, MPV, HDL, Calcium (Ca), Phosphorus, Vitamin B-12, Vitamin D levels were found to be significantly higher in female patients with adequate vitamin D levels (p<0.05).

Conclusion: In our study, it was observed that there was a significant relationship between vitamin D levels, age, gender, platelet level, monocyte, MCV, neutrophil, protein, HDL, calcium, and vitamin B12 levels. Beside the treatment and clinical examinations, it is necessary to monitor and evaluate the vitamin D levels of the patients, as well as hematological, biochemical and endocrinological parameter changes.

Keywords: Vitamin D, hematological parameters, body mass index

INTRODUCTION

Vitamin D, a steroid hormone, is very important for human health (1). Vitamin D, which is in the group of fat-soluble vitamins, is a group of sterols with hormone-like effects (2). Biologically inactive vitamin D acts by transforming into its active form, 1,25 dihydroxy vitamin D [1,25(OH)2], as a result of different biological mechanisms in the body (3). Since its only source is not a diet, it is not exactly a vitamin and is a prohormone synthesized from steroids with some steps in cases where it is not taken from outside with diet (3). The mechanism of action of vitamin D in the body is a functional hormone with a wide spectrum. In particular, its most important task was to regulate bone mineralization by providing calcium and phosphate balance in the skeletal system (4). Apart from these effects, many studies have shown that vitamin D plays an inhibitory role in the development of cardiovascular diseases, endocrinological diseases, especially diabetes, and many other diseases (5, 6).

Vitamin D deficiency is increasing rapidly all over the world. Vitamin D deficiency is common in our country (7, 8). Many hematological and hormonal parameters that show variable blood levels in vitamin D deficiency or insufficiency have been emphasized (10). There are studies showing variability in hemogram parameters such as mean platelet volume (MPV), red cell distribution width (RDW), and neutrophil to lymphocyte ratio with vitamin D deficiency (11). This study aimed to compare the hematological parameters values of subjects with vitamin D deficiency to those with normal serum vitamin D levels.

Research Article

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MATERIAL and METHODs

In our study, the vitamin D levels of 343 patients randomly selected from 864 patients who came to the internal medicine outpatient clinic of Ayancık State Hospital between April 2017 and November 2020 and whose vitamin D levels were checked were examined. The results of each case were obtained from the electronic records of our hospital. Patients were divided into two groups as 25(OH) vitamin D levels below 20 ng/ml and above 30 ng/ml. Simultaneously, other laboratory parameters and demographic characteristics of the patients who were tested for vitamin D were recorded from the system. The ethics committee of the study was obtained from Sakarya University Faculty of Medicine (dated 18.11.2022 and numbered E-71522473-050.01.04-194705). Those who were over 18 years old and did not have a known endocrinological disease were included in the study. Pregnant and breastfeeding people under18 years old, treated with vitamin D, and had an active infection on the day of the blood sample were excluded from the study.

Statistical analysis

Data analysis was done with SPSS 24.0 and results were evaluated at 95% confidence level. In the study, while the relationship between the group and gender was analyzed with the chi-square test, the normal distribution of quantitative variables was examined with the normality test and it was determined that the normal distribution was not achieved. Accordingly, the comparison of the groups in terms of quantitative variables was made with the Mann-Whitney test.

RESULTs

In our study, the electronic and file records of 343 patients were evaluated. 14% (n:48) of the patients had 25 (OH) vitamin D levels above 30 (sufficient) and 86% (n:295) below 20 (extremely insufficient) (Table 1). Of these patients, 277 (80.8%) were female, and 66 (19.2%) were male. 68.8% (n:33) of the group with vitamin D above 30 and 82.7% (n:244) of the group with vitamin D below 20 were women, and there was a statistically significant relationship between the group and gender (p. <0.05) (Table 2).

According to the results of the research, the age, Body Fat Ratio, PLT, Gran#/Neut#, MCV, Monocyte/MID#, Creatine, Protein, HDL, Calcium (Ca), HbA1C, Vitamin B-12, D vit and Urine pH were statistically significant (p<0.05). Age, Gran# / Neut#, MCV, Creatine, HDL, Calcium (Ca), HbA1C, Vitamin B-12, Vitamin D, and Urine pH values below 20 for those with Vitamin D over 30 Body Fat Rate, PLT, Geliş Monocyte/MID# and Protein values are lower than those with Vitamin D below 20 (Table 3).

According to the study results, there was a statistically significant difference between those with vitamin D above 30 and those below 20 in terms of age, Incidence HbA1C and Incidence D vit values (p<0.05). Age, HbA1C and Vitamin D vitamin D values of those with vitamin D above 30 are higher than those with vitamin D below 20 (Table 4).

According to the results of the study, age, MCV, MPV, HDL, Iron Binding Capacity, Advance Calcium (Ca), Phosphorus, Vitamin B-12, D vit and There was a statistically significant difference in terms of urine pH (p<0.05). While age, MCV, MPV, HDL, Calcium (Ca), Phosphorus, Vitamin B-12, Vitamin D and Urine pH values were higher in women with Vitamin D above 30 than those with Vitamin D below 20. Iron Binding Capacity values were lower than those with vitamin D below 20 (Table 4).

Tablo 1: Distribution of patients according to their vitamin D levels

	n	%
Vitamin D levels >30	48	14,0
Vitamin D levels <20	295	86,0
Total	343	100,0

Tablo 2: Evaluation of vitamin D levels by gender

	Vitamin D levels >30		Vitamin D levels <20		Total		Chi-Square Test	
	n	%	n	%	n	%	X^2	p
Male	15	31,3	51	17,3	66	19,2	**5,179**	**0,023***
Female	33	68,8	244	82,7	277	80,8		

*P<0.05

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Tablo 3: Evaluation of all patient group parameters of vitamin D levels

	Vitamin D levels >30			Vitamin D levels <20			Mann Whitney U Test	
Age	47,08	15,39	51,00	36,51	15,66	35,00	4446,000	0,000*
Height	160,12	22,70	161,00	164,17	76,97	160,00	6078,500	0,116
Body Weight	93,10	89,71	81,70	81,78	19,46	83,00	6913,000	0,822
Skeletal Muscle Pain	27,35	5,63	25,70	27,11	13,65	25,80	6683,000	0,533
Body Fat Weight	30,24	9,65	30,25	35,50	25,53	33,50	5934,000	0,072
Body Mass Index	30,13	5,42	29,95	32,09	7,45	31,50	6134,500	0,138
Body Fat Ratio	37,59	9,12	39,20	42,21	28,90	41,35	5680,000	0,030*
Inbody PUM	65,73	8,50	65,00	63,23	11,02	63,00	6128,000	0,135
WBC	6,81	1,41	6,60	7,13	1,69	6,90	5980,000	0,232
HGB	13,63	1,34	13,60	15,32	22,37	13,20	5744,000	0,078
PLT	222,95	67,68	224,00	252,12	59,04	247,00	5232,000	0,009*
RDW-CV	16,72	9,02	13,30	16,40	8,37	13,50	6374,000	0,455
LYM#	3,11	5,56	2,30	2,68	4,97	2,20	6446,000	0,527
Gran# / Neut#	5,05	8,85	3,60	4,97	6,28	4,10	5459,500	0,029*
MCV	86,23	5,94	87,80	83,31	7,70	84,90	4915,500	0,002*
MPV	9,70	1,21	9,60	9,40	1,17	9,30	5900,500	0,115
Monocyte/MID#	0,68	0,24	0,70	0,83	1,44	0,60	3978,000	0,037*
Fasting Glucose	113,79	49,04	98,00	109,46	47,18	97,00	6502,000	0,564
Urea	26,09	8,03	24,25	24,59	9,34	23,25	6113,000	0,156
Creatine	0,94	1,05	0,80	0,78	0,43	0,70	5504,000	0,013*
ALP	53,85	26,07	58,50	69,05	33,49	63,50	153,500	0,236
GGT	19,11	7,97	20,00	28,01	47,76	18,00	949,500	0,943
LDH	181,86	41,80	167,00	169,94	59,95	166,00	144,000	0,655
AST	20,59	7,07	19,00	19,71	8,86	18,00	5700,500	0,137
ALT	23,00	10,93	20,00	22,83	21,61	18,00	5803,500	0,117
Albumin	35,13	25,39	44,00	39,28	15,12	45,00	728,500	0,132
Protein	51,83	31,30	70,00	63,81	25,36	74,00	613,000	0,036*
HDL	52,02	14,07	49,50	49,01	26,26	45,30	5114,500	0,046*
LDL	119,83	45,51	119,00	118,89	51,95	109,10	5180,000	0,402
triglyceride	127,90	65,54	117,00	130,60	85,05	111,00	5425,000	0,832
Iron	79,86	26,09	76,00	71,48	33,05	68,00	948,500	0,195
Iron Binding Capacity	249,76	70,12	234,00	266,73	75,43	259,00	615,000	0,247
Sodium	138,52	2,68	138,00	138,70	2,41	139,00	5102,000	0,786
Potassium	4,40	0,35	4,30	4,44	0,50	4,40	5097,500	0,813
Calcium (Ca)	9,75	0,52	9,80	9,54	0,44	9,60	1950,000	0,020*
Phosphorus	4,15	1,81	3,70	3,43	0,46	3,40	218,000	0,058
CRP	4,24	3,92	3,10	6,16	8,88	2,90	4377,500	0,556
RF	4,89	5,67	3,00	5,39	8,34	3,00	223,000	0,943
HbA1C	6,74	1,97	5,75	5,97	1,51	5,60	1613,500	0,007*
Free T4	1,12	0,22	1,10	1,14	0,36	1,11	5149,000	0,743
TSH	5,58	22,58	1,84	3,23	10,39	2,04	5610,500	0,753
ferritin	51,40	51,72	35,70	46,24	90,90	29,10	5105,000	0,140
Vitamin B-12	432,30	179,62	398,00	356,05	152,78	318,00	4170,500	0,001*
Folate	11,82	4,97	11,55	10,96	4,77	9,62	3786,500	0,295
PTH	57,25	39,39	57,25	51,63	26,77	57,35	3,000	0,643
sedimentation	12,93	10,78	9,00	17,64	12,10	14,00	605,500	0,067
Vitamin D	37,43	10,97	34,91	12,03	4,37	11,44	0,000	0,000*
insulin	18,04	18,92	12,08	18,13	16,06	13,50	1261,000	0,455
C-Peptide	1,99	0,84	2,26	3,11	1,91	2,54	149,000	0,060
Urine Density	255,14	449,63	1,03	124,29	334,06	1,03	1921,000	0,760
Urine pH	6,07	0,80	6,00	5,72	0,72	5,50	1363,000	0,027*

Tablo 4: The relationship between vitamin D levels of female and male patients and other parameters

	Female								Male							
	Vitamin D levels >30			Vitamin D levels <20			Mann Whitney U Test		Vitamin D levels >30			Vitamin D levels <20			Mann Whitney U Test	
	X	SS	Median	X	SS	Median	U	p	X	SS	Median	X	SS	Median	U	p
Age	46,97	14,94	51,00	36,63	15,51	35,00	2515,500	0,001*	47,33	16,89	42,00	35,98	16,49	35,00	248,500	0,040*
Height	159,39	6,33	158,00	162,97	84,50	158,00	3716,000	0,472	161,73	40,43	172,00	169,92	9,20	171,00	356,000	0,684
Body Weight	96,12	108,16	78,20	80,39	19,19	81,45	3716,000	0,473	86,45	14,48	90,70	88,59	19,53	90,40	354,500	0,750
Skeletal Muscle Pain	24,68	3,66	24,40	25,95	14,40	25,10	3502,500	0,225	33,23	4,70	33,20	32,66	7,00	34,00	378,500	0,951
Body Fat Weight	31,56	9,57	31,30	36,54	27,43	34,70	3424,500	0,164	27,31	9,50	29,90	30,52	12,05	29,30	356,000	0,685
Body Mass Index	30,49	5,61	30,10	32,42	7,70	31,85	3503,000	0,226	29,34	5,07	29,80	30,55	5,91	30,10	363,000	0,765
Body Fat Ratio	40,76	7,51	42,20	44,05	31,16	43,10	3559,500	0,296	30,61	8,62	32,40	33,43	9,99	33,20	322,000	0,355
Inbody PUM	64,88	8,86	64,00	63,06	10,90	63,00	3668,500	0,408	67,60	7,60	68,00	64,08	11,67	65,00	313,500	0,291
WBC	6,77	1,40	6,60	7,09	1,69	6,80	3318,500	0,296	6,89	1,49	6,70	7,33	1,70	7,10	325,000	0,436
HGB	13,18	1,13	13,25	15,46	24,63	13,00	3450,500	0,351	14,58	1,26	15,00	14,65	1,44	14,60	380,500	0,976
PLT	228,38	71,64	232,00	254,77	60,38	249,50	3054,500	0,052	211,37	58,94	223,00	239,30	50,70	242,00	289,500	0,183
RDW-CV	17,15	9,69	13,50	16,85	8,66	13,60	3594,500	0,557	15,79	7,61	13,30	14,27	6,50	13,20	361,500	0,748
LYM#	3,46	6,73	2,20	2,38	1,91	2,20	3631,500	0,592	2,37	0,62	2,60	4,09	11,21	2,50	347,000	0,662
Gran# / Neut#	5,62	10,69	3,65	4,49	3,92	4,10	3139,500	0,094	3,83	1,31	3,60	7,26	12,28	4,20	271,000	0,105
MCV	86,37	6,28	88,40	83,10	8,07	84,90	2535,000	0,002*	85,92	5,36	84,10	84,29	5,56	85,10	349,000	0,608
MPV	9,92	1,17	9,90	9,44	1,20	9,30	2876,000	0,018*	9,22	1,19	9,00	9,22	1,01	9,10	363,000	0,765
Monocyte/MID#	0,66	0,26	0,60	0,78	1,39	0,60	2495,500	0,204	0,74	0,19	0,80	1,08	1,68	0,60	181,000	0,142
Fasting Glucose	111,72	45,10	97,50	106,94	39,15	97,00	3748,000	0,797	118,20	58,04	99,00	121,37	73,64	98,00	357,000	0,696
Urea	24,44	7,09	22,00	23,92	9,10	22,60	3697,000	0,490	29,71	8,99	27,70	27,84	9,87	26,30	325,000	0,436
Creatine	0,75	0,10	0,70	0,74	0,22	0,70	3318,500	0,100	1,35	1,84	0,80	0,99	0,90	0,90	354,500	0,661
ALP	52,83	27,99	56,00	65,75	26,79	63,00	114,500	0,249	61,00		61,00	90,29	60,52	75,00	3,000	0,826
GGT	17,47	6,66	17,00	28,73	51,81	17,00	596,500	0,692	25,25	10,50	20,00	24,19	12,57	20,50	25,000	0,507
LDH	184,33	45,22	167,50	165,64	60,76	166,00	90,000	0,580	167,00		167,00	183,64	57,88	176,00	5,000	0,885
AST	19,09	5,73	19,00	19,36	9,32	17,00	3368,000	0,304	24,00	8,76	21,00	21,38	6,03	22,00	303,000	0,444
ALT	20,97	9,48	19,00	21,20	22,49	17,00	3285,000	0,128	27,79	12,90	24,50	30,62	14,58	28,00	305,000	0,464

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Tablo 4: The relationship between vitamin D levels of female and male patients and other parameters

	Female								Male							
	Vitamin D levels >30			Vitamin D levels <20			Mann Whitney U Test		Vitamin D levels >30			Vitamin D levels <20			Mann Whitney U Test	
	X	SS	Median	X	SS	Median	U	p	X	SS	Median	X	SS	Median	U	p
Albumin	35,81	26,41	43,50	39,57	14,86	45,00	516,000	0,176	31,50	23,40	44,00	37,79	16,79	45,00	17,500	0,465
Protein	52,15	31,36	70,00	63,33	25,67	73,00	459,500	0,098	50,13	37,93	70,00	66,31	24,33	75,00	10,000	0,137
HDL	55,70	14,41	52,10	50,75	28,27	47,70	2579,000	0,015*	43,89	9,37	44,10	41,24	11,40	40,70	293,000	0,307
LDL	117,42	48,10	110,20	116,24	46,75	111,00	3022,000	0,518	125,64	39,89	125,35	130,81	70,13	107,30	287,500	0,824
triglyceride	119,39	63,37	107,50	125,89	80,71	108,00	3069,500	0,768	147,75	68,97	142,50	151,98	100,66	128,50	276,500	0,675
Iron	78,59	27,08	76,00	67,22	30,49	65,50	613,500	0,129	85,25	24,06	75,50	96,50	37,36	96,50	25,000	0,508
Iron Binding Capacity	243,57	75,61	218,50	278,19	70,04	271,50	338,000	0,040*	278,67	25,54	287,00	206,14	76,37	203,00	7,000	0,077
Sodium	138,43	3,04	138,00	138,69	2,47	139,00	2893,500	0,819	138,71	1,77	138,00	138,73	2,11	139,00	265,500	0,772
Potassium	4,41	0,32	4,40	4,43	0,53	4,40	2994,500	0,862	4,38	0,42	4,20	4,46	0,35	4,40	220,000	0,406
Calcium (Ca)	9,80	0,44	9,80	9,54	0,45	9,60	1092,000	0,015*	9,63	0,72	9,60	9,52	0,39	9,60	108,000	0,620
Phosphorus	4,47	2,09	4,00	3,42	0,46	3,40	96,000	0,018*	3,43	0,66	3,40	3,46	0,51	3,45	15,500	0,932
CRP	4,20	2,73	4,00	6,20	7,72	3,00	2872,500	0,871	4,37	6,52	2,00	5,93	13,58	2,50	146,500	0,294
RF	5,13	6,01	3,00	6,02	9,24	3,00	156,000	0,857	3,00		3,00	2,90	0,32	3,00	4,500	0,752
HbA1C	6,52	1,88	5,70	5,92	1,45	5,60	986,500	0,087	7,21	2,18	6,50	6,18	1,75	5,60	80,000	0,043*
Free T4	1,16	0,19	1,10	1,11	0,21	1,08	2649,000	0,228	1,03	0,26	1,11	1,26	0,71	1,18	178,000	0,060
TSH	2,27	1,19	1,84	2,83	5,72	2,16	3224,000	0,777	13,24	41,10	1,84	5,11	21,62	1,72	298,500	0,900
ferritin	40,30	36,41	30,05	32,76	31,88	24,20	2844,500	0,085	79,13	72,81	71,90	112,22	197,90	71,85	250,000	0,482
Vitamin B-12	452,97	206,24	408,00	354,92	156,23	313,00	2242,500	0,004*	389,50	98,45	392,00	361,51	136,30	362,50	296,500	0,506
Folate	12,50	5,61	11,62	11,00	4,79	9,53	2004,500	0,280	10,51	3,23	10,90	10,78	4,70	9,85	235,000	0,795
PTH	57,25	39,39	57,25	63,73	13,98	65,90	3,000	1,000				15,30		15,30		
Sedimentation	15,10	11,90	10,00	18,67	12,03	15,00	358,500	0,219	8,60	7,27	5,00	12,80	11,51	10,00	41,500	0,562
Vitamin D	37,31	10,60	34,92	11,56	4,33	11,01	0,000	0,000*	37,69	12,11	32,67	14,32	3,85	15,09	0,000	0,000*
Insulin	12,37	7,39	11,46	17,11	12,99	13,23	603,000	0,127	32,77	31,33	17,19	22,11	24,55	15,57	63,000	0,450
C-Peptide	2,06	0,65	1,78	2,84	1,42	2,45	64,000	0,094	1,88	1,20	2,33	3,80	2,78	3,39	13,000	0,182
Urine Density	319,14	487,33	1,03	126,93	337,13	1,03	1085,500	0,906	127,15	356,73	1,03	111,27	324,10	1,03	87,000	0,279
Urine pH	6,03	0,67	6,00	5,74	0,76	5,50	700,000	0,045*	6,13	1,06	5,75	5,62	0,48	5,50	91,000	0,324

DISCUSSION

Vitamin D deficiency is increasing rapidly all over the world, especially in developing countries (12). It is stated that the prevalence varies between 40% and 100% especially in the North Asian and Middle Eastern regions (13). Vitamin D deficiency is also seen at high rates in our country. Deficiency occurs especially with the decrease in physical activity with advanced age, decrease in sun exposure, decrease in vitamin d synthesis and decrease in vitamin d absorption with age (14). In addition, studies have revealed that vitamin D deficiency is more common in women (15). Our study, consistent with the literature, showed that vitamin d deficiency occurs more frequently in women with age.

Vitamin D has hormone-like effects on the body, and its deficiency has been shown to affect the course of many diseases. Deficiency affects prognosis negatively and increases mortality rates, especially in diseases progressing with inflammatory process. It has been shown to affect the course of many chronic diseases, especially hypertension, cardiopulmonary diseases, valve failure, and diabetes (16-20).

The relationship between obesity and vitamin D deficiency is not clear. However, due to the fact that vitamin D is a fat-soluble vitamin, it is withdrawn from the circulation in obese individuals and creates a deficiency. Many studies have shown low vitamin D levels in obese individuals (21). In particular, a relationship was found between body composition measurements such as body mass index and fat ratio and vitamin d level (22). Contrary to the literature, our study did not find a correlation between vitamin d levels and body mass index. However, studies are showing that there is a correlation between body fat ratio and vitamin D levels. It has been shown that there is a negative correlation between body fat ratio and serum vitamin d levels in older ages. High fat ratios are associated with low vitamin d levels (23). Contrary to the literature, our study found the fat ratio to be statistically higher in those with vitamin d above 30 ng/ml.We examined the relationship level between anemia parameters and vitamin d levels. However, contrary to the studies, we could not find a significant relationship between vitamin d levels and Hgb, iron, and ferritin levels in our study. Many studies have shown that high vitamin D levels have a positive effect on Hgb synthesis and increase Hgb (24). In addition, it has been shown that it increases erythrocyte synthesis in the bone marrow, therefore, severe deficiency causes anemia by inhibiting erythropoiesis (25).

The relationship between vitamin D levels and inflammation markers is a subject that has been studied and studied recently (26,27). It has been shown that chronic inflammation plays a role in the etiology of cardiac diseases, cancers, and many other specific diseases (28,29). It has been shown that vitamin D is a very important hormone, especially in many immunological and inflammatory processes (30). Experimental studies have shown that such diseases can be treated with vitamin D replacement (31). For this reason, inflammatory markers that may correlate with vitamin D levels were examined. C-reactive protein (CRP), Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), erythrocyte sedimentation rate are among the methods that correlate with the prognosis of inflammatory diseases (32-34). One of the important points is that these methods are cheap, easily measurable, and reproducible. Again, one of the points supporting the relationship between vitamin D and inflammation is the presence of significant studies with endothelial dysfunction (35-38). In addition, there are studies revealing the relationship between NLR, PLR and endothelial dysfunction (39,40).

When evaluated within this framework, there is a significant relationship between vitamin D and inflammatory markers. However, our study did not find a significant relationship between the inflammatory marker and vitamin d levels.

Vitamin D has a very important effect on calcium and phosphorus hemostasis. It regulates this balance with its effect on the parathyroid gland, bones, intestines and kidneys (41). Vitamin D regulates serum calcium levels with a synergistic effect with parathormone (42). Vitamin D deficiency results in low calcium and phosphorus levels (43). In our study, there was a statistically significant difference in the levels of calcium (Ca) and phosphorus ($p<0.05$) (Table 4) between those with vitamin D above 30 and those below 20 in female patients. However, no significant difference was found in male patients (Table 4).

Limitations

The most important limitation of our study is that it is a single-center and retrospective study. In addition, the diet of the participants, their exposure to the sun, and not knowing whether they have recently used vitamin D are other factors limiting our study.

CONCLUSION

In our study, we found that there was a significant relationship between vitamin D levels, age, gender, platelet level, monocyte, MCV, neutrophil, protein, HDL, calcium and vitamin B12 levels. Along with the treatment and clinical examinations, it is necessary to monitor and evaluate the vitamin D levels of the patients, as well as hematological, biochemical, and endocrinological parameter changes.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Impact of selective serotonin receptor inhibitors on gastric histopathology in patients with depression

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ABSTRACT

Objective: Antidepressant medications such as Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin and Norepinephrine Reuptake Inhibitors (SNRI) are used in the psychopharmacological treatment for various types conditions. This study aimed to investigate whether SSRIs and SNRIs could reduce gastric intestinal metaplasia.

Material Methods: A total of 212 patients who underwent upper gastrointestinal endoscopy plus biopsy in our clinic and were using selective serotonin reuptake inhibitors and other potent serotonin reuptake inhibitors were included in the study. A control group was created with a total of 230 age and gender matched patients who underwent upper gastrointestinal endoscopy plus biopsy but had no SSRI or SNRI usage. Patients' endoscopic and pathologic findings were recorded retrospectively and compared between the groups.

Results: The patient group consisted of 180 (84.9%) male and 32 (15.1%) female patients, while the control group included 175 (76.1%) male and 55 (23.29%) female patients. There was a statistically significant difference between the groups in terms of gender (p=0.020). The rates of erythematous antral gastritis (p<0.001), peptic ulcer (p=0.019), erosive gastropathy (p=0.001) and duodenitis (p=0.002) were statistically significantly lower in the patient group compared to the control group. The rates of H.Pylori(p=0.002), intestinal metaplasia (p=0.013), neutrophil activity (acute inflammation) (p<0.001) and chronic inflammation (p<0.001) were lower in the case group compared to the control group.

Conclusion: SSRIs/SNRIs may potentially be used in treating gastrointestinal inflammation and metaplasia. However, further prospective randomised studies with larger series are needed to support our findings.

Keywords: SSRI, SNRI, gastrointestinal tract, H.pylori, inflammation, intestinal metaplasia

INTRODUCTION

Antidepressant medications such as Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin and Norepinephrine Reuptake Inhibitors (SNRI) are used in the psychopharmacological treatment for various types of chronic pain, including tension-type and migraine-type headaches, neuropathic pain, fibromyalgia, low back pain or osteoarthritis pain, mood disorders such as major depressive disorder, anxiety disorders such as social anxiety disorder, and sleep disorders such as insomnia (1). SSRIs and SNRIs are the first-line pharmacotherapy for most patients with depression because they are effective and generally better tolerated when compared to other antidepressants (2).

Antidepressant prescription rates are increasing (3), and second-generation antidepressants, including SSRIs and SNRIs are among the most prescribed antidepressants (4). Therefore, effects and side effects of these drugs should be further investigated.

SSRIs and SNRIs are known to increase the amount of serotonin in the central nervous system by blocking or delaying the serotonin reuptake by the nerves. SSRIs and SNRs selectively increase the transmission of serotonin and noradrenaline by inhibiting only serotonin and also noradrenaline reuptake, respectively, resulting in a decrease in the number and sensitivity of postsynaptic receptors (1).

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SSRIs and SNRIs have various side effects on the gastrointestinal system. Serotonin is present in the gastrointestinal mucosa enterochromaffin cells and within neurons in the enteric nervous system. As an enteric neurotransmitter, serotonin initiates peristaltic reflexes, inhibits gastric acid secretion, stimulates the production and release of gastric and colonic mucus, and influences gastrointestinal blood flow (5). Therefore, some of the most frequently reported gastrointestinal system-related effects, such as nausea, vomiting, diarrhoea, constipation, dyspepsia, and abdominal pain, related to increased serotonin may occur, especially at the beginning of the treatment with SSRIs and SNRIs (4).

Either enteric or colonic mucosal immigration characterises gastric intestinal metaplasia (GIM) into the gastric mucosa (6). GIM is prevalent in subjects who live in Asia and could lead to gastric carcinoma at a rate of almost 1% annually. GIM is considered a precancerous lesion, increasing the risk of developing gastric cancer by 6-fold (7). Characteristics of the at-risk population for developing GIM include white race, obesity, and gastroesophageal reflux disease (GER) (8). Factors such as insufficient esophageal peristalsis, delayed gastric emptying and antroduodenal motility disorders and increased acid secretion play a role in the pathophysiology of GER (9).

This study aimed to investigate whether SSRIs and SNRIs could reduce gastric intestinal plasia.

MATERIAL and METHODs

Before the beginning, the study protocol was approved by the local ethics committee of our hospital with January 2019 dated and 2019/1/9 numbered decision.. Informed consent was waived because of the retrospective nature of the study. This study was conducted in line with the ethical principles of the declaration of Helsinki.

A total of 212 patients who underwent upper gastrointestinal endoscopy plus biopsy in our clinic and were using selective serotonin reuptake inhibitors and other potent serotonin reuptake inhibitors between 2017 and 2019 were included in the study. Patients who were confirmed to have been using antidepressants regularly for at least 6 months by the national health information network (MEDULA) pharmacy database were included in the study. Patients with hepatic and renal failure, those with rheumatic disease, diagnosis of malignancy, patients with primary immune insufficiency, those using immunosuppressive and aspirin-antithrombotic drugs, patients who underwent gastric surgery and those who had received H. pylori eradication therapy previously were excluded from the study.

Patients' demographic data such as age and gender, endoscopic and histopathologic findings were recorded. In addition, duration of SSRI/SNRI usage and the drugs used were recorded. Endoscopic findings included the presence of esophagitis, erythematous antral gastritis, erythematous pangastritis, gastric polyps, peptic ulcer, gland polyps, erosive gastropathy and duodenitis. The histopathological results evaluated according to Sydney classification were included in the study. Histopathological findings included the presence of H.pylori, intestinal metaplasia, (focal, complete, and incomplete), gastric dysplasia, gastric neoplasia, neutrophil activity (acute inflammation), and chronic inflammation. Data used in this study was obtained from the electronic database of the hospital and patient files.

A control group was created with a total of 230, age and gender-matched patients who underwent upper gastrointestinal endoscopy plus biopsy, but who had no SSRI or SNRI usage.

Statistical Analysis

Data obtained in this study were statistically analyzed using the SPSS version 22.0 (Statistical Package for Social Sciences, IBM Inc., Armonk, NY, USA) software. Among the descriptive statistics, categorical variables are expressed as number and percentage, while continuous variables are given as mean ± standard deviation. The normality of the continuous variables was evaluated using the Kolmogorov-Smirnov/Shapiro-Wilk tests and visual (histogram and probability charts). Normally distributed variables were compared with the independent t-test and non-normally variables with the Mann-Whitney test between the two groups. Categorical variables were compared using Pearson's Chi-square ($\chi 2$) test. In Pearson Chi-square analysis, results are presented with Odds Ratio (OR) and 95% Confidence interval. $p<0.05$ values were considered statistically significant.

RESULTs

This study included 212 cases who had undergone EGD (esophagogastroduodenoscopy) and biopsy due to dyspeptic complaints and had been using the regular antidepressive treatment for at least 6 months, and a control group of 230 people with similar age and gender characteristics. The patient group consisted of 180 (84.9%) male and 32 (15.1%) female patients, while the control group included 175 (76.1%) male and 55 (23.29%) female patients. There was a statistically significant difference between the groups in terms of gender (p=0.020). The most commonly used SSRI was Essitalopram, followed by Sertraline and Paroxetine. Distribution of the patients according to the active ingredients of the antidepressant drugs is given in Table 1 and Figure 1.

Table 1. Demographic data on the use of antidepressants in the patient group

	(n)	(%)
Duration of drug usage		
< 1 year	77	36.3
≥ 1 year	135	63.7
Active ingredient		
Escitalopram-SSRI	42	19.8
Sertraline-SSRI	41	19.3
Paroxetine-SSRI	25	11.8
Venlafaxine-SNRI	22	10.4
Duloxetine-SNRI	18	8.5
Fluoxetine-SSRI	17	8.0
Citalopram-SSRI	10	4.7
Trazodone-YELLOW	6	2.8
Milnacipran-SNRI	2	0.9
Fluvoxamine-SSRI	1	0.5
Mirtazapine-NASSA	1	0.5
Unknown	27	12.7

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Considering the endoscopic findings; the rates of erythematous antral gastritis (p<0.001), peptic ulcer (p=0.019), erosive gastropathy (p=0.001), and duodenitis (p=0.002) were statistically significantly lower in the patient group compared to the control group. Accordingly, the probability of erythematous antral gastritis increased by 2.5 folds, peptic ulcer by 3.6 folds, erosive gastropathy by 3.4 folds and duodenitis by 1 fold.The relationship between antidepressant usage and "Endoscopic Findings" is given in Table 2 and Figure 2.

Considering the pathologic findings; the rates of H.Pylori(p=0.002), intestinal metaplazi (p=0.013), neutrophil activity (acute inflammation) (p<0.001) and chronic inflammation (p<0.001) were lower in the case group compared to the control group. Accordingly, the probability of H.Pylori increased by 1.8 folds, intestinal plasia by 1.8 folds, neutrophil activity by 2.1 folds and chronic activity by 7 folds. The relationship between antidepressant usage and "Pathologic Findings" is given in Table 3 and Figure 2.

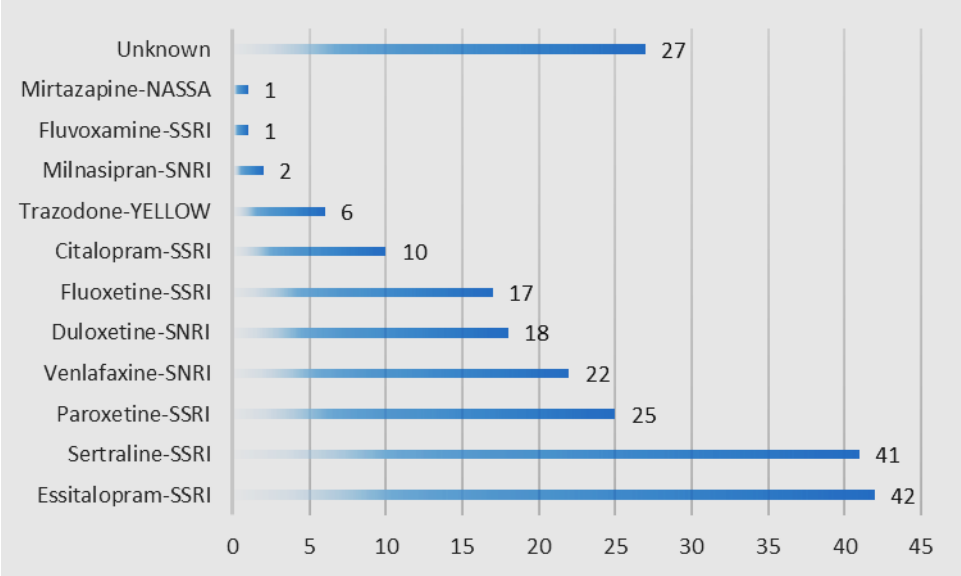

Figure 1. Distribution of active ingredients of the drugs used

Table 2. Endoscopic findings

	Case (n:212)	Control (n:230)	p	AOR	95%CI
Esophagitis					
Yes	58 (27.4)	70 (30.4)	0.476[b]		
No	154 (72.6)	160 (69.6)			
Erythematous antral gastritis					
Yes	70 (33.0)	128 (55.7)	**<0.001[b]**	**2.544**	**1.730-3.745**
No	142 (60.3)	102 (44.3)			
Erythematous Pangastritis					
Yes	52 (24.5)	63 (27.4)	0.493[b]		
No	160 (75.5)	167 (72.6)			
Gastric polyps					
Yes	9 (4.2)	5 (2.2)	0.214[b]		
No	203 (95.8)	225 (97.8)			
Peptic ulcer					
Yes	4 (1.9)	15 (6.5)	**0.019[c]**	**3.623**	**1.111- 3.623**
No	133 (97.8)	368 (95.2)			
Gland polyps					
Yes	7 (3.3)	5 (2.2)	0.466[b]		
No	205 (96.7)	225 (97.8)			
Erosive gastropathy					
Yes	9 (4.2)	30 (13.0)	**0.001[b]**	**3.378**	**1.567-7.692**
No	203 (95.8)	200 (87.0)			
Duodenitis					
Yes	0 (0)	10 (4.3)	**0.002[c]**	**1.044**	**1.017-1.074**
No	212 (100)	220 (95.7)			

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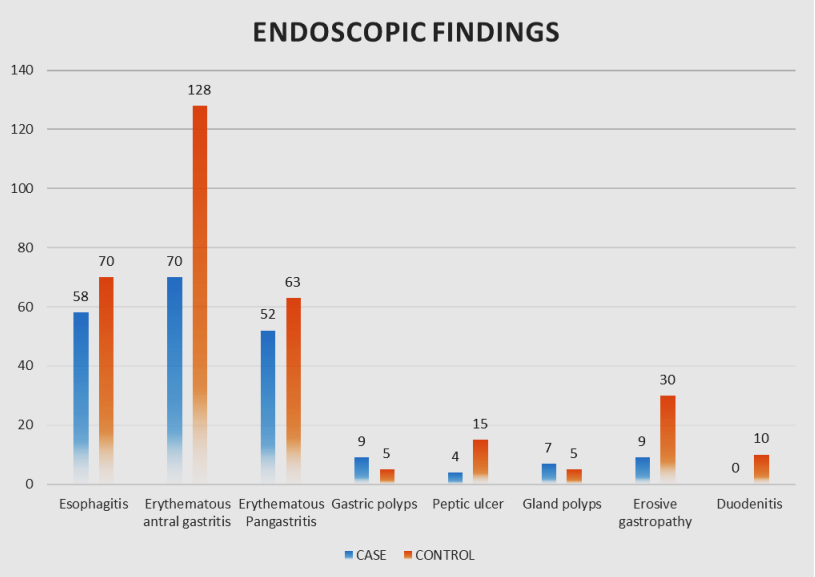

Figure 2. Endoscopic findings of the groups

Table 3. Pathologic findings

	Case	Control	p	AOR	95% CI
H.Pylori	n (%)	n (%)			
Yes	90 (42,2)	132 (57,4)	**0,002**[a]	**1,824**	**1,251-2.666**
No	122 (57,5)	98 (42,6)			
Intestinal metaplasia					
Yes	34 (16,0)	59 (25,7)	**0,013**[a]	**1,805**	**1,127-2,890**
No	178 (84,0)	171 (74,3)			
IM focal					
Yes	7 (3,3)	8(3,5)	0,919[a]		
No	205 (96,7)	222 (96,5)			
IM Complete					
Yes	6 (2,8)	3 (1,4)	0,331[b]		
No	206 (97,2)	217 (98,6)			
IM Incomplete					
Yes	0 (0,0)	1 (0,5)	1[b]		
No	212 (100)	218 (99,5)			
Atrophic gastritis					
Yes	40 (18,9)	50 (21,7)	0,454[a]		
No	172 (81,1)	180 (78, 3)			
Gastric dysplasia					
Yes	0 (0)	5 (2,2)	0,062[b]		
No	212 (100)	225 (97,8)			
Gastric neoplasia					
Yes	0 (0)	1 (0,2)	1[b]		
No	212 (100)	229 (99,7)			
Neutrophil activity (acute inflammation)					
Yes	86 (40,6)	136 (59,1)	**<0,001**[a]	**2,118**	**1,449-3,095**
No	69 (50,7)	147 (37,7)			
Chronic Inflammation					
Yes	139 (65, 6)	214 (93,0)	**<0,001**[a]	**7,042**	**12,50-3,921**
No	73 (34,4)	16 (7,0)			

DISCUSSION

In the present study, we investigated the effects of SSRIs/SNRIs on gastric histopathology in patients with depression for the first time in the literature. We found that, SSRIs/SNRIs may decrease the risk of developing gastrointestinal metaplasia.

In the brain, selective serotonin reuptake inhibitors (SSRIs) are known to downregulate serotonin (5-hydroxytryptamine [5HT]) receptors and used to treat depressive diseases amid elevated serotonin levels (10). Enterochromaffin cells in the gastrointestinal system are the major source of 5HT. After being produced and released into the GI tract, 5HT is captured by platelets and metabolized by the liver or pulmonary vascular endothelium (11).

Serotonin has key roles in the central nervous system, including brain development, sleep, mood, and appetite, and these effects are also closely related to the gut system, also called gut-brain axis (12). At another perspective, serotonin-secreted enterochromaffin (EC) cells in the intestinal mucosa have reportedly determined a number of gastrointestinal functions including peristalsis, secretion, vasodilation, and perception of pain or nausea. In our study, erythematous antral gastritis, peptic ulcers, erosive gastropathy and duodenitis were significantly lower in the patients who received SSRIs/SNRIs compared to the control group, suggesting the role of serotonin in endoscopic findings of patients with depression.

A recent study involving patients who had been treated both aspirin and SSRIs amid their depressive diseases showed that inhibition of serotonin reuptake into neurons and platelets caused a damage on platelet accumulation (13). It has also been reported that SSRI users have experienced more gastrointestinal bleeding attacks due to increased gastric acid secretion and the inhibition of serotonin's access into platelets (14). Dall et al. suggested an association between SSRIs and uncomplicated peptic ulcers (15).

On the other hand, in a study by Laursen et al., the use of selective serotonin receptor inhibitors (SSRIs) was not associated with increased risk of endoscopy-refractory bleeding, rebleeding or mortality in peptic ulcer bleeding (16). Similarly, in our study, we did not observe endoscopy-refractory bleeding, and the rate of peptic ulcers was low in the patients receiving SSRIs.

Erythematous pangastritis and antral nodularity on endoscopic findings had a correlation with H. pylori positivity (17). In the present study, the rate of H. pylori was lower in the patients receiving SSRIs/SNRIs whose erythematous pangastritis and antral nodularity was also lower compared to the control group, consistent with the literature.

In the present study, considering pathological findings; the rates of H.Pylori ($p=0.002$), intestinal metaplazi ($p=0.013$), neutrophil activity (acute inflammation) ($p<0.001$), and chronic inflammation ($p<0.001$) were lower in the case group compared to the control group. The probability of H.Pylori increased by 1.8 folds, intestinal plasia by 1.8 folds, neutrophil activity by 2.1 folds, and chronic activity by 7 folds in patients with gastrointestinal pathologies who have not been receiving SSRIs/SNRIs.

Dall et al. claimed that H. pylori infection increases the risk of SSRI-related serious upper gastrointestinal bleeding (UGB) (15). Our study did not observe an association between H.pylori and UGB.

GIM is an important precursor lesion in the pathway to gastric cancer (GC), and regional prevalence of GIM correlates closely with the incidence of GC worldwide (18). Gastrointestinal metaplasia (GIM) results from diverted differentiation of gastric stem cells towards cells of the small intestine or colonic phenotypes.

The presence of mucin-containing, intestinal-type, goblet cells, absorptive cells and Paneth cells characterizes it. Risk factors of GIM have been reported as the presence of H. pylori infection, older ages, smoking history, strong spicy food, occupation status, and IL10-592 C/A (19). In our study, the lower rate of H.pylori was in parallel with the low rate of GIM in patients receiving SSRIs/SNRIs. In addition, low rates of acute and chronic inflammation in the patient group receiving SSRIs/SNRIs may explain the low rate of GIM.

Our findings indicate lower rates of H.pylori, acute and chronic inflammation and GIM, in the patients receiving SSRIs/SNRIs, suggesting that these drugs may have the potential for treatment of these conditions. However, since there is no study regarding effects of the use of these agents on gastric histopathology, we could not compare our results exactly.

Study Limitations

Main limitations of this study include its retrospective nature and being conducted in a single center. However, the number of patients is relatively large and this study is the first to investigate the effects of antidepressants on gastrointestinal histopathology.

CONCLUSION

The rates of erythematous antral gastritis, peptic ulcer, erosive gastropathy, duodenitis, H.Pylori, gastrointestinal metaplazi, neutrophil activity (acute inflammation) and chronic inflammation were significantly lower in patients receiving SSRIs/SNRIs compared to those who have not been using these drugs, suggesting that these agents may have the potential for using in the treatment of gastrointestinal inflammation and metaplasia. However, further prospective randomised studies with larger series are needed to support our findings.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical

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Prognostic value of the prognostic nutritional index in severe COVID-19 infection

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ABSTRACT

Objective: Nutritional status plays an important role in defense against infection. This study aimed to investigate the effect of the prognostic nutritional index (PNI), which consists of inflammation and nutritional markers, on prognosis and survival in patients with severe COVID-19 infection.

Material and Methods: Data were retrospectively collected by screening the files of 146 patients diagnosed with COVID-19 infection in 2020 and 2021. The PNI values of the patients were calculated using the obtained data. The cut-off value of PNI was determined with the receiver operating characteristic analysis. Multivariate and univariate analyses were undertaken to evaluate the prognostic value of PNI and its relationship with clinical features and overall survival (OS) in patients with severe COVID-19 infection.

Results: The study included a total of 146 patients, of whom 83 (60%) were male, and 55 (39.9%) were female. The mean age was 62 years. The cut-off value of PNI was 45. PNI was found to be associated with prognosis in both univariate and multivariate analyses. Survival and prognosis were statistically significantly better in the group with a PNI higher than the cut-off value (P<0.005).

Conclusion: PNI was determined to have independent prognostic value and predict OS in severe COVID-19 infection. The results showed that COVID-19 infection was more severe and had a worse prognosis in the patients with a low PNI (<45). Based on the measurement of simple, inexpensive, and easily available biomarkers, PNI can be beneficial in clinical practice.

Keywords: COVID-19, PNI, Prognosis

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2. The clinical presentation of COVID-19 varies from the asymptomatic carriage or mild acute respiratory disease to severe pneumonia, acute respiratory failure (ARDS), and multiorgan failure (1-3). COVID-19 infection is associated with immune dysregulation, and hyperinflammation. ARDS develops in approximately 25% of severe COVID-19 cases. In those developing ARDS, the rate of mortality is 60%. Risk factors for the development of severe COVID-19 include male gender, age > 65 years, presence of diabetes mellitus, and history of cardiovascular or respiratory disease (4). Severe COVID-19 infection presents with the excessive secretion of interleukin (IL)-6, IL-2, IL-7, IL-10, granulocyte colony-stimulating factor, interferon-γ-inducible protein, monocyte chemoattractant protein, macrophage inflammatory protein 1 alpha, and tumor necrosis factor-alpha.

The release of these inflammatory cytokines leads to the development of an uncontrollable inflammatory response, ARDS, and multi-organ failure. There is also an increase in lymphocytes and monocytes in the pulmonary vascular bed, endotheliitis, thrombosis, and inflammation due to angiogenesis (5-7). Tocilizumab is a monoclonal anti-IL-6 receptor-alpha blocking antibody used in patients with bilateral severe lung involvement and high IL-6 levels. Tocilizumab corrects impaired alveolo-capillary dysfunction by reducing the cytokine storm, thereby increasing oxygenation and preventing progression to pulmonary fibrosis. Clinically, mechanical ventilation requirement decreases, and lung findings improve (Figure 1) (8-11).

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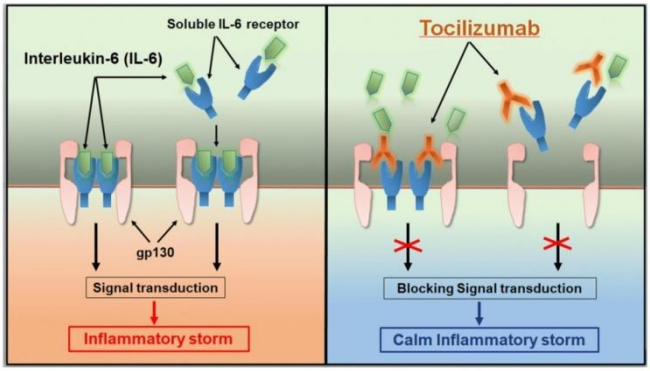
In severe COVID-19 infection, individualized prognostic factors are needed to determine risk and predict survival and recovery clinically. The progression and prognosis of these patients are correlated with their inflammatory and nutritional status. The prognostic nutritional index (PNI) indicates nutritional, inflammatory, and immunological status. In many malignant diseases, systemic inflammation is a prognostic factor that is associated with malnutrition (12,13). In this study, we aimed to investigate the predictive and prognostic value of PNI in patients prescribed tocilizumab diagnosed with severe COVID 19 infection.

Figure 1: Mechanism of action of tocilizumab (8-11)

(https://translationalmedicine.biomedcentral.com/articles/10.1186/s12967-020-02339-3/figures/2)



MATERIAL and METHODs

The study included patients who presented to the Internal Medicine Clinic of Yuzuncu Yil University from March 1, 2020, through September 31, 2021, with any of the complaints of fever, cough, loss of taste and smell, myalgia, shortness of breath and were diagnosed with COVID-19 based on the polymerase chain reaction test positivity and/or thorax computed tomography findings. The files of a total of 146 patients were retrospectively reviewed. Age, gender, complete blood count parameters (leukocyte, hemoglobin, and lymphocyte), alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), albumin, urea, creatinine were recorded from the hospital registration system. PNI was calculated based on the data obtained. Patients with a history of malignancy, other infections, or chronic inflammatory disease were excluded from the study. The patients were divided into two groups, with and without tocilizumab treatment. Both groups were compared in terms of clinical findings.

Onodera's PNI was calculated as follows: 10 x serum albumin level (g/dL) + (0.005 × lymphocyte count in peripheral blood (×109/L) (14).

Overall survival (OS) was defined as the time from the diagnosis of COVID-19 to death. OS was evaluated with multivariate and univariate analyses.

Statistical analysis: Descriptive statistics were presented as numbers and percentages for categorical variables, and median (minimum-maximum) and mean ± standard deviation values for numerical variables. The cut-off value of PNI was analyzed using the receiver operating characteristics (ROC) curve analysis. Visual (histogram) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) were used to determine the distribution of variables. Normally distributed parameters were compared with Student's t-test and those without a normal distribution were compared with the Mann-Whitney U test. Differences between independent groups were compared with either the chi-square or Fisher's exact test. Survival curves were obtained using the Kaplan-Meier analysis. The Statistical Package for the Social Sciences (SPSS) v. 21 and R softwares were used for statistical analyses. $P < 0.05$ was considered statistically significant.

RESULTs

The study included a total of 146 patients, of whom 83 (60%) were male, and 55 (39.9%) were female. The mean age was 62 years. The median follow-up time was two months. Of the patients, 103 (70%) were hospitalized and given combination therapy with favipiravir and prednisolone. Tocilizumab treatment was initiated in 43 (30%) patients who did not respond to the combined therapy. Leukocyte count was significantly lower in the tocilizumab group than in the group not treated with tocilizumab ($p < 0.05$). The mean lymphocyte count was significantly higher, and the platelet count was significantly lower in the tocilizumab group compared to the control group ($p < 0.05$). The blood glucose level was also significantly higher in the tocilizumab group than in the control group ($p < 0.05$). The AST level was significantly higher in the control group compared to the tocilizumab group ($p < 0.05$), but the ALT levels did not significantly differ. The CRP level was significantly higher in the tocilizumab group than in the control group ($p < 0.05$). The mean length of hospital stay was 20 days in the patients receiving tocilizumab and 7 days in the control group, indicating statistically significantly longer hospitalization in the former ($p < 0.05$). The cut-off value of PNI was determined as 45. PNI was associated with prognosis according to both the univariate and multivariate analyses. Survival and prognosis were statistically significantly better in the group with a PNI above the cut-off value ($p < 0.005$) (Table 1).

Table 1: Demographic and clinical data of the patients

Parameter		
Age, median (min-max)		62 (28-83)
Gender	Male	83 (60%)
	Female	55 (39.9%)
PNI, median (min-max)		45 (31.5-82)
Lymphocyte (/µL), median (min-max)		1,5 (0.08-7.5)
Hemoglobin (g/dl), mean ± SD		12.2 ± 1.5
Albumin (g/dl), mean ± SD		3.7 (2.6-5)
Favipiravir-steroid combined therapy		103 (70%)
Tocilizumab therapy		43 (30%)
Length of hospital stay	Tocilizumab (+)	20 days
	Kontrol (Tocilizumab (-))	7 days

DISCUSSION

In the literature, many studies investigate the prognostic value of inflammatory and nutritional parameters in many malignant or non-malignant diseases. Based on this idea, we conducted the current study to determine whether PNI, which is both a nutritional and inflammatory marker, had prognostic value and affected survival in patients with severe COVID-19 infection. We determined that a low PNI was an independent factor of poor prognosis in severe COVID-19 infection. A healthy diet is necessary for the protection against infections and formation of immune response. Individuals with severe COVID-19 infection develop malnutrition due to severe inflammation and anorexia. The European Society for Clinical Nutrition and Metabolism emphasizes that the risk of malnutrition should be identified early in those infected with COVID-19 (15,16). Liu et al. conducted a retrospective study to evaluate nutritional risks and the correlation of COVID-19 with clinical outcomes among elderly COVID-19 cases aged over 65 years. The authors showed that the Nutrition Risk Screening-2002, Mini Nutritional Assessment Short-Form, and nutritional risk index were useful and practical for screening nutritional risk in patients with COVID-19 (17). Inflammation and nutritional status significantly affect the progression and survival of inflammatory diseases (12). Local inflammation is indicative of the systemic inflammatory response. Immunomodulatory cytokines and systemic inflammatory markers (neutrophils, lymphocytes, IL-1, 6, 8, and 9, and tumor necrosis factor-alpha) in the inflammation site play an important role in the progression of infection. High metabolic rate, anorexia, and hypoalbuminemia seen in the presence of infection cause malnutrition, which then leads to the impairment of cytokine response and immune system activation. Peripheral blood cells are an indicator of inflammatory and immune response against tumors and have independent prognostic significance (16-18). However, the underlying mechanism of the relationship between PNI and the severity of COVID-19 remains unclear. PNI is a combination of peripheral blood lymphocyte count and albumin concentration and correlates nutritional status with immune response. Nutritional status is known to play a critical role in the immune response. Nutritional deficiency is associated with immunodeficiency, which manifests as the disruption of cell-mediated immunity, phagocyte function, complement system, and cytokine production (19,20). The serum albumin level is generally an indicator of malnutrition. Beside malnutrition, other pathological acute or chronic conditions presenting with inflammation (liver failure, nephrotic syndrome, and protein-losing enteropathy) decrease the serum albumin levels. Some proinflammatory cytokines also reduce albumin synthesis. Peripheral lymphocytes are also known to show the immunological and nutritional status of individuals. Therefore, PNI, calculated based on serum albumin and lymphocyte values, is more significant in terms of prognosis. Recent studies have shown that a low PNI is associated with a poor prognosis in many gastrointestinal system malignancies. In the current study, we obtained similar results. In a study by Nalbant et al., PNI was shown to be an independent prognostic factor in patients with severe COVID-19 infection followed up in the intensive care unit (21). In another study, Hu et al. reported that malnutrition was associated with severe COVID-19 infection, and patients with a low PNI had a worse prognosis (22). Wang et al. detected a relationship between PNI and mortality due to COVID-19 infection (23). In a retrospective meta-analysis of 13 studies, Hung et al. found PNI to be a predictive factor of disease severity and mortality in COVID-19 infection (24). In the literature, the cut-off value of PNI has been reported in a wide range from 40 to 55, and there is no standard threshold (25).The cut-off value of PNI varies depending on the number of patients and differences in the technical methods used.There are some limitations to our study. It had a retrospective and single-center design, which also resulted in a small sample size. In addition, the nutritional status of the patients at the time of admission could not be evaluated.

CONCLUSION

Nutrition and inflammatory markers have independent prognostic significance in COVID-19 infection. PNI is an independent prognostic factor of severe COVID-19 infection. The results of this study showed that COVID-19 infection had a more severe and clinically worse prognosis in those with a low PNI (<45). Based on the measurement of simple, inexpensive, and easily available biomarkers, PNI can be beneficial in clinical practice. Nutritional status should be improved by providing nutritional support for patients before treatment to increase the quality of life, life expectancy, and prognosis of patients during the follow-up. There are very few studies in the literature investigating the prognostic significance of PNI in COVID-19 infection. Therefore, we consider that the results of this study are important and will contribute to the literature.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Non-Invasive Clinical Research Ethics Committee of Yuzuncu Yil University Faculty of Medicine approved the study (decision date: 16/10/2020, number: 2020/07-11).

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Assessment of endothelial dysfunction and inflammation in type 2 diabetic postmenopausal women

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ABSTRACT

Objective: Vascular complications in type 2 diabetes mellitus are an important cause of morbidity and mortality. Also, endothelial dysfunction arises with vascular ageing during the postmenopausal period. Our objective in this study was to evaluate inflammation and endothelial function parameters and their possible diagnostic roles in type 2 diabetic postmenopausal patients.

Material and Methods: The study was conducted on four groups, including type 2 diabetic premenopausal (n:20), non-diabetic premenopausal (n:20), type 2 diabetic postmenopausal (n:20), and non-diabetic postmenopausal subjects (n:20). Serum endothelin-1 (ET-1), endothelial nitric oxide synthetase (eNOS), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and chitinase-3-like protein 1 (YKL-40) levels were determined as inflammatory and endothelial function markers using ELISA kits.

Results: Serum ET-1, IL-6, and YKL-40 levels were higher in the type 2 diabetic postmenopausal group compared to the non-diabetic premenopausal group ($p<0.01$, $p<0.05$, and $p<0.01$, respectively). ET-1, IL-6, and YKL-40 levels were higher in the type 2 diabetic postmenopausal group compared to the non-diabetic postmenopausal group ($p<0.001$, $p<0.05$, and $p<0.01$ respectively). ROC analysis revealed serum ET-1 (AUC 0.933, sensitivity 87.5%, specificity 85.7%), IL-6 (AUC 0.812, sensitivity 56.3%, specificity 92.8%), and YKL-40 (AUC 0.880, sensitivity 81.2%, specificity 92.8%), as good diagnostic parameters, especially in the type 2 diabetic premenopausal vs. non-diabetic premenopausal cohorts.

Conclusion: Serum ET-1, IL-6, and YKL-40 levels were at the highest levels in the 2 diabetic postmenopausal group, and the increase in these markers was remarkable in diabetes compared with menopausal periods. Also, ET-1, IL-6, and YKL-40 were good diagnostic parameters for detecting endothelial function and inflammation in type 2 diabetic postmenopausal and non-diabetic premenopausal cohorts.

Keywords: Type 2 diabetes mellitus; menopause; endothelial function; inflammation.

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INTRODUCTION

Menopause is a normal physiologic event reflecting ovarian follicular function loss, oestrogen and progesterone levels decline, amenorrhoea continues for a year, and the reproduction period ends (1). Besides increasing somatic and psychological symptoms in the menopausal period, vascular ageing becomes faster. Arterial stiffening and endothelial dysfunction form with vascular ageing (2).

Type 2 diabetes mellitus is an important progressive disease with a prevalence increasing with age. Endothelial-dysfunction-related micro-and macrovascular complications occur in type 2 diabetes mellitus, which is an endocrinal metabolism disease characterised by chronic inflammation (3). Endothelial dysfunction is characterised by three main metabolic disorders in type 2 diabetes. These are hyperlipidaemia, early hyperinsulinemia, and pancreatic cell deficiency causing hyperglycaemia after hyperinsulinemia (4).

Endothelial tissue dysfunction is related to the imbalance of vasoconstrictor and vasodilator molecules secreted by the endothelium. Endothelin-1 (ET-1) is the strongest vasoconstrictor molecule functioning in the provision of molecule exchange order of endothelial tissue (5). Endothelium-derived synthesised nitric oxide (NO) takes functions in vascular tone regulation, leukocyte adhesion, aggregation of thrombocytes, and proliferation of vascular smooth muscles. NO synthesis from L-arginine and oxygen in endothelial cells is conducted through the endothelial nitric oxide synthase (eNOS) enzyme (6).

The development of atherosclerosis among vascular pathologies depends on the changing behaviour of endothelial cells and vascular smooth muscle cells. Inflammation is an important risk factor in the development of atherosclerosis (7). Tumor necrosis factor α (TNF-α) is known to be a potent promoter of inflammation, as well as many normal physiological functions in homeostasis. It is secreted in the acute phase of many inflammatory reactions and is produced in macrophage, endothelial and adipose tissues. It has been reported that TNF-α is an important proinflammatory cytokine, is associated with recurrent coronary artery occlusions. (8).

Interleukin-6 (IL-6) is mostly regarded as a pro-inflammatory cytokine, but it also has many regenerative or anti-inflammatory activities. As a multifunctional cytokine, IL-6 was shown to increase the secretion of endothelial-derived adhesion structures. It is an important independent molecule that is considered effective in risk determination in cardiovascular events (3, 9).

YKL-40 protein, known as chitinase-3-like protein 1 (CHI3L1) is secreted by vascular smooth muscle and macrophage cells, and stimulated for natural immune response realisation. It has been reported that the It has been reported that the YKL-40 may play a role in endothelial dysfunction and atherosclerosis (3).

Considering this information, we reviewed the literature and saw that there were studies reporting inflammation and endothelial function in type 2 diabetes mellitus, and in the menopause period, but studies evaluating the menopausal period and type 2 diabetes mellitus were limited. Also, the mechanism of vascular pathogenesis forming in this period is not completely clear yet. Thus, our objective in this study was to investigate serum ET-1, eNOS, IL-6, TNF-α, and YKL-40 levels in pre and post-menopausal women with and without type 2 diabetes. Also, we evaluated the diagnostic performance of these markers for detecting inflammation and endothelial function in non-diabetic, and subjects with diabetes in pre- and postmenopausal status.

MATERIAL and METHODs

Case selection: This study was conducted on a total of 80 individuals including postmenopausal type 2 diabetic (n:20), postmenopausal non-diabetic (n:20), premenopausal type 2 diabetic (n:20), premenopausal non-diabetic (n:20) individuals, who applied to Suluntepe Family Health Center. The present study was approved by the Istanbul University-Cerrahpasa Medical Faculty Ethics Committee (approval number: 332891/2017) and was performed in accordance with The Declaration of Helsinki. All participants gave written informed consent.

The individuals with amenorrhoea constituted postmenopausal groups. Type 2 diabetic patients were selected according to the Endocrinology and Metabolism Society's Diagnosis, Treatment, and Follow-up Guidelines for Diabetes Mellitus and Complications. During the last six months, the participants have not used any hormonal contraceptives, also during the last four weeks, they have not used antihypertensive, lipid-lowering, and anti-inflammatory drugs. Moreover, they did not undergo hysterectomy or oophorectomy operation and did not have any chronic diseases.

Sample collection: Five milliliters of venous blood samples were taken after 12 h of fasting from all individuals. Blood samples were centrifuged at 3000 x g for 10 min, and the obtained serum samples were kept at −80°C until analysis. ET-1, eNOS, IL-6, TNF-α, and YKL-40 levels were determined in serum samples. Glucose, HbA1c, insulin, and insulin resistance levels were routine markers examined in Istanbul Public Health Laboratory. Homeostatic Model Assessment Score (HOMA) was used to determine insulin resistance (1).

Measurement of endothelial function and proinflammatory markers: The levels of ET-1, eNOS, IL-6, TNF-α, and YKL-40 in serum samples were quantified according to the manufacturer's instructions and guidelines using ELISA kits (Boster Bio, Pleasanton, CA, USA, for all).

Statistical evaluation: Data were presented as mean ± the standard deviation (SD). After checking for normality assumptions with the Shapiro-Wilk normality test, statistical significance was determined using one-way ANOVA followed by Holm-Sidak's multiple comparison test or Kruskal-Wallis test with Dunn's multiple comparisons. Receiver operating characteristic (ROC) analysis and area under the ROC curve (AUC) was used the determination of the diagnostic performance of inflammation and endothelial function markers. Statistical Package for the Social Sciences-SPSS 21.0 for Windows (SPSS Inc, Chicago, IL, USA) was used for calculations. $p<0.05$ was considered to indicate a statistically significant difference.

RESULTs

Demographic Data

Age, body mass index (BMI), duration of menopause, duration of diabetes, systolic blood pressure (SBP), diastolic blood pressure (DBP), glucose, HbA1c, insulin, and insulin resistance values of all groups were presented in Table 1 as the mean ± SD. No significant differences were found in age and BMI values between the type 2 diabetic premenopausal and the non-diabetic premenopausal groups. Age values were higher in the non-diabetic postmenopausal than the non-diabetic premenopausal group ($p<0.001$). Also, the age results were increased in the non-diabetic postmenopausal group compared with the type 2 diabetic premenopausal group ($p<0.01$). The values of the type 2 diabetic postmenopausal group were increased than the non-diabetic, and type 2 diabetic premenopausal groups ($p<0.001$, for both).

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SBP, DBP, glucose, HbA1c, insulin, and insulin resistance results were higher in the type 2 diabetic premenopausal group than the non-diabetic premenopausal group ($p<0.01$, $p<0.05$, $p<0.001$, $p<0.001$, $p<0.01$, and $p<0.001$, respectively). SBP, glucose, HbA1c, insulin, and insulin resistance results were higher in the type 2 diabetic postmenopausal group than the non-diabetic postmenopausal group ($p<0.01$, $p<0.001$, $p<0.001$, $p<0.01$, and $p<0.001$, respectively). Insulin, and insulin resistance levels increased in the non-diabetic postmenopausal group compared with the non-diabetic premenopausal group ($p<0.05$, for both). The glucose, HbA1c, and insulin resistance values of the type 2 diabetic postmenopausal group were increased than the non-diabetic premenopausal group ($p<0.001$, $p<0.001$, and $p<0.05$, respectively) (**Table 1**).

Comparison of inflammation and endothelial function markers

Serum ET-1 levels were found significantly higher in the type 2 diabetic premenopausal group compared to the non-diabetic premenopausal group and the non-diabetic premenopausal group ($p<0.05$, and $p<0.01$, respectively). ET-1, IL-6, and YKL-40 values were increased in the type 2 diabetic premenopausal group than the non-diabetic premenopausal group, although the differences were not significant. ET-1, IL-6, and YKL-40 values were found to be significantly higher in the type 2 diabetic postmenopausal group compared with the non-diabetic postmenopausal group ($p<0.001$, $p<0.05$, $p<0.01$, respectively). ET-1, IL-6, and YKL-40 values were higher in the type 2 diabetic postmenopausal group compared with the non-diabetic premenopausal group ($p<0.01$, $p<0.05$, $p<0.01$, respectively). There were no significant differences in serum eNOS and TNF values in the comparison of the groups ($p>0.05$) (**Table 2**).

ROC curve analysis of inflammation and endothelial function markers

In the next step, we wanted to evaluate the diagnostic information of inflammation and endothelial function markers concerning menopause status and type 2 diabetes. First, the AUC values were determined for serum ET-1 (AUC=0.839, $p=0.001$) between the type 2 diabetic premenopausal vs. the non-diabetic premenopausal groups. Second, the AUC values of serum ET-1 (AUC=0.847, $p=0.001$), IL-6 (AUC=0.811, $p<0.01$), and YKL-40 (AUC=0.840, $p=0.001$) were determined between the type 2 diabetic postmenopausal vs. the non-diabetic postmenopausal groups. Then, ROC curve analysis was performed between the type 2 diabetic postmenopausal vs. the non-diabetic premenopausal groups. The AUC values were calculated for serum ET-1 (AUC=0.933, $p<0.001$), IL-6 (AUC=0.812, $p<0.01$), and YKL-40 (AUC=0.880, $p<0.001$). Finally, ROC curve analysis was performed between the type 2 diabetic postmenopausal vs. the type 2 diabetic premenopausal groups. The significance was determined in serum YKL-40 values (AUC=0.732, $p<0.05$) (Table 3). There were no statistically significant differences in the other parameters. For all testing, sensitivity and specificity values were given in **Table 3**.

Table 1. Comparison of demographic variables

	Non-diabetic Premenopausal (n:20)	Type 2 diabetic Premenopausal (n:20)	Non-diabetic Postmenopausal (n:20)	Type 2 diabetic Postmenopausal (n:20)
Age (Years)	40.12±10.78	43.86±7.35	58.29±6.42^{b***,c**}	63.60±8.14^{d***,e***}
BMI (kg/m^2)	29.86±4.89	32.36±3.92	30.90±7.07	33.24±7.49
Menopause duration (Years)	NA	NA	11.56±7.32	15.73±10.01
Diabetes duration (Years)	NA	9.45±4.67	NA	12.11±3.07
SBP (mmHg)	112.50±14.37	129.71±10.27^{a**}	127.41±19.09	139.20±25.55^{e**}
DBP (mmHg)	71.06±8.54	82.00±8.29^{a*}	74.82±13.96	78.27±8.15
Glucose (mg/dl)	87.38±6.01	115.86±22.00^{a***}	92.35±12.36^{c*}	134.40±41.70^{e***,f***}
HbA1c (%)	5.55±0.40	7.16±0.86^{a***}	5.57±0.44^{c***}	7.03±1.16^{e***,f***}
Insulin (mIU/L)	9.37±3.43	15.06±4.36^{a**}	13.04±5.91^{b*}	16.37±7.02^{e**}
Insulin resistance (mg/dl)	1.99±0.72	4.16±1.18^{a***}	3.00±1.45^{b*}	5.34±2.38^{e***,f*}

Values are given as Mean ± Standard Deviation; BMI, Body mass index; NA, not applicable; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HbA1c, Glycated haemoglobin A1c; LDL, Low density lipoprotein; HDL, High density lipoprotein; [a]Type 2 diabetic premenopausal vs. Non-diabetic premenopausal; [b]Non-diabetic postmenopausal vs. Non-diabetic premenopausal; [c]Non-diabetic postmenopausal vs. Type 2 diabetic premenopausal; [d]Type 2 diabetic postmenopausal vs. Type 2 diabetic premenopausal; [e]Type 2 diabetic postmenopausal vs. Non-diabetic premenopausal; [f]Type 2 diabetic postmenopausal vs. Non-diabetic postmenopausal¸*p<0.05, **p<0.01, ***p<0.001.

Table 2. Comparison of serum proinflammatory and endothelial function parameters

	Non-diabetic Premenopausal (n:20)	Type 2 diabetic Premenopausal (n:20)	Non-diabetic Postmenopausal (n:20)	Type 2 diabetic Postmenopausal (n:20)
ET-1 (pg/ml)	0.51±0.29	0.93±0.43^{a*,b**}	0.43±0.36	0.97±0.31^{c***,d**}
eNOS (pg/ml)	0.20±0.05	0.21±0.03	0.21±0.04	0.23±0.05
IL-6 (pg/ml)	2.73±0.40	3.38±0.97	2.72±0.42	3.47±0.75^{c*,d*}
TNF-α (pg/ml)	26.22±1.57	26.18±2.03	26.11±1.60	26.46±2.94
YKL-40 (pg/ml)	1178.51±223.45	1282.43±292.74	1226.28±259.38	1483.12±194.64^{c**,d**}

Values are given as Mean ± Standard Deviation. [a]Type 2 diabetic premenopausal vs. Non-diyabetic premenopausal; [b]Non-diabetic postmenopausal vs. Type 2 diabetic premenopausal ; [c]Type 2 diabetic postmenopausal vs. Non-diabetic postmenopausal ; [d]Type 2 diabetic postmenopausal vs. Non-diabetic premenopausal ; *p<0.05, **p<0.01, ***p<0.001.

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Table 3. Diagnostic information of serum endothelial function and proinflammatory parameters

	Sensitivity	Specificity	AUC (95%CI)	p
Serum ET-1				
Type 2 diabetic premenopausal vs. Non-diabetic premenopausal	87.5%	71.4%	0.839(0.693-0.986)	0.001
Type 2 diabetic postmenopausal vs. Non-diabetic postmenopausal	76.5%	85.8%	0.847(0.707-0.987)	0.001
Type 2 diabetic postmenopausal vs. Non- diabetic premenopausal	87.5%	85.7%	0.933(0.846-0.999)	<0.001
Type 2 diabetic postmenopausal vs. Type 2 diabetic premenopausal	42.9%	71.4%	0.510(0.278-0.742)	NS
Non- diabetic postmenopausal vs. Non-diabetic premenopausal	43.8%	64.7%	0.610(0.404-0.816)	NS
Serum eNOS				
Type 2 diabetic premenopausal vs. Non-diabetic premenopausal	62.5%	64.7%	0.656(0.458-0.855)	NS
Type 2 diabetic postmenopausal vs. Non-diabetic postmenopausal	41.2%	50.1%	0.519(0.304-0.734)	NS
Type 2 diabetic postmenopausal vs. Non- diabetic premenopausal	62.5%	71.4%	0.596(0.372-0.820)	NS
Type 2 diabetic postmenopausal vs. Type 2 diabetic premenopausal	42.9%	50.2%	0.528(0.306-0.750)	NS
Non- diabetic postmenopausal vs. Non-diabetic premenopausal	62.5%	76.5%	0.658(0.467-0.849)	NS
Serum IL-6				
Type 2 diabetic premenopausal vs. Non-diabetic premenopausal	43.8%	78.6%	0.670(0.472-0.868)	NS
Type 2 diabetic postmenopausal vs. Non-diabetic postmenopausal	58.8%	92.9%	0.811(0.678-0.956)	<0.01
Type 2 diabetic postmenopausal vs. Non- diabetic premenopausal	56.3%	92.8%	0.812(0.660-0.965)	<0.01
Type 2 diabetic postmenopausal vs. Type 2 diabetic premenopausal	57.1%	64.3%	0.607(0.373-0.841)	NS
Non- diabetic postmenopausal vs. Non-diabetic premenopausal	37.5%	64.7%	0.513(0.308-0.718)	NS
Serum TNF-α				
Type 2 diabetic premenopausal vs. Non-diabetic premenopausal	75.0%	50.0%	0.547(0.327-0.766)	NS
Type 2 diabetic postmenopausal vs. Non-diabetic postmenopausal	41.2%	64.3%	0.559(0.349-0.769)	NS
Type 2 diabetic postmenopausal vs. Non- diabetic premenopausal	50.1%	64.4%	0.592(0.382-0.801)	NS
Type 2 diabetic postmenopausal vs. Type 2 diabetic premenopausal	42.9%	92.8%	0.635(0.421-0.849)	NS
Non- diabetic postmenopausal vs. Non-diabetic premenopausal	43.8%	64.7%	0.542(0.341-0.744)	NS
Serum YKL-40				
Type 2 diabetic premenopausal vs. Non-diabetic premenopausal	56.3%	57.1%	0.589(0.377-0.801)	NS
Type 2 diabetic postmenopausal vs. Non-diabetic postmenopausal	76.5%	92.9%	0.840(0.693-0.987)	0.001
Type 2 diabetic postmenopausal vs. Non- diabetic premenopausal	81.2%	92.8%	0.880(0.747-0.998)	<0.001
Type 2 diabetic postmenopausal vs. Type 2 diabetic premenopausal	64.3%	71.4%	0.732(0.534-0.930)	<0.05
Non- diabetic postmenopausal vs. Non-diabetic premenopausal	62.5%	58.8%	0.522(0.319-0.725)	NS

AUC, area under the curve; NS, not significant.

DISCUSSION

Menopause is the period, when progesterone secretion ends, the function of ovary losses, and follicles undergo atresia due to ageing . During this period, the decreasing oestrogenlevel causes dysfunction in the endothelial tissue. Type 2 diabetes mellitus is a disease, which can cause endothelial dysfunction and vascular diseases (2).

In the literature, endothelial dysfunction and inflammatory status have been evaluated with various markers in the menopausal period and type 2 diabetes mellitus (3-5) but, there are limited studies providing information about type 2 diabetes in the postmenopausal period. Therefore, in this study, endothelial function and inflammatory status were investigated by serum ET-1, eNOS, IL-6, TNF-α, and YKL-40 levels, and were evaluated the diagnostic efficacy of these markers in postmenopausal type 2 diabetes mellitus. Additionally, it was evaluated that the menopausal period and/or type 2 diabetes were more effective in endothelial dysfunction.

ET-1 is a molecule, which causes inhibition of vasoactive agent secretion from the endothelium with its proinflammatory and constrictor effects. Endothelial dysfunction develops due to ET-1 activity, and vascular complications such as nephropathy and retinopathy occur in diabetes. Impairment of vascular tissue regulation promotes the formation of atherosclerosis in patients with diabetes (6).

When we evaluated our ET-1 findings due to diabetes, a significant increase was observed in type 2 diabetic postmenopausal compared with non-diabetic postmenopausal subjects (p <0.01). Similarly, higher serum ET-1 values were obtained in patients with the type 2 diabetic premenopausal compared with the non-diabetic premenopausal group (p <0.05). (Table 2). ET-1 levels due to menopausal status showed that there was no significant difference between the non-diabetic postmenopausal and the type 2 diabetic postmenopausal, the non-diabetic premenopausal, and the type 2 diabetic premenopausal patients. The ET-1 values showed that a significant increase occurred in type 2 diabetic postmenopausal patients compared with the non-diabetic pre- and postmenopausal groups (p <0.01, and p<0.001, respectively) (Table 2).

In the literature, contradictory findings have been reported in studies examining the ET-1 levels in diabetes. Besides reports, which showed increased ET-1 levels, there were decreased ET-1 levels in other (7-11). Studies evaluating ET-1 levels in menopausal periods have reported that plasma ET-1 levels increased in postmenopausal women compared with the premenopausal group (12-14). Our findings showed that the serum ET-1 level increased in type 2 diabetes, no significant change was observed during the menopause period, but the increase was at the highest level in type 2 diabetic postmenopausal individuals.

These findings could indicate endothelial dysfunction in postmenopausal diabetes.

Endothelial dysfunction and atherosclerosis occur because of impaired compensatory mechanisms of the circulatory system. The synthesis of many molecules, including NO, was damaged during this period (15). NO is an important protective molecule in the vasculature, and the eNOS enzyme is responsible for most of the vascular NO production. NO is a potent vasodilator in vascular smooth muscle, regulates regional blood flow, and also has antithrombotic, anti-inflammatory, and antiproliferative effects. Loss of NO contributes to impaired vascular relaxation, platelet aggregation, increased proliferation of vascular smooth muscle, and leukocyte adhesion to the endothelium (16).

When our eNOS results were evaluated, there was no significant difference between eNOS levels of type 2 diabetic postmenopausal patients and non-diabetic postmenopausal individuals. Similarly, there was no significant change between eNOS levels in type 2 diabetic premenopausal patients and non-diabetic premenopausal individuals. Also, when we assessed eNOS values between the pre- and postmenopausal periods, there was no significant change (Table 2).

In the literature, studies have been conducted on NO levels in patients with diabetes, and conflicting results have been reported. Adela et al. reported that serum NO levels increased in type 2 diabetes patients compared with the control group, but other studies were reporting decreased, or not changed NO levels (17-19). Our findings show that the possible NO deficiency in type 2 diabetes and the postmenopausal period is not due to decreased eNOS levels or activity. Our serum eNOS levels may not have changed significantly, due to the lack ofvascular complications in our diabetic patients.

It has been reported that inflammation and glucose metabolism impairment affect diabetes pathogenesis (3). IL-6 is a cytokine, which contributes to inflammation, and has pleiotropic effects ranging from immune system stimulation to tissue damage (20). TNF-α, another proinflammatory cytokine, plays a role in the pathogenesis of type 2 diabetes. It is also reported that the expression of proinflammatory and prothrombotic factors might contribute to endothelial activation (21). Therefore, our study was examined serum levels of TNF-α and IL-6 in the postmenopausal period and type 2 diabetes disease.

Our findings showed elevation of serum IL-6 levels in the type 2 diabetic postmenopausal group compared with the non-diabetic postmenopausal group. Additionally, IL-6 levels were increased in type 2 diabetic postmenopausal individuals compared with non-diabetic premenopausal individuals. There was no significant difference in serum TNF-α levels related to type 2 diabetes, and the postmenopausal period (Table 2).

In the literature, many studies reported that TNF-α was increased in diabetes and postmenopausal period (5, 22, 23). Doganay et al. reported that TNF-α and IL-6 levels were higher in diabetic individuals, who developed retinopathy, compared with patients without complications, and there was no significant difference between patients without complications and healthy individuals (24).

Conflicting results were reported in studies examining IL-6 and TNF-α levels related to menopausal periods. It has been reported that IL-6 levels increased, but TNF-α values did not change (25), IL-6 levels increased and TNF-α decreased (4), TNF-α levels increased and IL-6 levels did not change in the postmenopausal period (26). Mascarenhas-Melo et al. reported an increase in TNF-α values in postmenopausal diabetic cases compared with premenopausal cases (27). In another study, no significant increase was found in TNF-α values in the postmenopausal period compared to the premenopausal period (28). Our findings showed that IL-6 is more effective than TNF-α in the proinflammatory process related to diabetes and the menopause period, and IL-6 is at the highest level in the type 2 diabetic postmenopausal group (Table 2).

Recently, YKL-40 levels have been used as inflammatory markers in different diseases. It has been shown that the YKL-40 synthesis level is an indicator of the presence and degree of inflammation, and is associated with angiogenesis and fibrosis in the healing process of damaged tissue (29). In our study, we examined whether this marker can be used for inflammatory evaluation in the postmenopausal period and in diabetes.

Our findings were showed that serum YKL-40 levels increased in the type 2 diabetic postmenopausal group compared with the non-diabetic postmenopausal group ($p < 0.01$). Additionally,YKL-40 levels of type 2 diabetic postmenopausal individuals were increased compared with the non-diabetic premenopausal individuals ($p < 0.01$).

Studies examining the YKL-40 level in diabetes reported that levels in the circulation were increased (29, 30). Kaya et al. reported that increased serum YKL-40 values were in patients with diabetic retinopathy compared with the control group (31). It was also stated that the increased YKL-40 in type 2 diabetes is associated with hyperglycemia and insulin resistance, and it can be considered an appropriate parameter for preventing endothelial dysfunctions and complications in diabetes (32).

According to our findings, we may say that serum YKL-40 increases in diabetes. Decreased estrogen activity in the postmenopausal period and inflammatory disorders on the vascular system could be an important causes of increased YKL-40 secretion in the postmenopausal type 2 diabetic subjects.

In this study, we also evaluated the diagnostic performance of endothelial function and inflammation markers by comparing type 2 diabetic and non-diabetic women in pre-and post-menopausal periods. Our results showed that ET-1, IL-6, and YKL-40 could distinguish type 2 diabetic postmenopausal and non-diabetic premenopausal cohorts (AUC: 0.933; AUC:0.812, and AUC:880, respectively). ET-1, IL-6, and YKL-40 performedsimilarly in distinguishing type 2 diabetic postmenopausal and non-diabetic postmenopausal cohorts (AUC: 0.847; AUC:0.811, and AUC:840, respectively) (Table 3).

CONCLUSION

Our findings showed that the highest serum ET-1, IL-6, and YKL-40 levels occur in type 2 diabetes, especially in the postmenopausal period. Increased levels of these parameters might indicate endothelial dysfunction and inflammation in the postmenopausal period and diabetes. Analysis of ROC curves also showed that ET-1, IL-6, and YKL-40 could distinguish type 2 diabetic postmenopausal and non-diabetic premenopausal cohorts. If these markers

are examined in type 2 diabetic postmenopausal individuals, inflammation could be detected at an early stage, and the risk of vascular complications might be reduced.

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Author Contributions: Conceived and designed the experiments: **ST, YA, and NB**. Enrolled patients: **YA and HCA**. Analyzed the data: **YA, HCA, and NB**. Wrote the first draft of the manuscript: **NB.** Contributed to the writing of the manuscript: all authors. All the authors agreed with the manuscript's results and conclusions. All the authors have read, and confirm that they meet, ICMJE criteria for authorship.

Ethical approval: This study was approved by the Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty (Approval Number: 332891/2017). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

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Assessing period poverty in Trinidad and Tobago: An exploratory approach

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ABSTRACT

Objective: The purpose of this study was to assess period poverty in Trinidad and Tobago

Material and Methods: A nationally-drawn sample of 504 women between the ages of 18-48 was used from various urban areas of the country. A cross-sectional research design using a 14-item questionnaire with a mix of closed and open-ended questions was utilised to obtain data about women's experiences concerning the affordability of period products and how they cope with their periods

Results: The findings show that 76% of the sample did not believe that period products are affordable and that 51% reported that they struggled to obtain period products. Furthermore, 55% indicated that they had to borrow or change their current brand of the period product, and 51% revealed that they had to improvise or use alternative products such as toilet paper, napkins, and paper towels. The vast majority of the women also reported that their workplace and schools did not provide them with sanitary products and 99% believe that they should provide them with these products

Conclusion: Considering these findings, it can be concluded that period poverty exists in Trinidad and Tobago, and recommendations include enacting proper legislation and policies to eliminate or reduce this problem.

Key words: Period Poverty; Menstruation; Menstrual Hygiene, Trinidad and Tobago.

INTRODUCTION

Over the years, the lack of access for women and girls to adequate menstrual sanitary products has caused concern for stakeholders seeking to alleviate growing levels of period poverty (1-3). Period poverty is defined as "a lack of access to menstrual products, education, hygiene facilities, waste management, or a combination of these" (2). In particular, the problem has been exacerbated by the inability of women to afford such products, especially those from low-income households, but increasingly, this has become widespread across all income-levels due to the impacts of the ongoing COVID-19 global pandemic (1,3). Women have approximately 500 menstrual cycles during their reproductive life (4), and the financial burden they have to bear are often debilitating. It has been estimated that a woman will spend, on average, US$18,171 (approximately TT$125,016) on period products over her lifetime (5).

Globally, approximately 500 million women and girls experience period poverty which has been attributed to a scarcity of resources and associated stigmas surrounding menstruation (6). Women worldwide have long struggled with the financial burden of obtaining sanitary products around menstruation. Issues around period poverty are especially prevalent in economically disadvantaged societies such as Trinidad and Tobago. There have been campaigns by local Non-Governmental Organisations (NGOs) and companies to alleviate this problem by distributing feminine hygiene products to vulnerable girls and women in the country (7). The options available to women are often inadequate in meeting their menstrual health and can lead to infections (8,9).

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Despite recent successes in reducing menstrual inequalities in several countries, most notably in the United Kingdom (U.K.), Canada, and Australia (10) there has been relatively little research on how to reduce period poverty in low-income countries. This is especially true for the Caribbean, and most studies cited that address the impacts of period poverty have been made outside the region. One study of women's access to menstrual products in low and often middle-income countries reflects the growing socio-economic inequalities of proper menstrual health management between the wealthy and poor (11). For high-income countries, these trends are similar. Studies (10,12) have shown that the poor and vulnerable women and girls in these countries are most at risk of not having adequate access to menstruation products.

More recent research has estimated that in the United States (U.S.), 16.9 million menstruating women live in poverty and that two-thirds of these low-income women cannot afford menstrual products, having to choose between these products or food (13). Studies of 'vulnerable' women in the U.K. who access homeless shelters, drug-support groups, day centers, and food-banks highlight difficulties in accessing menstruation products and often resorted to using make-shift absorbents such as toilet tissue or shoplifting (14). Two qualitative studies centered around homeless women in the U.S. similarly found that women often had to resort to shoplifting or foregoing purchasing food in order to afford supplies (15,16). Moreover, in other studies, women reported that they resorted to using cloth, rags, tissue paper, or paper towels as alternatives to period products when necessary (17,18).

A few quantitative studies that primarily focussed on the U.S., show that a significant proportion of respondents experienced period poverty occasionally, with a few unable to afford adequate menstrual products every month (10). One such study found that 64% of U.S. women on low incomes reported experiencing period poverty over the last year, and a monthly occurrence for around one-fifth or 21% of the women (18). Period poverty was also documented in a small-scale study of 58 high school students in the U.S. It was found that almost half the students were unable to afford products during at least one menses in the school year, whilst 12% were unable to afford them on 'most' months (19).

A recent study drawn from a sample of 471 college-attending women in the U.S. found that 14.2% experienced period poverty in the past year, while 10% experienced it every month (2). The researchers also found that 72.8% had to borrow products, 52.6% used alternative products, 48.3% used pads or tampons, and 26.3% did not use any products. Poor menstruation hygiene management (MHM) has been attributed to a lack of knowledge and information of menstruation (20) and cultural and stigma taboos (21). For instance, a qualitative study found that young girls in the Pindar Valley who experienced menarche were secluded from their families and were not allowed to use sanitary facilities (22). The authors concluded that menstrual taboos had significant impacts on the mobility, health education, and self-esteem of women and young girls.

Moreover, women and girls face negative effects of poor menstruation hygiene, such as school absenteeism and disengagement (12,23). A survey polled 2000 Canadian women found that 83% of the participants felt that their period prevented them from participating in activities, and 70% of women under the age of 25 years stated that they had missed work or school because of their period (24). A more recent study found that 17% of high school girls missed at least one day of school because of an inadequate supply of period products (19). The inability to access period products has significantly impacted mental health. In one study, women who could not afford period products on a monthly basis were more likely to report moderate or severe depression (2).

The onset of the Covid-19 pandemic has exacerbated period poverty for many women and girls (25,26). In one study of 1,037 women, it was found that 30% of the sample found it difficult to access period products during the pandemic, 29% struggled to purchase period products during the past year, and 18% missed work due to lack of period products (1). Similarly, research has concluded that income loss due to the Covid-19 pandemic was a strong predictor for menstrual product insecurity. This was strongly felt by populations with lower-income and educational attainment (15).

Moreover, women are faced with the 'tampon tax' burden, which further exacerbates period poverty. One study has found that in the U.S., thirty-five states have imposed taxes on menstrual products, increasing women's difficulties in accessing such products (27). Inevitably, poor and vulnerable women face the harshest consequences as a result of these taxes. Various recommendations have been put forward to combat these challenges including the provision of at least one free period product (10), educating women and girls about proper menstrual hygiene management (19), changing of policies to make period products more affordable and accessible (1) and establishing laws that seek to eliminate period poverty (25). This study aimed to assess period poverty in Trinidad and Tobago. As an exploratory study, we also gathered women's experiences with their periods, the affordability and accessibility of period products, and any other coping strategies they employed during their periods.

MATERIAL and METHODs

Ethical approval for this study was obtained by the National Ethics Committee of the Ministry of Health (reference number He: 3/13/441 Vol. II) before commencing this study. Consent for participation was first obtained. This consent form was read orally, and a copy was provided once the participant had signed and agreed to participate. Respondents were selected between the ages of 18-48 years. Participants who had no menstruation due to medical reasons, pregnancy, surgical intervention, or those who had approached the climacteric were excluded. Afterward, participants were required to fill out information regarding their knowledge, attitude, and practice concerning sanitary product use. Questions were generated to closely mirror those used in a report published in 2018 by the Scottish Government on accessibility to hygienic products (28). In addition, these questions were adapted to suit the local female population and were validated by experts in the medical fields and gender studies at the University of the West Indies, St. Augustine Campus, Trinidad, and Tobago. Data collection was done over a 4-month period that commenced on July 2022 and was completed on October 2022. A total of 514 participants were randomly targeted and selected from various workplaces and

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urban areas across the East/ West corridor (Port-of Spain to Arima) and the North/South communities (Mt. Hope to San Fernando) in Trinidad and Tobago.

Period poverty was assessed using several questions that asked about the affordability of products ("Do you think period products are affordable?", "Are you able to afford your menstrual products monthly, or do you struggle sometimes?", "Have you had to borrow/change your sanitary product due to cost?"). Participants were also required to indicate if they had to improvise or replace their sanitary products due to cost, whether or not their periods have affected their daily functioning and whether or not they had to visit their doctors for their periods. Most questions required the participants to choose from three options: "yes", "no," and "don't know". In cases where there were follow-up questions, participants were afforded the opportunity to write down their answers. Such questions required them to indicate relevant costs for medical visits, medication, days they were absent from school and/or work, choice of sanitary product, and its associated costs per month.

Statistical Analysis: Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y. USA). Categorical variables were expressed as frequencies and percentages, and quantitative variables were expressed as means, medians, and standard deviations.

RESULTs

A total of 514 questionnaires were completed, however, 10 of these were rejected as their ages deviated from the age range or failure to respond to two or more questions. This provided a response rate of 98%. The mean age of the sample (N = 504) was 33.11 years (**Table 1**). Forty percent (40%) reported their ethnicity as Mixed, while 31.3% reported being African and 25.8% reported being East Indian. Fourteen participants did not specify any ethnicity, which accounted for 2.8% of the sample (**Table 2**). The mean age of participants who experienced their first period was 12.13 years (**Table 1**). Among our sample, 76.2% of women do not believe that period products are affordable, while 21.6% believe that they are affordable and a further 2.2% indicated that they did not know if period products are inexpensive (**Table 3**). Additionally, women spent a median amount of $100 TTD (Trinidad and Tobago Dollars) per month on period products (**Table 4**). Women were also asked to indicate if they could afford their period products monthly, and 47.8% reported that they could do so. About half of the participants (50.6%) indicated that they sometimes struggle to afford period products and 1.6% stated that they could not afford period products (**Table 3**).

When asked to indicate if they ever had to borrow or change their sanitary product due to cost, over half of the women (54.6%) stated that they did so, while 45.4% did not think this was the case (**Table 3**). In terms of having to improvise or replace sanitary wear due to cost, 51.1% of women stated that they had to improvise or change their sanitary wear, while 48.9% indicated that they did not have to do so (**Table 3**). Of the women who indicated that they had to improvise or replace their sanitary wear, 17.8% stated that they had to use toilet paper, 63.7% stated that they switched to other sanitary brands (e.g. Stayfree™ to Always™) and 18.5% used other alternatives (e.g. paper napkins, tampons, paper-towels). Women also reported disruptions in their jobs and schools due to their periods.

Asked whether they have skipped school or work because of their period, 68.5% reported that they have, while 31.5% indicated this was not the case (**Table 5**). On average, women skipped approximately 3 days of work or school due to their periods.

A greater percentage of women also indicated that their periods affected their daily functioning, with 81.5%, while 18.5% reported that they did not (**Table 5**). Moreover, just over half of the women in the sample stated that they had to lie or make up an alternate excuse because of their period (55.5%) compared to 44.5% that did not do so (**Table 5**). Not only have periods affected their daily functioning or made them skip work or school, women often have to seek medical treatment and bear the costs of medical visits for it as well. While most women indicated that they did not have to seek medical attention (53.7%), those participants who did access medical services (47.3%) spent a median amount of $600 TTD on each visit to a medical doctor (**Table 4**).

An overwhelming majority indicated that they had to use medication for their periods (82.1%) and spent a median amount of $50 TTD on medications (**Tables 4, 5**). Most women (94.6%) believe that their school or workplace should offer or support free menstrual products, as compared to 3.2% who indicated that their school or workplace does offer these products for free, while 2.2% reported that they did not know if their school or workplace offer them (**Table 6**).

Most women are also of the view that they would benefit from at least one free menstrual product (96%). Similarly, an overwhelming majority believe that at least one menstrual product should be made freely available in the public sector or other places of work (99.4%) (**Table 6**).

Table 1: Age Range of Participants and Age at First Period in Trinidad and Tobago

Ages	Mean	Standard Deviation	Minimum	Maximum
Age of respondent	33.09	8.31	18	48
Age at first period	12.13	1.62	8	19

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Table 2: Demographic Characteristics of the Respondents in Trinidad and Tobago

Ethnicity	n	%
African	158	31.3
East-Indian	130	25.8
Mixed	202	40.1
Did Not Specify	14	2.8

Table 3: Assessing Affordability of Sanitary Products in Trinidad and Tobago

Question	n	%
Do you think period products are affordable?		
Yes	109	21.6
No	384	76.2
Don't Know	11	2.2
Are you able to afford menstrual products monthly or do you struggle sometimes?		
Able to Afford	241	47.8
Unable to Afford	8	1.6
Struggle Sometimes	255	50.6
Have you had to borrow/change your sanitary product due to cost?		
Yes	275	54.6
No	229	45.4
Have you had to improvise or replace sanitary wear due to cost?		
Yes	257	51.1
No	246	48.9

Table 4: Results of Money Spent on Period Products, Doctor Visits and Medication and Days Spent away from Work/School in Trinidad and Tobago

Question	Mean	Median	Minimum	Maximum
On average how much do you spend on period products monthly?	$118.36	$100	$15	$1000
What was the relevant cost for medical treatment?	$640.50	$600	$0	$3500
What was the relevant cost for medication?	$87.99	$50	$1	$1000
How many days have you skipped work/school?	2.70	2	0	100

Table 5: Assessing how Women in Trinidad and Tobago Cope with their Menstruation

Question	n	%
Have you skipped school/work because of your period?		
Yes	344	68.5
No	158	31.5
Has your period ever affected your daily functioning?		
Yes	409	81.5
No	93	18.5
Have you had to lie or made up an alternate excuse because of your period?		
Yes	279	55.5
No	224	44.5
Have you ever visited a doctor for your period?		
Yes	233	46.3
No	270	53.7
Have you ever used medication for your period?		
Yes	413	82.1
No	89	17.7
Don't Know	1	0.2

Table 6: Assessing Support for Period Products for Women in Trinidad and Tobago

Question	n	%
Does your school/work offer or support free menstrual products?		
Yes	16	3.2
No	476	94.6
Don't Know	11	2.2
Do you think you would benefit from at least one free menstrual product?		
Yes	484	96.0
No	13	2.6
Don't Know	7	1.4
Do you think at least one menstrual product should be made available free in the public sector (e.g., work) or in educational centres?		
Yes	501	99.4
No	2	0.4
Don't Know	1	0.2

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DISCUSSION

This study has sought to assess period poverty in Trinidad and Tobago with the aim of providing at least one free menstrual product to women. To our knowledge, this is the first comprehensive study on period poverty in the country and, by extension, the region. We found that most women do not believe period products are affordable and about half of the sample indicated that they sometimes struggled to buy period products. These large percentages demonstrate the high cost of period products that remain inaccessible to many women in the country. These findings mirror that belief as evidenced by women in other countries (2,10). Furthermore, over half the women sampled indicated that they had to borrow or change their period products, which parallels findings from previous research that stated that 72.8% of women had to borrow products (2). Our findings provide further evidence of the critical importance of period product affordability, especially when Trinidad and Tobago is experiencing a harsh economic climate. While the country does not impose any taxes on menstrual products, this does not necessarily equate to affordability as these products may be subject to high import levies since they are not produced domestically.

For those who improvised their period products, women preferred toilet paper, napkins, tampons, and paper towels. The most popular option, according to our sample, was switching to a cheaper brand of sanitary wear. This finding highlights the stark reality women face where they have to balance their spending habits to prioritise other essential goods such as food, lighting, and other public amenities. Although menstrual products are considered essential items, our findings suggest that they are out of reach for many women, where even switching to a cheaper brand can be too costly. Such ways of improvising or accessing menstrual products are described frequently in the literature (2,17,18).

Another dominant theme that emerged from this study was the effect periods had on the daily functioning of women. A vast majority of women in our sample reported that their period negatively affected their daily lives, and they had to make excuses because of it. This is consistent with other research that reported similar findings (24). We also found that a large percentage of women and girls are prevented from going to work and school because of their periods, as evidenced in previous studies (12). Although we did not measure the loss of income due to menstrual problems in this study, we anticipate that women who are daily-paid workers, for instance, would lose income for every day they spend away from work. This can be devastating for women who reported staying away from work for an average of three days due to their periods.

Women not only have to contend with the high costs of period products, but for those who seek medical attention for their periods, the costs are amplified due to medical bills and medications as our findings have shown. Given that the majority of the women do not believe their workplace or schools offer free period products, the burden on them to provide their own becomes even greater. This is why they believe that workplaces and schools should offer at least one free period product for use. To our knowledge, there is no set policy or guideline that allows for workplaces or schools to distribute free period products for women or girls. While efforts are made to make period products more affordable and accessible to women in several countries, Scotland and New Zealand are the only countries that provide free menstrual products for women and girls (29,30).

Limitations

This study has some limitations. Firstly, there is no standard way to assess period poverty. Although the measures used in our study were consistent with previous quantitative and qualitative research, we believe that more research is needed to validate the measures used for this study. Secondly, the stigma around menstruation was another limitation in the study due to internalized shame around menstruation. Even with privacy protections in place, some women were unwilling to answer questions about their periods. Furthermore, the sample is drawn from mainly urban areas of Trinidad and Tobago with rural areas under-represented. We anticipate, however, that results would be broadly similar or worse for the latter when compared to urban areas, but future studies should be conducted in these areas to corroborate or add to the findings of this study. Therefore, our results are only generalisable to the demographic characteristics of this study.

CONCLUSION

This study has found that women experience period poverty in Trinidad and Tobago. Women find it difficult to afford and access period products and often have to resort to using alternative products to suit their needs. Additionally, this study highlighted other issues that women face during their periods, such as high costs of medication and medical visits as well as loss of daily functioning and absenteeism from work and schools. In light of these issues, we recommend that legislation be drafted to designate period products as essential so that every woman and girl by right has access to period products that are freely available or at a reduced cost. We also recommend policies or guidelines be put in place at schools or workplaces for the provision of free menstrual products for women and girls. We propose such practices are implemented in collaboration with the relevant stakeholders including those at the governmental level and NGOs. In that case, we believe that the problem of period poverty experienced by women can be eliminated or, at the very least, reduced.

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Ethical approval: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all women prior to being included in the study.

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Evaluation of the Anxiety Status of the Individuals in the COVID-19 Testing Process

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ABSTRACT

Objective: The coronavirus disease (COVID-19) pandemic has been stressful for individuals and societies. This study aimed to assess the individuals' anxiety status in the COVID-19 testing process.

Material and Methods: This research is a descriptive study. The study was conducted within the COVID-19 testing process. Questionnaire form and State-Trait Anxiety Inventory were used as data collection tools through a face-to-face interview with a psychiatric nurse before the COVID-19 testing.

Results: In total, 296 individuals participated in the study. Among the participants and the family members they live with, the rate of individuals with chronic diseases were 18.9% and 24.3%, respectively. Of the participants, 22.3% had a family member with a positive COVID-19 test. The mean State-Trait Anxiety Inventory score of the participants in the study was 46.58±10.71 (40-59 points: moderate anxiety). The mean anxiety score was significantly elevated in individuals who were female, had a chronic illness, had a family member with a chronic condition, had a family member who had tested positive for COVID-19, and had a spouse who had tested positive for COVID-19 ($p<0.05$).

Conclusion: It is essential to raise awareness among healthcare professionals about common psychological complaints such as anxiety during pandemics, and to provide biopsychosocial monitoring to individuals by teams including family physicians and psychiatric nurses with a holistic health approach.

Keywords: COVID-19, pandemic, anxiety, family physician, nurse, biopsychosocial, holistic health.

INTRODUCTION

The pandemics may cause devastating psychosocial health concerns (1). Fear of infection, suffering, and demiss for oneself and for loved ones, and sadness after bereavement may lead to severe distress (1). Factors such as uncertainty, life style changes, altered routines, financial worries, social isolation, and loneliness have also all been cited as stressors. The psychological effects of the pandemic may be noticeable, more extensive, more widespread, and longer lasting than the purely somatic effects of the infection (1,2). Previous infectious outbreaks revealed the severity of emotional distress (1,2)

World Health Organization has recognized the impact of COVID-19 pandemic on mental health (3). World Health Assembly adopted the updated Comprehensive Mental Health Action Plan 2013-2030, which includes an indicator on preparedness for mental health and psychosocial support in such public health emergencies (4). Fear, worry, and disstress are normal responses to threats, hence, it is understandable that people are experiencing anxiety in the context of the COVID-19 pandemic (1-4).

Anxiety is a future-oriented unpleasant, and negative mental state induced by potential threats (5). While anxiety response typically serves an adaptive purpose, and can help to engage the appropriate defensive strategy based on the proximity of the threat, when experienced in an extreme, unregulated, and generalized manner, they can become maladaptive (6,7).

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Anxiety can be subdivided into momentary or state stress and stable or trait anxiety. Momentary or state anxiety reflects the psychological and physiological transient reactions directly related to adverse situations in a specific moment, while the term stable or trait anxiety refers to a trait of personality, describing individual differences related to a tendency to present state anxiety (5).

This study aims to evaluate the individuals' anxiety status in the COVID-19 testing process.

MATERIAL and METHODs

Design of the Study: This research is a descriptive study. It was conducted the individuals who were in the COVID-19 diagnostic testing process at Mardin Training and Research Hospital, between 1st and 30th October 2020. Data were collected with a questionnaire form and State-Trait Anxiety Inventory. Data collection tools were administered to the participants before the COVID-19 test by a specialist psychiatric nurse through a face-to-face interview.

Questionnaire Form: It consists of 15 questions consisting of sociodemographic and introductory characteristics of individuals.

State-Trait Anxiety Inventory (STAI): It was developed by Spielberger et al. in 1970 and is a test administered to those over the age of 14 (8). The validity and reliability studies of Turkish version were performed by Öner and Le Compte (9). The STAI can be applied to the same individuals at different times to detect changes in anxiety levels. It is a psychological inventory consisting of forty self-report items on a four-point Likert scale. The STAI measures both state anxiety and trait anxiety separately. Each type of anxiety has its own scale of twenty questions (10). Scores range between twenty and eighty; while low scores correlate with mild anxiety, higher scores correlate with a more severe condition (9, 10).

Research and Publication Ethics: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Istanbul Medipol University, Istanbul, Turkey (Date: 17.09.2020, No: 715).

Statistical Analysis: The data were evaluated in computer environment using the SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA). In the evaluation of the data, percentage, arithmetic mean, standard deviation values, minimum and maximum values were used as descriptive statistics. The Shapiro-Wilk test was used to determine whether the numerical variables showed normal distribution or not. In accordance with the distribution of the data, Mann-Whitney U test was used in paired group comparisons, and Kruskal-Wallis H test was used in comparisons of three or more groups. Analysis of variance (ANOVA) was used to determine whether the means of three or more groups are different. F-tests were used to statistically test the equality of means. The $p<0.05$ value was considered statistically significant in comparisons.

RESULTs

In total, 296 participants were included in the study. When the socio-demographic characteristics of the participants in the study were examined, 54.1% were male, 90.2% were under the age of 45 (min-max: 18-88 years), the mean age was 31.25±11.17. It was determined that 55.7% of the participants were married, 62.5% were workers, and 63.9% were middle-income (**Table 1**).

Among the participants, 18.9% had a chronic disease, and 48.2% of those with chronic diseases had asthma; 24.3% of the participants had family members with a chronic disease, and 34.7% of these individuals had asthma, and 22.3% of the participants had family members with a positive COVID-19 test (**Table 2**).

The mean anxiety score was significantly elevated in individuals who were female, had a chronic illness, had a family member with a chronic condition, had a family member who had tested positive for COVID-19, and had a spouse who had tested positive for COVID-19 ($p<0.05$), as shown by **Table 1** and **Table 2**.

In the study, no significant relationship was found between the number of children of the participants, the number of people they live with in their families, the type of chronic disease of the participant with a chronic disease, the type of chronic disease of the individual with a chronic disease in their family, and their anxiety score averages ($p>0.05$).

Table 1. Distribution of the mean scores of the State-Trait Anxiety Inventory (STAI), according to various sociodemographic characteristics (n=296).

Sociodemographic characteristics	Mean±SD	Test*	P**
Gender			
Female	48.83±9.74	U: 7954.500	**p<0.001**
Male	44.66±11.14		
Age			
18-23	48.28±9.76	KW: 11.255	0.081
24-31	46.90±11.77		
32-38	45.46±10.60		
39-45	46.20±10.44		
46-52	37.90±9.19		
53-59	45.00±9.35		
60 and over	45.83±10.59		
Marital status			
Single	46.34±11.03	KW:1.231	0.540
Married	46.79±10.43		
Divorced	52.00±2.82		
Educational Status			
Primary education	47.10±9.59	KW: 4.224	0.518
High school	45.80±9.94		
Associate degree	44.17±11.74		
Licence	47.17±12.10		
Graduate	50.21±9.78		
Working Status			
Working	46.10±10.83	U: 9044.500	0.086
Not working	47.37±10.51		
Economical status			
Low-income	50.73±11.43	KW: 3.768	0.152
Middle-income	46.21±10.36		
High-income	45.85±11.05		
Having a Child			
Yes	46.20±10.85	U: 10402.000	0.469
No	46.92±10.60		

* Mann-Whitney U test was used in paired group comparisons, and KruskalWallis H test was used in comparisons of three or more groups. Analysis of variance (ANOVA) was used to determine whether the means of three or more groups are different. F-tests were used to statistically test the equality of means. **The $p<0.05$ value was considered statistically significant in comparisons. SD: Standard deviation

Table 2. Distribution of the mean scores of the State-Trait Anxiety Inver
the participants and their family members (n=296).

Health Conditions	
Chronic Disease Status	
Yes	5
No	4
Having a case with a chronic disease within the immediate family	

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DISCUSSION

In the current study, the mean anxiety score of individuals in the process of COVID-19 testing was found to be 46.58±10.71; therefore, it was observed that individuals experienced moderate anxiety. COVID-19 pandemic causes fear and anxiety among people due to its spread rate and severe clinical course (10-11). Wang et al. reported that approximately one-third of China's general population experienced moderate to severe anxiety during the initial phase of the COVID-19 outbreak (10). Fardin stated in his review that COVID-19 causes various psychological effects, including increased anxiety (11).

In the study, the mean score of anxiety was found to be significantly higher in women. Lai et al. stated that the risk of developing psychological problems is higher in women during the COVID-19 epidemic in China (12). Wang et al. found a significant relationship between the female gender and high levels of stress, anxiety, and depression (10). Our study results show parallelism with the literature. This may be a reason why women use emotion-focused coping more and experience negative emotions more intensely. In addition, in the context of their traditional family roles, women can naturally be intensely affected in an epidemic picture as mothers, spouses, and caregivers.

In the study, the mean score of anxiety; It was found to be statistically significantly higher in those with a chronic disease, in those with a person with a chronic disease in their family members, in those with a positive COVID-19 test, in people with whom they live, and in those whose spouses have a positive COVID-19 test. It is emphasized in various studies that individuals with chronic disease, who are considered to be a risky group, experience more fear and anxiety than other individuals during the pandemic period (13,14). Dağlı et al. stated the difficulties of being a relative of a patient as well as being sick during the pandemic, and pointed out that being diagnosed with COVID-19 is a process full of uncertainty, involving intense stress and anxiety for the family members as well as for the individual (15).

In the study of Wang et al., 75.2% of the participants were concerned about their family members (10).

During severe health conditions, family members become more sensitive and want to be close to their patients (16). However, because COVID-19 is a life-threatening infectious disease, family members are often not allowed to be close to their patients. Additionally, it is worth noting that the fear of losing a loved one to a disease can also cause intense anxiety in family members.

CONCLUSION

Anxiety is a prevalent psychological issue during pandemics such as COVID-19. It is crucial to prioritize the psychological well-being of the population through proactive psychological interventions during the pandemic. The findings of this study highlight the importance of raising awareness among healthcare workers and society about the psychological impact of pandemics, such as anxiety. It is crucial to implement early and effective public mental health interventions provided by healthcare practitioners to manage the outbreak of pandemics. A holistic approach, including biopsychosocial follow-ups by family physicians and psychiatric nurses during pandemics, is essential to provide comprehensive care.

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Ethical approval: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Istanbul Medipol University, Istanbul, Turkey (Date: 17.09.2020, No: 715).

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Smartphone addiction and Sleep Quality in adolescents

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ABSTRACT

Objective: To determine the frequency of smartphone addiction and poor sleep in high school adolescents and to evaluate the relationship between phone addiction and sleep, together with demographic characteristics.

Methods: A face-to-face survey was applied to 730 high school students in the Kahta district of Adıyaman, Turkey, between November 2021 and January 2022. The Smartphone Addiction Inventory-Short Form (SPAI-SF) was used to assess smartphone addiction, and the Pittsburgh Sleep Quality Index (PSQI) was used to evaluate sleep quality.

Results: The rate of smartphone addiction in adolescents was 41%, and poor sleep quality was 61%. When smartphone addiction increases, sleep quality decreases, and when sleep quality decreases smartphone addiction increases. Smartphone addiction and poor sleep quality were higher in girls compared to boys. As the parents' education level and family income increase, the level of addiction increases, but sleep quality remain the same. We found that as age increases, the risk of smartphone addiction and the risk of deterioration in sleep quality increase.

Conclusion: Smartphone addiction and poor sleep quality trigger each other in a vicious circle. The COVID-19 pandemic may have made smartphone addiction the most common addiction in the world. This addiction can increase the risk of substance addiction by impairing the quality of sleep in adolescents and lead to many physical, social, and mental problems. A multidisciplinary approach is vital for solving the problem.

Keywords: Smartphone addiction, sleep quality, adolescent, problematic phone use, screen time

INTRODUCTION

Depending on the development of technology, smartphones have become an indispensable part of daily life. Mobile phones with smartphone features have made it easy to access information and entertainment since they can be connected to the internet anywhere. The complete experience offered through various applications, especially social media, opens the door to a different world for people of all ages. However, this ease and comfort provided to people also bring difficulties (1).

Smartphone addiction, or in other words, problematic phone use (PSU), is spending time with a smartphone excessively and uncontrollably in daily life (2). In addition to physical disorders, this addiction can lead to many mental problems, such as decreased sleep quality, depression, anxiety, attention deficit, and social communication disorder. Adolescence, which is the most sensitive for all types of addiction, is also the riskiest for smartphone addiction (1,3).

The COVID-19 pandemic has affected the whole world and has increased the time spent at home and phone use, especially for adolescents, due to worldwide restrictions. As a result, the pandemic has caused an increase in the risk of smartphone addiction and addiction-related daytime sleepiness and a decrease in sleep quality in adolescents (4).

Spending excessive time with a smartphone before going to sleep shortens young people's sleep time, impairs their sleep quality, and causes adolescents to be unproductive while listening to lectures or studying. In addition, students' phone use at school reduces their school success by reducing their interest in lessons and distracting them (1).

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Adequate and quality sleep is vital for one's physical and mental well-being, and decreased sleep quality has been shown to cause daytime sleepiness and poor academic performance. In addition, insufficient and poor-quality sleep may lead to obesity and cardio-metabolic diseases in adolescents due to less physical activity (5).

Uncontrolled use of smartphones is a significant problem that affects the physical, mental, and academic quality of life of adolescents due to both excessive screen time and the sleep problems it causes. Decreased sleep quality can lead to long-term sleep deprivation, which may increase the rate of smoking and alcohol use in adolescents (6). Our study aims to determine the frequency of smartphone addiction and poor sleep in high school adolescents in Adıyaman's Kahta district and to evaluate the relationship between smartphone addiction and sleep quality, along with demographic characteristics. This way, contributions will be made to studies that offer integrative suggestions with physiological, psychological, and social dimensions to find solutions to adolescents' problems.

MATERIAL and METHODs

Study Design and Study Group

The research is a cross-sectional and descriptive study. The research population consists of students studying in high schools in the Adıyaman Kahta district center. Data were collected between November 2021 and January 2022. Schools were selected by cluster sampling method. It was planned to take at least 384 people with a 95% confidence level 0.05 margin of error, and 730 students participated in the research. A questionnaire form was used as a data collection tool. After obtaining permission from the National Education Directorate, consent forms were acquired from the students and their parents.

Study Tools

Short-form Smartphone Addiction Inventory (SPAI-SF) was used for smartphone addiction revised from SPAI by Lin et al. (7,8). The short form of this 26-item scale consists of 10 items. Arpacı et al. conducted the Turkish validity and reliability study in 2018 (9). There are four-point Likert-type options "1= I strongly disagree, 2= I disagree, 3=I agree, 4=I strongly agree. The score range of the scale is between 10-40. The cut-off point of the scale is 24. Those who are 24 and above are determined as smartphone addicts.

The Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep quality. This scale, developed by Buysse et al. in 1989, was adapted into Turkish by Ağargün et al. in 1996 (10,11). The scale evaluates sleep quality and disturbance in the last month and consists of 24 questions. Nineteen questions are self-report questions, and the remaining five are answered by the spouse or friend of the person in the same room. The 18 questions scored consist of seven components: subjective sleep quality perceived by the individual, sleep latency (time from going to bed to falling asleep), sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping pills, and finally, daytime dysfunction. Each component is given a score between 0 and 3. The scale's total score is found by adding the scores from the seven components. Values greater than 5 for the total scale score, ranging from 0 to 21, indicate poor sleep quality.

Statistical Analysis

Analyzes were evaluated in 22 package programs of SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL). In the study, descriptive data are shown as n and % values in categorical data and mean ± standard deviation (Mean ± SD) values in continuous data. Chi-square analysis (Pearson Chi-square) was used to compare categorical variables between groups. The Kolmogorov-Smirnov test evaluated the conformity of continuous variables to normal distribution. Mann Whitney U-test was used to compare paired groups, One Way ANOVA analysis was used for those with normal distribution compared to more than two variables, and the Kruskal Wallis test was used for those who did not. The spearman correlation test was used to examine the relationship between continuous variables. Linear Regression analysis was applied to determine the predictors of the SPAI-SF and PSQI scale. While creating the model, the Enter method was used. Moreover, those with a significant relationship in the correlation test were included in the model. The statistical significance level in the analysis was accepted as $p<0.05$.

Ethics committee approval was obtained with the decision of The non-Interventional Clinical Research Ethics Committee of Adıyaman University, dated 26/10/2021, and numbered 2021/08-21.

RESULTs

Seven hundred thirty adolescents with a mean age of 15.6±1.3 (min=13-max=18) were included in the study. 36% of adolescents are boys, and 64% are girls. The mother's education level of 68.8% of the participants, and the father of 49.5% is a secondary school or below. The family income level of 42.7% of the adolescents is 3000 TL or less, 41.6% have an income of 3001-5000 TL, and 15.6% have an income of more than 5000 TL. 81.8% of the participants live with their parents, 7.5% live with their parents, and 10.7% live with their dormitory/housemates. 41.5% of the adolescents have a private room, 73.8% have a nuclear family. The average usage time of adolescents is 2.1 ± 1.5 years, and the average daily usage time is 5.0±2.0 hours. 43.2% of adolescents use social media, 28.6% use messaging, 55.3% use games, 22.5% use a smartphone for education, and 16.6% use smartphones to access information. While 41% of adolescents have smartphone addiction, 61% have poor sleep quality (**Table 1**).

The girls' SPAI-SF ($p<0.001$) and PSQI ($p=0.001$) scores were found to be significantly higher than the boys' scores. The SPAI-SF scores of those whose mother's education level ($p=0.019$) and father's education level ($p=0.028$) were high school and above and were found to be significantly higher than those with secondary school and below. There was a significant difference between the monthly income and SPAI-SF score. The difference was only due to the difference between those who received 3000 TL or less and those who received more than 5000 TL groups ($p=0.023$). The SPAI-SF score of those who had a private room was significantly higher than those who did not ($p=0.01$). The SPAI-SF ($p=0.007$) and PSQI ($p=0.012$) scores of those who used smartphones for social media were found to be significantly higher.

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The SPAI-SF (p=0.009) and PSQI (p<0.001) scores of those using smartphones for messaging were found to be considerably higher. The SPAI-SF (p=0.021) and PSQI (p<0.001) scores of those who used smartphones for gaming were found to be significantly higher. The SPAI-SF (p=0.048) and PSQI (p<0.001) scores of those using smartphones for educational purposes were found to be significantly lower. The SPAI-SF (p=0.001) and PSQI (p<0.001) scores of those who used smartphones to access information were found to be significantly lower. The SPAI-SF (p<0.001) and PSQI (p<0.001) scores of those with smartphone addiction were found to be significantly higher than those without smartphone addiction. Those with poor sleep quality had significantly higher SPAI-SF (p=0.013) and PSQI (p<0.001) scores than those with good sleep quality (**Table 2**).

67.6% of smartphone addicts had poor sleep quality, 56.4% of non-smartphone addicts had poor sleep quality, and there was a statistically significant difference between these rates (p=0.002) (**Figure 1**). According to the correlation analysis, there was a positive and significant correlation between the SPAI-SF score and PSQI, age, total phone usage time, daily phone usage time, and monthly income. There was a positive and significant correlation between PSQI and age, total phone use time, and daily phone use time (**Table 3**).

According to the multiple linear regression analysis, The SPAI-SF scale score was predicted by PSQI (β=.241, p=0.011), age (β=.575, p=0.048), and duration of phone use (β=1.165, p<0.001). The PSQI scale score was evaluated by SPAI-SF (β=.061, p=0.013), age (β=.580, p<0.001), duration of phone use (β=.474, p=0.001), and duration of daily phone use (β=.,365, p<0.001) (**Table 4**).

Table 1. All characteristics of the adolescents included in the study

		Number	%
Age, Mean ± SD		15.6 ± 1.3	
Gender	Male	263	36.0
	Female	467	64.0
Mother's education	Middle school and below	502	68.8
	High school and above	228	31.2
Father's education	Middle school and below	361	49.5
	High school and above	369	50.5
Monthly income (Turkish Liras)	≤3000	312	42.7
	3001-5000	304	41.6
	>5000	114	15.6
with whom does he/she live	with mother and father	597	81.8
	with mother or father	55	7.5
	Dorm/housemate	78	10.7
Private room	Yes	303	41.5
	No	427	58.5
Type of family	Nuclear family	539	73.8
	Extended family	191	26.2
Phone usage time (years), Mean ± SD		2,1 ± 1.5	
Daily phone usage time (hours), Mean ± SD		5.0 ± 2.0	
Smartphone usage purpose*	Social media	315	43.2
	Messaging	209	28.6
	Game	404	55.3
	Education	164	22.5
	Access to information	121	16.6
Smartphone addiction	Addicted	299	41.0
	not Addicted	431	59.0
Sleep Quality	Poor sleep	445	61.0
	Good sleep	285	39.0

*Multiple answers can be selected

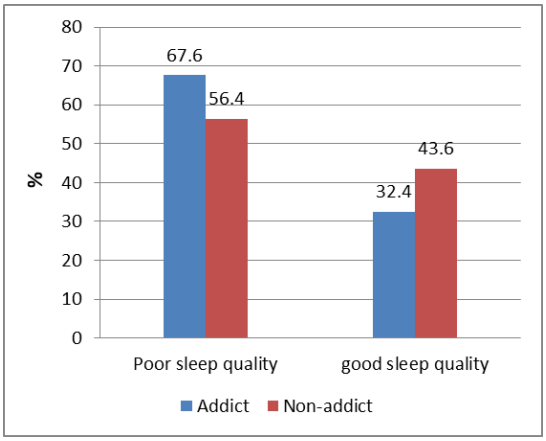

Figure 1. Comparison of sleep quality according to the presence of smartphone addiction

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Table 2. Comparison of scale scores according to all characteristics of adolescents

		SPAI-SF		PSQI	
		Mean ± SD	p*	Mean± SD	p*
Gender	Male	22.7± 7.5	**<0.001**	6.4±3.2	**0.001**
	Female	25.6± 8.5		7.7±4.3	
Mother's education	Middle school and below	24.0±8.0	**0.019**	7.1±4.0	0.071
	High school and above	25.7±8.6		7.6±4.1	
Father's education	Middle school and below	23.8±8.1	**0.028**	7.1±4.1	0.224
	High school and above	25.2±8.3		7.4±3.9	
Monthly income (Turkish Liras)	≤3000	23.7±7.9[a]	**0.023****	7.2±3.8	0.680**
	3001-5000	24.8±8.4[a,b]		7.4±4.2	
	>5000	26.3±8.4[b]		6.9±4.0	
with whom does he/she live	mother and father	24.4±8.2	0.737	7.2±4.0	0.409
	mother or father	24.8±7.9		7.9±4.3	
	Dorm/housemate	25.3±8.8		7.3±3.8	
Private room	Yes	25.6±8.7	**0.01**	7.1±4.1	0.204
	No	23.8±7.8		7.4±4.0	
Type of family	Nuclear family	24.8±8.2	0.163	7.2±4.0	0.530
	Extended family	23.9±8.3		7.4±4.0	
for social media purposes	Yes	25.3±7.9	**0.007**	7.8±4.3	**0.012**
	No	24.0±8.4		6.8±3.7	
for messaging purpose	Yes	25.6±8.1	**0.009**	8.5±4.8	**<0.001**
	No	24.1±8.3		6.8±3.6	
for game purpose	Yes	25.2±8.4	**0.021**	7.3±5.1	**<0.001**
	No	23.7±7.9		7.2±2.1	
for education purpose	Yes	23.0±7.7	**0.048**	5.8±3.4	**<0.001**
	No	25.0±8.3		7.7±4.1	
for accessing information purposes	Yes	22.2±7.2	**0.001**	4.6±4.1	**<0.001**
	No	25.0±8.4		7.8±3.8	
Smartphone addiction	Addicted	33.1±5.3	**<0.001**	8.2±4.3	**<0.001**
	not Addicted	18.6±3.0		6.6±3.7	
Sleep Quality	Poor sleep	25.2±8.4	**0.013**	9.5±3.4	**<0.001**
	Good sleep	23.6±7.9		3.7±1.6	

*Mann Whitney U test, **Kruskal Wallis analysis was applied.

Table 3. Correlation of scale scores with various measurement data

		SPAI-SF	PSQI
PSQI	r	**.140**	
	p	**.000**	
Age	r	**.103**	**.097**
	p	**.005**	**.008**
Phone usage time (years)	r	**.221**	**.098**
	p	**.000**	**.041**
Daily phone usage time (hours)	r	**.098**	**.217**
	p	**.008**	**.000**
Monthly income	r	**.097**	-.025
	p	**.009**	.508

Table 4. Linear Regression Analysis of Factors Associated With SPAI-SF and PSQI

	β	SE	Standard β	t	p
SPAI-SF (R^2=0.106; F=11,238; p<0.001)					
PSQI	.241	.094	.125	2.556	**0.011**
Age	.575	.290	.095	1.981	**0.048**
Phone usage time (years)	1.165	.265	.210	4.403	**<0.001**
Daily phone usage time (hours)	.325	.187	.081	1.738	0.083
Monthly income	.859	.527	.076	1.632	0.104
PSQI (R^2=0.131; F=17,151; p<0.001)					
SPAI-SF	.061	.025	.119	2.505	**0.013**
Age	.580	.145	.186	4.001	**<0.001**
Phone usage time (years)	.474	.136	.165	3.488	**0.001**
Daily phone usage time (hours)	.365	.094	.176	3.876	**<0.001**

DISCUSSION

Many studies indicate that phone addiction is high and sleep quality is low in adolescents compared to other age groups (1,3,4,12). Smartphone addiction was found in 41% of the adolescents participating in the present study, and poor sleep quality in 61%. These rates are higher than the rates in the literature. In a study conducted by Açıkgöz et al. in 2022, when they examined the use of smartphones by adolescents, they found 72.4% to be standard, 19.2% to be problematic, and 8.4% to be pathological (13). They found low sleep quality in 58.7% of adolescents. In a study by Chen et al. in 2017 (14), the smartphone addiction rate in adolescents was 29.8%, and Soni et al. found 33.3% (15). In the study conducted by Zou et al. in 2019, they found smartphone addiction in 27.5% of adolescents and sleep problems in 15.6% (16).

Boumosleh & Jaalouk in 2017 and Deveci in 2021 stated that gender did not affect smartphone addiction (12,17). However, in the present study, phone addiction in girls was higher than in boys, which supports most studies (1,3,5,13,18,19). In line with most studies, we found the sleep quality in girls to be lower (5,6,13,18,19). However, in his study, Deveci stated that gender did not affect sleep quality either (12).

In the present study, the risk of smartphone addiction was found to be higher in those whose parents had higher education levels. In his study, Deveci stated that the mother's education level affected addiction, but the father's education level did not make a significant difference (12). In the study conducted by Al-Barashdi et al. in 2015, they did not find a relationship between the parents' education level and smartphone addiction (20).

In the present study, no relationship was found between the parents' education level and quality of sleep. Deveci, on the other hand, stated in his study that sleep quality differs significantly according to the parents' education level (12). On the other hand, Açıkgöz et al. stated that the mother's education level had no effect (13). However, the adolescents' sleep quality increased as the father's education level increased.

Similar to the study of Al-Barashdi et al. (20), we also found that the risk of smartphone addiction increases as the monthly income increases. JH Kim, in his study in 2021, stated that smartphone addiction is higher in adolescents with a low family economic level (21).

Açıkgöz et al. and Philbrook et al. reported in their study that sleep disorders were more common in adolescents with low-income family economic status (13,22). In a study by Lima et al. in 2014, they showed no relationship between the economic status of the family and the sleep quality of adolescents (23). Our study did not find a relationship between the family's economic level and sleep quality.

As most studies show, a significant correlation was found between smartphone addiction and poor sleep quality in adolescents (4-6,12,13). However, in a study conducted in 2014, Park argued that although smartphones cause a delay in sleep time, they do not cause sleep disorders (24).

The study by Park et al. in 2022 determined that the risk of both phone addiction and deterioration in sleep quality increases with age in adolescents (6). A study by Kim et al. in 2020 and Chen et al. in 2017 showed that smartphone addiction increases with increasing age in adolescents (14,25). Lin et al. and Andrade et al. stated that age is not associated with adolescent smartphone addiction (8,26). Our study found that both the risk of smartphone addiction and poor sleep quality increase with increasing age in adolescents.

Our study revealed that smartphone addiction is more common in adolescents with private rooms, showing that parents should regularly check children at a regular frequency.

CONCLUSION

In the present study, high rates of smartphone addiction (41%) and poor sleep quality (61%) were detected in adolescents who are sensitive to all addictions. It has also been found that the risk of poor sleep quality is higher in those with smartphone addiction. Similarly, it was observed that the risk of smartphone addiction was higher in those with poor sleep quality. In short, both situations trigger each other in a vicious circle. The COVID-19 pandemic may have made smartphone addiction the most common addiction in the world. This addiction can increase the risk of other substance addictions by impairing the quality of sleep in adolescents and can also lead to many physical, social, and mental problems. A multidisciplinary approach is vital for solving the problem.

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Ethical approval: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study. Adıyaman University Non-Interventional Ethical Committee approved the method of the study (IRB Number:2021/08-21).

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