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Prostate Cancer Screening Behaviors and Health Beliefs Regarding Prostate Cancer Screening of Individuals Over 50 Years of Age: A Descriptive, Cross-Sectional Study

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ABSTRACT:

Purpose: This descriptive cross-sectional study was conducted to assess prostate cancer screening behaviors and health beliefs related to prostate cancer screening among individuals aged 50 and over.

Material and Methods: The study sample consisted of 72 men aged 50 and over receiving treatment at the Orthopedics and Traumatology Clinic of a university hospital. Data were collected between December 20, 2022, and March 20, 2023, using a "Personal Information Form" and the "Prostate Cancer Screening Health Belief Model Scale". Data analysis involved the use of frequency distributions, means, standard deviations, Chi-square analyses, the Mann-Whitney U test, and the Kruskal-Wallis test.

Results: The mean age of the participants in the study was 61.59 ± 8.51 years. It was found that 22.2% of the participants had undergone Prostate-Specific Antigen testing, 73.6% had no knowledge about prostate cancer, and 75% had no knowledge about early detection tests for prostate cancer. Furthermore, participants who had knowledge about prostate cancer and early detection, had a family history of prostate cancer, and considered undergoing prostate examination had a higher rate of undergoing Prostate-Specific Antigen testing. Those who had never undergone a prostate examination, had no knowledge about prostate cancer and early detection tests, and did not plan to undergo prostate examination within the next six months had higher scores on the barrier perception scale, while those who had undergone Prostate-Specific Antigen testing and planned to undergo prostate examination within the next six months had higher scores on the health motivation perception scale.

Conclusion: The study revealed a low rate of Prostate-Specific Antigen testing for early detection of prostate cancer, and participants' knowledge and health beliefs and perceptions related to prostate cancer and early detection tests were identified as key factors influencing prostate cancer screening behaviors.

Keywords: Health belief model; Prostate cancer; Screening

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INTRODUCTION

Prostate cancer incidence has been steadily increasing in recent years (Poppel et al., 2022; Chung et al., 2020). According to International Cancer Data, prostate cancer is the 2nd most common type of cancer in men with a prevalence rate of 14.2% (Global Cancer Observatory, 2024). In Turkey, according to the 2018 cancer data, prostate cancer is the second most common cancer type in men after lung cancer, with an incidence rate of 40.3 per hundred thousand (Turkey Cancer Statistics, 2024).

The survival rate of prostate cancer is closely related to the clinical and pathological stage of the disease at the time of diagnosis, as prostate cancer is often asymptomatic (Abuadas et al., 2017; Zare et al., 2016). When prostate cancer is detected in the early stage, the five-year survival rate is 100%, whereas in metastatic prostate cancer, this rate drops to as low as 29.8% (Ivlev et al., 2018). Therefore, to reduce mortality rates associated with prostate cancer, the American Cancer Society recommends informing all men aged 50 and over with a life expectancy of at

least 10 years about early prostate cancer detection and screening and suggests performing a Prostate-Specific Antigen (PSA) test based on individual preference. PSA testing is the most commonly recommended practice for the early detection of prostate cancer and treatment planning (Chung et al., 2020; Jamieson et al., 2022; Zare et al., 2016), and this practice is supported by level C evidence (Jamieson et al., 2022). While participation in screening programs for prostate cancer is crucial in the fight against the disease, low awareness and participation rates in screening programs for the early detection of prostate cancer are observed worldwide (Abuadas et al., 2017; Aflakseir, 2016; Bilgili & Kitiş, 2019; Demirbaş & Onmaz, 2021; Yeboah-Asiamah et al., 2017).

Studies investigating the participation of the community in prostate cancer screening programs and the factors influencing it have reported that older age (Jamieson et al., 2022; Ogunsanya et al., 2016), higher education (Jamieson et al., 2022), higher income level (Jamieson et al., 2022; Ogunsanya et al., 2016), being informed about PSA by a healthcare professional (Ogunsanya et al., 2016), being married (Jamieson et al., 2022), regular visits to healthcare facilities (Ogunsanya et al., 2016), knowing someone diagnosed with prostate cancer, experiencing urinary system complaints, and having a high sensitivity and seriousness perception increase participation in screening programs (Abuadas et al., 2017; Çapık & Gözüm, 2011; Demirbaş & Onmaz, 2021; Kahraman & Kılıç; 2019). On the other hand, perceiving prostate cancer as a disease of old age, lack of knowledge, considering oneself healthy, finding prostate examinations embarrassing and painful, fear of death and cancer, and a high barrier perception significantly hinder participation in prostate cancer screenings (Alshammari et al., 2021; Bamidele et al., 2022; Bilgili & Kitiş; 2019; Mbugua[a] et al., 2021; Mbugua[b] et al., 2021; Yeboah-Asiamah et al., 2017; Zare et al., 2016). The Health Belief Model (HBM) is a widely used model to determine the attitudes and beliefs that motivate individuals to take or not take actions related to health, such as prostate cancer screening behaviors and compliance with recommended medical regimens (Alshammari et al., 2021;

Demirbaş & Onmaz, 2021; Kahraman & Kılıç; 2019; Zare et al., 2016). A literature review indicates that there is limited research in Turkey that evaluates patients' prostate cancer screening behaviors using the HBM (Bilgili & Kitiş; 2019; Demirbaş & Onmaz, 2021; Kahraman & Kılıç; 2019). Considering the increasing number of individuals with prostate cancer, evaluating individuals' prostate cancer screening behaviors and their levels of health beliefs regarding these behaviors can contribute to increasing the early detection of prostate cancer and improving survival rates.

MATERIAL and METHODS
Purpose and Type of the Study
This study was conducted to assess the prostate cancer screening behaviors of individuals aged 50 and over and their health beliefs related to prostate cancer screenings. This study is a descriptive, single-center, and cross-sectional study.

Research Questions
The research questions that this study aimed to answer were as follows:
•   What are the factors influencing the prostate cancer screening behaviors of individuals aged 50 and over?
•   What are the health beliefs of individuals aged 50 and over regarding prostate cancer screenings?

Sampling and Participant
This study was conducted at the Orthopedics and Traumatology Clinic of XXX University Research and Practice Hospital. The study population consisted of 160 patients receiving treatment at the Orthopedics and Traumatology Clinic of a university's Research and Practice Hospital between December 20, 2022, and March 20, 2023. The reason for choosing the Orthopedics and Traumatology Clinic was that statistical data showed a higher number of males aged 50 and above admitted to the clinic within one year. Participants included individuals who were 50 years of age or older, spoke Turkish, had no history of cancer diagnosis, and agreed to participate in the study. A total of 88 individuals were excluded from the study, including those under 50 years old (71),

non-Turkish speakers (4), individuals aged 50 and above who had previously been diagnosed with colon (3) and prostate (2) cancer and declined to participate (8). Thus, the sample of the study consisted of 72 male participants.

Data Collection

Patients were accommodated in single, double, or quadruple rooms. Therefore, it was considered that the presence of other individuals during data collection could affect the accuracy of responses. Data were collected in the plaster-dressing room of the orthopedics and traumatology clinic during hours when plaster/dressing procedures were not being performed. Data of participants staying in single rooms were collected in their patient rooms. The plaster-dressing room and single-patient rooms were well-lit and had an environment that did not distract the participants. Face-to-face interview technique was used for data collection. Each participant's completion of the questionnaire took approximately 30 minutes.

Data Collection Tools

In this study, two data collection tools were used: "Personal Information Form" and "Prostate Cancer Screenings Health Belief Model Scale (PCSHBMS)."

Personal Information Form: The form, based on the literature (Alshammari et al., 2021; Demirbaş & Onmaz, 2021; Kahraman & Kılıç, 2019), was developed by the researchers and consisted of 15 questions. The form included 4 questions about participants' demographics such as age, education level, monthly income, marital status, and 11 questions related to prostate cancer knowledge and behaviors.

Prostate Cancer Screenings Health Belief Model Scale (PCSHBMS): PCSHBMS was developed by Çapık and Gözüm (2011) in 2009 based on the health belief theory and tested to be valid and reliable. The scale is a five-point Likert scale (1- Strongly Disagree, 2- Disagree, 3- Undecided, 4- Agree, 5- Strongly Agree) and consists of five sub-dimensions: sensitivity perception (5 items), seriousness perception (4 items), health motivation perception (12 items),

barrier perception (16 items), and benefit perception (7 items), totaling 41 items. The scale does not have a total score; each sub-dimension has its own total score. Higher scores in sensitivity, seriousness, motivation, and benefit sub-dimensions indicate a positive condition, while a higher score in the barrier perception sub-dimension indicates a negative condition. In Çapık and Gözüm's (2011) study, the Cronbach's alpha coefficient of the scale was determined as 0.90 for sensitivity perception, 0.89 for seriousness perception, 0.96 for health motivation perception, 0.94 for barrier perception, and 0.91 for benefit perception. In this study, the Cronbach's alpha coefficients of the scale were determined as 0.88 for sensitivity perception, 0.94 for seriousness perception, 0.79 for health motivation perception, 0.92 for barrier perception, and 0.88 for benefit perception.

Statistical Analysis

The data obtained from the study were analyzed using IBM SPSS Statistics 22.00 software (IBM Corporation, Armonk, NY, USA). For descriptive variables, numbers, percentage distributions, means, and standard deviations were used. Chi-square analyses (Pearson's Chi-square test, Fisher's Exact Chi-square test) were applied to reveal the relationship between variables. The normality of the data was assessed using the Kolmogorov-Smirnov (K-S) test. Due to the data not following a normal distribution, the Mann-Whitney U test was used for comparisons between two groups, and the Kruskal-Wallis test was used for comparisons between more than two groups. The level of statistical significance was set at $p < .05$.

Ethical Approval

Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of a university (Decision no: 2022-11/06; dated 16.11.2022), and institutional permission was obtained from the hospital where the study was conducted (Number: 2022-E1215). Written and verbal consent was obtained from the participants in the sample. The study was conducted in accordance with the Helsinki Declaration and research and publication ethics.

RESULTS

The average age of the participants in the study was 61.59 ± 8.51 years. It was determined that 52.8% of the participants were between the ages of 51-60, 40.3% had primary education, 87.5% were married, and 52.8% had a moderate monthly income (Table 1).

Table 1. Demographic Characteristics of Participants (n=72)

Characteristics	n	%
Mean age: 61.59 (SD=±8.51)		
Ages		
51-60 years	38	52.8
61 years and over	34	47.2
Educational Level		
Illiterate/Literate	18	25
Primary School	29	40.3
High School	15	20.8
University	10	13.9
Marital Status		
Married	63	87.5
Single	9	12.5
Monthly Income Status		
Low	27	37.5
Moderate	38	52.8
High	7	9.7
Total	72	100.0

SD: Standard deviation

The participants' knowledge and screening behaviors related to prostate cancer are presented in Table 2. When the table was evaluated, it was found that 31.9% of the participants had previously undergone prostate examination, and in 81.8% of these cases, the reason for the examination was related to prostate-related complaints. Additionally, 26.4% of the participants knew about prostate cancer, 25% were aware of early detection tests for prostate cancer, 22.2% had undergone a PSA test, and 12.5% had a family member with prostate cancer.

In the study, it was found that 80.6% of the participants did not plan to have a prostate examination within the next six months, and among the reasons for not considering it, 47.2% considered themselves healthy, 18.1% had time constraints, and 13.9% stated that prostate examinations is embarrassing.

In the study, it was determined that the status of undergoing a PSA test did not statistically differ based on age, income status, marital status, and educational background (p > 0.05). However, among participants who had previously undergone a prostate examination, had knowledge about prostate cancer and early detection tests, had a family history of prostate cancer, and planned to have a prostate examination within the next six months, the rate of undergoing a PSA test was statistically significantly higher (p < 0.05) (Table 3).

When the participants' health beliefs regarding prostate cancer screening behaviors were evaluated, sensitivity perception score was determined as 11.13 ± 4.52, seriousness perception score as 13.02 ± 4.11, health motivation perception score as 31.45 ± 7.89, barrier perception score as 44.58 ± 13.55, and benefit perception score as 27.38 ± 5.79 according to the sub-dimensions of the scale.

It was found that there was no significant difference in the scores of PCSHBMS sub-dimensions according to the demographic characteristics of the participants, such as age, monthly income, marital status, and the presence of a family member with

prostate cancer (p > 0.05).

It was found that participants with a lower level of education, those who had not previously undergone a prostate examination, those who did not know about prostate cancer and early detection tests, and those who did not plan to have an examination for prostate cancer within the next six months had higher barrier perception scale scores. Those who underwent a PSA test and those who planned to have an examination for prostate cancer within the next six months had higher health motivation perception scale scores and lower barrier perception scale scores, and the differences between the groups were found to be significant (p < 0.05) (Table 4).

Table 2. Participants' Knowledge and Screening Behaviors Related to Prostate Cancer (n=72)

	n	%
Having a prostate examination before		
Yes	23	31.9
No	49	68.1
Timing of Prostate Examination		
Within the last 0-3 months	3	13.0
Within the last 3-6 months	1	4.3
Within the last 6-9 months	5	21.7
Within the last 9-12 months	2	8.7
More than 1 year ago	12	52.3
Reason for Prostate Examination		
Having prostate-related symptoms	18	81.8
Receiving a recommendation from a healthcare professional	3	13.1
Reading brochures or written materials about prostate cancer	2	5.1
Knowledge about Prostate Cancer		
Yes	19	26.4
No	53	73.6
Someone in The Family Has Prostate Cancer		
Yes	9	12.5
No	63	87.5
Knowing About Early Detection Tests for Prostate Cancer		
Yes	18	25.0
No	54	75.0
Undergoing PSA Testing		
Yes	16	22.2
No	56	77.8
The Time Since The PSA Test /Month	20.93±1.14	
Reason for undergoing PSA test		
Having symptoms related to the prostate.	12	75.5
Recommendation from a healthcare professional.	3	18.8
Reading brochures or written materials about prostate cancer	1	5.7
Thinking about Getting Screened for Prostate Cancer within The Next Six Months		
Yes	14	19.4
No	58	80.6
Reasons for not Considering Undergoing Prostate Examination for Early Diagnosis of Prostate Cancer within The Next Six Months*		
Seeing oneself as healthy	34	47.2
Lack of time	13	18.1
Embarrassment about prostate examination	10	13.9
Not knowing where to apply	10	13.9
Transportation problems	7	9.7
Fear of undergoing prostate surgery	7	9.7
Fear of having prostate cancer	6	8.3
No specific reason	6	8.3

More than one answer has been given

Table 3. Factors Affecting Participants' PSA Testing Behavior (n=72)

	PSA Tested		Not PSA Tested		
Characteristics	**n**	**%**	**n**	**%**	*Test*
Ages					
51-60 years	9	23.6	29	76.3	χ2=1.876
61 years and over	7	20.6	27	79.4	p=.373
Educational Level					
Illiterate/Literate	2	10.0	16	90.0	
Primary School	8	27.6	21	72.4	χ2=4.299
High School	2	13.3	13	86.7	p=.367
University	4	40.0	6	60.0	
Monthly Income Status					
Low	4	14.8	23	85.2	
Moderate	10	26.3	28	73.7	χ2=1.389
High	2	28.6	5	71.4	p=.499
Having a Prostate Examination Before					
Yes	14	60.9	9	39.1	χ2=29.205
No	2	4.1	47	95.9	**p<.001***
Knowledge about Prostate Cancer					
Yes	9	47.4	10	52.6	χ2=9.433
No	7	13.2	46	86.8	**p=.002***
Someone in The Family Has Prostate Cancer					
Yes	5	55.6	4	44.4	χ2=6.661
No	11	17.5	52	82.5	**p=.010***
Knowing about Early Detection Tests for Prostate Cancer					
Yes	9	50.0	9	50.0	χ2=10.714
No	7	13.0	47	87.0	**p=.001***
Thinking about Getting Screened for Prostate Cancer within The Next Six Months					
Yes	8	57.1	6	42.9	χ2=12.262
No	8	13.8	50	86.2	**p=.002***

*p<.05, **p≤.001

Table 4. Comparison of Health Belief Model Scale Sub-Dimension Scores According to Participants' Demographic Characteristics (n=72)

Demographic Characteristics	Sensitivity Perception	Seriousness Perception	Health Motivation Perception	Barrier Perception	Benefit Perception
General score	11.13±4.52	13.02±4.11	31.45±7.89	44.58±13.55	27.38±5.79
Ages					
51-60 years	10.22±4.16	14.59±4.43	32.23±9.18	40.80±13.02	27.88±6.15
61 years and over	11.35±4.96	13.05±3.86	31.17±6.90	48.17±14.17	26.79±5.28
Test	Z=0.655 p=.721	Z=1.364 p=.506	Z=0.243 p=.886	Z=4.143 p=.126	Z=1.936 p=.380
Monthly Income Status					
Low	11.14±4.87	11.92±3.85	31.29±7.47	47.44±14.12	26.29±6.69
Moderate	11.00±4.13	13.36±4.06	31.10±8.43	43.23±12.83	27.76±5.37
High	11.85±5.72	15.42±4.54	34.00±7.02	40.85±15.10	29.57±3.55
Test	KW=0.091 p=.956	KW=4.616 p=.099	KW=0.720 p=.698	KW=3.035 p=.219	KW=1.938 p=.379
Marital Status					
Married	11.58±4.41	12.77±4.10	30.53±7.87	44.92±13.04	27.06±5.87
Single	7.00±3.16	14.62±4.20	38.12±4.70	43.00±18.47	30.37±4.68
Test	Z=-2.917 p=.314	Z=-1.170 p=.242	Z=-2.676 p=.117	Z=-0.600 p=.548	Z=-1.353 p=.176

*p<.05

Table 4. (Continued) Comparison of Health Belief Model Scale Sub-Dimension Scores According to Participants' Demographic Characteristics (n=72)

Demographic Characteristics		Sensitivity Perception	Seriousness Perception	Health Motivation Perception	Barrier Perception	Benefit Perception
Educational Level						
Illiterate/Literate		12.44±6.031	12.22±4.09	30.61±7.15	52.72±14.01	26.00±6.05
Primary School		10.62±3.72	12.65±4.41	29.93±8.63	43.24±12.08	26.82±6.30
High School		10.53±3.09	13.06±3.41	32.06±7.62	42.20±11.14	28.40±5.53
University		11.20±5.45	15.50±3.77	36.50±5.93	37.40±14.99	30.00±3.12
	Test	KW=1.025 p=.599	KW=0.576 p=.750	KW=0.806 p=.669	**KW=6.163 p=.046***	KW=2.316 p=.314
Having A Prostate Examination Before						
Yes		12.26±5.65	13.34±4.98	31.21±8.12	39.13±11.33	26.65±6.60
No		10.61±3.83	12.87±3.67	31.57±7.87	47.14±13.84	27.73±5.41
	Test	Z=-0.786 p=.432	Z=-0.668 p=.504	Z=-0.042 p=.966	**Z=-2.626 p=.009***	Z=-0.437 p=.662
Knowledge about Prostate Cancer						
Yes		12.22±3.55	14.33±4.33	32.00±8.29	39.11±12.21	26.77±7.03
No		10.77±4.77	12.59±3.97	31.27±7.83	46.70±13.58	27.59±5.37
	Test	Z=-0.515 p=.606	Z=-0.418 p=.676	Z=-0.154 p=.878	**Z=-2.269 p=.020***	Z=-0.527 p=.598
Knowing about Early Detection Tests for Prostate Cancer						
Yes		12.22±3.55	14.33±4.33	32.00±8.29	39.11±12.21	26.77±7.03
No		10.77±4.77	12.59±3.97	31.27±7.83	46.40±13.58	27.59±5.37
	Test	Z=-1.495 p=.135	Z=-1.531 p=.126	Z=-0.345 p=.730	**Z=-2.459 p=.014***	Z=-0.360 p=.719
Undergoing PSA Testing						
Yes		11.43±5.22	15.18±3.78	31.87±9.78	40.37±13.71	25.43±7.44
No		11.05±4.35	12.41±4.02	31.33±7.37	45.78±13.38	27.94±5.17
	Test	Z=-0.34 p=.973	**Z=-2.473 p=.010***	Z=-0.502 p=.616	Z=-1.742 p=.820	Z=-1.062 p=.288
Someone in The Family Has Prostate Cancer						
Yes		13.77±5.04	14.11±3.21	33.44±7.85	37.55±7.61	27.11±4.25
No		10.76±4.35	12.87±4.22	31.17±7.93	45.58±13.95	27.42±6.00
	Test	Z=-1.717 p=.086	Z=-1.019 p=.308	Z=-0.324 p=.726	Z=-1.789 p=.074	Z=-0.599 p=.549
Thinking about Getting Screened for Prostate Cancer within The Next Six Months						
Yes		12.78±5.23	14.57±3.79	37.00±7.47	36.14±9.99	29.42±4.29
No		10.74±4.29	12.65±4.12	30.12±7.45	46.6±13.57	26.89±6.02
	Test	Z=1.299 p=.194	Z=-1.653 p=.980	**Z=-2.750 p=.006***	**Z=-2.677 p=.007***	Z=-1.409 p=.159

*p<.05

DISCUSSION

Cancer screening programs have been developed globally with the aim of detecting breast, cervix, colon-rectum, and prostate cancers at an early stage to increase the chances of recovery and reduce the probability of metastasis and cancer-related mortality (Chung et al., 2020; Jamieson et al., 2022; Poppel et al., 2022). Despite efforts to promote the widespread adoption of approaches aimed at early detection of cancers, it has been reported that the rate of recommended PSA testing for early detection of prostate cancer is universally low (5%-47.6%) (Abuadas et al., 2017; Aflakseir, 2016; Mbugua[a] et al., 2021; Mbugua[b] et al., 2021; Shungu & Sterba, 2021). In Turkey, participation rates in prostate cancer screenings vary between 4% and 21.2%, which are insufficient (Bilgili & Kitiş, 2019; Çapık, 2014; Demirbaş & Onmaz, 2021; Kahraman & Kılıç, 2019). In this study evaluating prostate cancer screening behaviors, it was found that 31.9% of the participants had undergone prostate examination, and 22.2% had undergone PSA testing for early diagnosis of prostate cancer. While the PSA testing rate obtained in this study is relatively high

compared to some national (Çapık, 2014; Demirbaş & Onmaz, 2021; Kahraman & Kılıç, 2019) and international studies (Abuadas et al., 2017; Aflakseir, 2016; Alshammari et al., 2021; Mbugua[a] et al., 2021), it is still not at the desired level. This suggests the possibility of delays in the early diagnosis of prostate cancer in our sample group.

In this study, it was determined that the primary reason for participants to undergo PSA testing was prostate-related complaints, and the majority did not consider getting screened for prostate cancer within the next six months. Reasons for not considering screening included seeing oneself as healthy, time constraints, embarrassment associated with prostate examination, not knowing where to go for examination, transportation problems, and fear of prostate surgery and cancer. Prostate cancer is often perceived as a disease of old age by most men, leading middle-aged individuals without symptoms to view themselves as healthy and perceive their risk of prostate cancer as low. Consequently, due to considering prostate examination via the rectal route as embarrassing, uncomfortable, and painful, individuals tend to avoid going to the hospital for prostate examination, significantly hindering participation in screenings (Alshammari et al., 2021; Bamidele et al., 2022; Bilgili & Kitiş, 2019; Mbugua[a] et al., 2021; Mbugua[b] et al., 2021; Shungu & Sterba, 2021; Zare et al., 2016). Individuals' thoughts related to prostate cancer, including the perception that the diagnosis and treatment of prostate cancer are major life events causing stress (Jakimowicz et al., 2020), lack of knowledge and awareness, the fear of cancer diagnosis affecting their masculinity, and fear of death, as well as financial constraints, have been reported as reasons for not undergoing prostate examination and early diagnosis testing (Bamidele et al., 2022; Bilgili & Kitiş, 2019; Demirbaş & Onmaz, 2021; Zare et al., 2016). Due to such thoughts of individuals related to prostate cancer, 75% of prostate cancer cases are diagnosed at an advanced stage, significantly reducing the chances of treatment and increasing mortality rates (Yeboah-Asiamah et al., 2017). In line with the results obtained from the literature and this study, it can be said that developing routine screening programs for

PSA testing for men aged 50 and over, close monitoring of healthcare services on digital platforms, identification of factors affecting participation in prostate cancer screening programs, determining motivating and inhibiting factors for individuals, and providing information to overcome barriers may increase early diagnosis and cancer-related survival rates.

In this study, it was found that the PSA testing status did not differ according to sociodemographic factors such as age, income level, marital status, and education level. These findings differ from most of the studies conducted on the subject (Aflakseir, 2016; Bilgili & Kitiş, 2019; Demirbaş & Onmaz, 2021). In the literature, sociodemographic factors are considered important in participation in screening programs, with advanced age, higher education level, and employment status increasing the participation rate in prostate cancer screening behaviors (Aflakseir, 2016; Bilgili & Kitiş, 2019; Demirbaş & Onmaz, 2021). The difference between our study and other studies may be due to differences in the sociodemographic characteristics of the sample group studied. However, research findings of the study conducted by Çapık (2012) support our study. These different results in the literature suggest the need for more extensive multi-center studies and the importance of integrating the results with screening programs. In this study, it is observed that having a family history of prostate cancer increases the participation rate in prostate cancer screening behaviors. In the literature, having a family member diagnosed with prostate cancer is emphasized as an important factor affecting the willingness to undergo PSA testing (Abuadas et al., 2017; Aflakseir, 2016; Bilgili & Kitiş, 2019; Demirbaş & Onmaz, 2021). The finding from this study and the literature suggests that participants with a family history of prostate cancer may believe they are genetically predisposed to cancer, share the experiences of their relatives diagnosed with prostate cancer closely during their fight against cancer, and therefore be aware of the importance of early diagnosis in cancer.

In this study, where we evaluated individuals' health beliefs regarding prostate cancer screenings, the sensitivity perception scale score was determined as

11.13±4.52, the seriousness perception score was 13.02±4.11, the health motivation perception score was 31.45±7.89, the obstacle perception score was 44.58±13.55, and the benefit perception score was 27.38±5.79. These findings obtained from the study can be interpreted as individuals' perception of their susceptibility to prostate cancer was low and their perception of obstacles to prostate cancer screening behaviors was high. The sensitivity, seriousness, health motivation and benefit perception scores obtained from the study are similar to the results of other studies conducted on the subject (Zare et al. 2016; Abhar et al. 2022; Demirbaş and Onmaz 2021; Kahraman and Kılıç 2019), but the obstacle perception score was significantly higher than the results of other studies (Abhar et al. 2022; Demirbaş and Onmaz 2021; Kahraman and Kılıç 2019). This finding shows that individuals have obstacles to prostate cancer screening and interventions should be planned to identify and eliminate obstacles.

When the scale scores were compared according to the characteristics of the individuals in the study, it was found that there was no difference between the scale scores according to age, monthly income, marital status, and having someone in the family diagnosed with prostate cancer (p>0.05), while the obstacle perception scale score was higher in individuals with lower education levels. In Demirbaş and Onmaz's (2021) study, it was determined that the obstacle perception score was higher in those who were not working, and there was no relationship between other variables and health belief sub-dimensions. In Kahraman and Kılıç's study, it was determined that working time and age significantly affected the perception of seriousness. Yeboah-Asiamah et al. (2017) found that there was no relationship between demographic variables and perceptions about prostate cancer.

In the study, the obstacle perception scale score was found to be high in those who had not had a prostate examination before, who did not know about prostate cancer and early diagnosis methods, and who did not plan to be examined for the diagnosis of prostate cancer within six months. In the study, it was also determined that the health motivation perception scale score was higher in those who had a PSA test and planned to be examined for the

diagnosis of prostate cancer within six months. These findings obtained from the study show that health motivation perception specific to prostate cancer is important in the participants' decision to have a PSA test, and obstacle perception is important in not having or considering having a PSA test. Similar studies evaluating individuals' prostate cancer screening behaviors using the health belief model also reported that individuals with high scale scores of prostate cancer-specific sensitivity (Abuadas et al. 2017), seriousness (Kahraman and Kılıç, 2019), benefit (Abuadas et al. 2017; Demirbaş and Kanmaz, 2021; Kahraman and Kılıç, 2019), health motivation perception (Abuadas et al. 2017; Demirbaş and Kanmaz, 2021; Bilgili, Kitiş, 2019) and low obstacle perception scale score (Abuadas et al. 2017 Demirbaş and Kanmaz, 2021; Bilgili, Kitiş, 2021) had a higher rate of PSA testing. In line with the findings obtained from this study, it can be said that planning interventions that increase individuals' motivation for prostate cancer screening and reduce their obstacle perceptions can increase the rate of PSA testing.

CONCLUSION

The study revealed that individuals have low level of knowledge regarding prostate cancer and early diagnostic tests, the rate of PSA testing is low and motivation and obstacle perception are important for prostate cancer screening. Health beliefs and perceptions were identified as fundamental factors influencing prostate cancer screening behaviors. Information provided by healthcare professionals plays a significant role in patients' decisions to participate in cancer screening. Therefore, healthcare professionals should provide information about prostate cancer and screening both in clinical settings and at the community level, assess individuals' perceptions regarding screenings, and support men in making decisions about undergoing tests. The results of this study serve as a preliminary assessment for future research. Therefore, we recommend to support nurse-intensive work areas to increase cancer screenings and to conduct studies with a large number of samples.

Limitations

There are some limitations to this study. Firstly, the PSA values of the participants were not known. Secondly, the relatively small sample size in single-center is another limitation of the research.

Conflict of Interest

There is no conflict of interest between the authors.

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Türk Fen ve Sağlık Dergisi

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Examining The Effect of Menopausal Symptoms on General Health Status in Postmenopausal Women

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ABSTRACT:

Purpose: The aim of this study is to examine the effect of menopausal symptoms on general health status in postmenopausal women.

Material and Methods: Our study is a descriptive type of study. It was conducted on 223 women aged 45-65 who applied to a family health center between October and November 2019 and at least 12 months had passed since their last menstrual period. A personal information form developed by the researcher, Menopause Symptom Scale (MSDS) and General Health Questionnaire-28 (GHQ-28) were distributed to women who agreed to participate in the study. Descriptive statistics are used for individual information during statistical analysis of data. Chi-square test was used to evaluate the data obtained by counting.

Results: The mean MSDS score for women was 22.72. In the General Health Survey, it was determined that the subsections most affected by menopausal symptoms experienced by women were somatic symptoms, anxiety, sleep disorders and depression, social functioning and depression. Highly significant positive relationships were found between the Menopause Symptoms Assessment Scale and its subscales experienced by women and GHQ-28.

Conclusion: Menopause symptoms seen in postmenopausal women affect the general health of women. Women registered at the family health center need to plan menopause education and train regularly.

Keywords: Menopause; Menopausal Symptoms; Women's Health

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INTRODUCTION

When human life is considered as a period, it is divided into certain periods because each period is unique and shows physical, emotional and hormonal changes (Çelik, 2015). The stages of a woman's life are discussed in four stages: adolescence, sexual maturity, climax and old age (Taşkın, 2016).

Menopause is one of the life periods of a woman and is a natural process that is a part of aging. The word menopause consists of the words meno (month) and pausis (pause), which are used to describe the end of the menstrual cycle. (Yavan and Köprülü, 2022). According to Turkish Statistical Institute (TUIK, 2020) data; The average life expectancy of women in

Turkey is 81.3 years (Turkish Statistical Institute [TUIK], 2020). With the increase in life expectancy, the time women spend in the menopausal period is increasing, and the menopausal period constitutes an important part of women's lives. The number of women in the postmenopausal period is expected to exceed 1.1 billion in 2025 (Çelikkanat and Sohbet, 2020; Yavan and Köprülü, 2022)

Some changes occur in women due to the hormonal changes that occur during menopause. During the menopausal period, women experience changes in sexual function, physiological and psychosocial changes, from vasomotor symptoms to mood changes (Tümer and Kartal, 2018; Çelikkanat and

Sohbet, 2020). During menopause, women experience somatic complaints such as headache, palpitations, shortness of breath, sleep disorders, muscle and joint disorders, cardiovascular system diseases, vasomotor symptoms such as hot flashes and sweating, psychological complaints such as fatigue, malaise, weakness, anxiety, irritability, depression, and Urogenital complaints such as decreased sexual desire, stress incontinence, vaginal dryness, dyspareunia may be observed. While some women perceive these changes as normal and part of a natural process, some women may experience serious problems that negatively affect their lives. The incidence and severity of problems experienced during the menopausal period vary depending on the woman's sociocultural status, the way she entered menopause, her age at menopause, her sexual activity, her level of education, and her personal thoughts about menopause (Çelikkanat and Sohbet, 2020; Kurt and Arslan, 2020; Gönenç and Koç, 2019).

It is suggested that nurses and midwives play an active role in reducing the severity and negative effects of menopause symptoms, helping women develop positive attitudes towards menopause and coping with the symptoms (Tümer and Kartal, 2018). Although it is a common problem during menopause, it has been reported that many women are reluctant to discuss sexual health problems with other women or doctors because they find them embarrassing (Nappi and ark., 2018). For this reason, it is recommended that nurses working with menopause diagnose the sexual health of women in menopause, provide training and consultancy to improve the quality of women's sexual life, plan appropriate treatment procedures and refer them to a specialist if necessary (Süt and Küçükkaya, 2018).

For example, women's health nurses have the role of providing care, consultancy and education to improve the quality of life of women who spend an important and long period of their lives during menopause (Taşkın, 2016). In this period when life expectancy increases, the changes caused by menopause, which is a long period, cannot be ignored. This study was conducted to determine the effect of menopausal symptoms experienced by menopausal women on their general health.

MATERIAL and METHODS
Purpose and Type of the Study
This descriptive study was conducted to determine the effect of menopausal symptoms on general health status in postmenopausal women.

Research Questions
1. What is the incidence and rate of menopausal fertility in women?
2. General health effects during menopause?
3. Is there a relationship between menopausal championship and general health status?
4. What are the factors affecting menopausal victories?

Sampling and participant
The population of the research consisted of women between the ages of 45-65 who were registered to the family health center and at least 12 months had passed since their last menstrual period. Since the number of individuals in the target population is unknown, the sampling formula is used to determine the sample size when the population is unknown. In a previous study, the average score of the Menopause Symptoms Assessment Scale in women was found to be 14.65±7.62 (Tümer and Kartal, 2018) When the sample was calculated based on this average score, it was revealed that 223 women should be included in the study. The criteria for inclusion in the sample of the study were as follows: Women who agreed to participate in the study, who were affiliated with the family health center where the research was conducted, at least 12 months had passed since the last menstrual period, and who were between the ages of 45-65, were included.

Data Collection Tools
Personal Information Form, General Health Survey-28 (GHQ-28) and Menopause Symptoms Assessment Scale (MSDS) were used to collect data.
In our study, data collection forms were applied through face-to-face interviews between October 2019 and November 2019 from women who applied to the Alibaba Family Health Center in the city center of Sivas and met the research criteria and agreed to participate in the study. Before the forms were applied, women were informed about the research.

The interviews lasted approximately 25 minutes for each woman, with an average of 5 minutes for the Personal Information Form and 20 minutes for the scales. In our research, the forms were filled out by the researcher.

Personal Information Form

A personal information form containing the descriptive characteristics of women was developed by the researcher based on the literature and consisted of 15 questions. The personal information form includes questions regarding socio-demographic characteristics such as age, education level, smoking and alcohol consumption. Questions regarding obstetric and gynecological features; It arises from questions about the number of pregnancies, the number of surviving children, the method of menopause, the use of hormone replacement therapy, and if menopause was achieved, by what means.

Menopause Symptom Scale (MSDS)

The scale was developed in German by Schneider, Heinemann et al. (1992). The currentness and development of the scale was studied by Gürkan (2005). Likert-type scale options for menopause are: 0: none, 1: mild, 2: moderate, 3: severe, and 4: very severe. The lowest score calculated from the scale is "0" and the highest score is "44". The scale covering menopause symptoms consists of 3 subscales and 11 items. Sub-dimensions are physical complaints (items 1, 2, 3 and 11), psychological complaints (items 4, 5, 6 and 7). Urogenital complaints (8th, 9th and 10th items). An increase in the total score obtained from the scale indicates that the diseases are getting worse, and the quality of life is negatively affected. The Cronbach's alpha reliability coefficient of the initial form of the scale is 0.84. Cronbach's alpha values of the subscales were found to be 0.65 for somatic symptoms, 0.79 for psychological symptoms and 0.72 for genital symptoms (Gürkan, 2005). In our study, the Cronbach's alpha value was calculated as 0.76.

General Health Questionnaire-28 (GHQ-28)

The general health questionnaire was developed by Goldberg in 1972, and the study on the validity and reliability of the questionnaire in Turkey was conducted by Kılıç in 1996. In the study conducted by Kılıç, the reliability (Cronbach's alpha) of GHQ-28 was found to be 0.94. The survey consisted of four subsections, each consisting of seven items. These parts: Physical symptoms include anxiety and sleep disorders, impairment in social functioning, and severe depression. The 28-item scale includes a question about whether each individual has recently filed a complaint and four-item responses ranging from "less than normal" to "more than normal." Accordingly, elements a, b are taken as "(0) 0", and elements c, d are taken as "(1) one". After the application, a minimum of 0 and a maximum of 28 points can be obtained, and higher scores increase the risk of mental health disorders (Kılıç, 1996).

Statistical Analysis

The data obtained from our study were evaluated using the SPSS 23.0 program. Normality of data was tested using the Kolmogorov-Smirnov test. If the data met parametric conditions, they were analyzed by independent samples t test for two independent groups and F test (ANOVA) for more than two groups. When ANOVA was used to make comparisons with more than two groups, it was determined which groups deviated from the assumption using Tukey tests for those that met the homogeneity assumption and Tamhane's T2 tests for those that did not meet the homogeneity assumption. If one or all of the assumptions were not met, the Mann Whitney U test was applied to two independent groups and the Kruskal Wallis test was applied to more than two independent groups. Chi-square test was used to evaluate the data obtained by counting. The deviation level was taken as 0.05.

Ethical Approval

Before implementation, ethics committee approval was obtained from the Non-Interventional Ethics Committee of Sivas Cumhuriyet University Faculty of Medicine, with the decision dated 07.08.2019 and numbered 2019-08/03. Turkish Republic, where the family health center where the study will be conducted is affiliated. Approval was received from Sivas Governorship Sivas Provincial Health Directorate. Since participation in the research was

voluntary, women were informed about the study and necessary permissions were obtained.

RESULTS

Table 1 presents the statistical data and Cronbach Alpha values of women's MSDS and its subscales. In our study, women's mean score in the "somatic symptoms" subscale of MSDS is 9.07±1.86, their mean score in the "psychological symptoms" subscale is 8.04±2.30, and their mean score in the "urogenital symptoms" subscale is 5.60±2. .05, total MSDS score average was found to be 22.72±4.82.

Table 2 shows the findings regarding the severity of menopause symptoms in women. As can be seen when the table is examined, 55.6% had severe hot flashes and sweating, 39.5% had moderate heart problems, 51.1% had severe sleep problems, and

62.3% had malaise. , 54.7% reported being irritable, 51.6% experienced moderate levels of anxiety, 57% experienced severe physical and mental fatigue, 32.3% experienced severe sexual problems, 44% It was determined that 4.4% of the patients experienced moderate urinary problems, 47.5% experienced moderate vaginal dryness, and 69.5% experienced moderate bone and muscle disorders.

Table 3 examines the differences in the descriptive characteristics of women in terms of the menopause symptoms evaluation scale. Accordingly, while the difference between women's age groups in the scale sub-dimensions of somatic complaints (p=0.000) and urogenital complaints (p=0.001) was found to be significant (p<0.05), the difference in the psychological complaints dimension (p=0.667) was deemed insignificant (p>0.05).

Table 1. Statistical data of women's MSDS and its subscales, Cronbach Alpha values

MSDS subdimensions	Number of items	Lower and upper values that can be taken	Marked lower and upper values	Scale Cover. ±SS	Cronbach Alpha value
Somatic Symptoms	4	0-16	3,00-13,00	9,07±1,86	0,74
Psychological Symptoms	4	0-16	2,00-14,00	8,04±2,30	0,75
Urogenital Symptoms	3	0-12	1,00±10,00	5,60±2,05	0,78
Total MSDS	11	0-44	8,00±34,00	22,72±4,82	0,76

MSDS: Menopause Symptoms Assessment Scale, Mean: average, SD: Standard Deviation, t-test

Table 2. Distribution of Menopausal Symptoms Experienced by Women According to Severity

MSDS items	None (0)		Mild (1)		Moderate (2)		Severe (3)		Very severe (4)	
	n	%	n	%	n	%	n	%	n	%
1. Hot flashes, sweats	8	3,6	84	37,7	-	-	124	55,6	7	3,1
2. Heart disorders	28	12,6	80	35,9	88	39,5	25	11,2	2	0,9
3. Sleep problems	9	4,0	-	-	52	23,3	114	51,1	48	21,5
4. State of malaise	6	2,7	32	14,3	139	62,3	42	18,8	4	1,8
5. Irritability	10	4,5	65	29,1	122	54,7	26	11,7	-	-
6. Worry/Anxiety	15	6,7	61	27,4	115	51,6	30	13,5	2	0,9
7. Phys. and mental fatigue	-	-	10	4,5	84	37,7	127	57,0	2	0,9
8. Sexual problems	20	9,0	58	26,0	66	29,6	72	32,3	7	3,1
9. Urinary problems	33	14,8	70	31,4	99	44,4	19	8,5	2	0,9
10. Dryness in the vagina	3	1,3	39	17,5	106	47,5	69	30,9	6	2,7
11. Joint and muscle disorders	3	1,3	23	10,3	155	69,5	40	17,9	2	0,9

[MSDS] Menopause symptoms assessment scale. T test

While the difference between women's marital status and the somatic complaints (p=0.141) and psychological complaints (p=0.972) sub-dimensions was deemed insignificant (p>0.05), the difference between the urogenital complaints (p=0.000) dimension was statistically significant (p<0.05).

Table 3. Examination of the Differentiation of Women's Descriptive Characteristics According to the Menopause Symptoms Evaluation Scale

Variable	somatic complaints			psychological complaints			Urogenital complaints		
Age	$\bar{x}$ ±SS	Min	max	$\bar{x}$ ±SS	Min	max	$\bar{x}$ ±SS	Min	max
45-50	7,85±2,19	3,00	13,00	8,01±2,44	2,00	14,00	4,85±2,19	1,00	10,00
51-55	9,11±1,67	6,00	13,00	8,09±2,39	2,00	13,00	5,31±2,05	1,00	9,00
56-60	9,50±1,61	6,00	13,00	7,78±2,24	2,00	12,00	5,76±2,02	2,00	10,00
61>	9,71±1,34	7,00	13,00	8,30±2,16	4,00	13,00	6,30±1,70	2,00	9,00
Analysis	**KW=13,420; p=0,000**			KW= 0,523; p=0,667			**KW=5,625; p=0,001**		
Marital status									
Married	9,07±1,92	3,00	13,00	8,07±2,24	2,00	14,00	6,02±1,94	1,00	10,00
Single	9,47±1,55	6,00	13,00	7,97±2,44	2,00	12,00	5,05±2,03	2,00	9,00
Divorced	8,58±1,85	5,00	13,00	8,03±2,48	2,00	12,00	4,16±1,84	1,00	8,00
Analysis	KW= 1,978; p=0,141			KW= 0,028; p=0,972			**KW= 13,651; p=0,000**		
Education									
illiterate	9,75±1,73	7,00	13,00	8,02±2,02	3,00	12,00	6,20±2,09	2,00	10,00
literate	9,14±1,97	3,00	13,00	8,50±2,62	2,00	14,00	5,82±1,96	2,00	10,00
Primary school	8,60±1,69	4,00	12,00	8,00±1,98	2,00	12,00	5,30±2,22	1,00	8,00
Middle school	7,43±2,27	3,00	13,00	7,39±7,39	2,00	11,00	4,13±1,69	1,00	7,00
High school	9,10±1,16	7,00	12,00	7,60±2,76	4,00	13,00	5,23±1,74	2,00	9,00
University and above	9,82±1,19	7,00	12,00	8,65±1,90	6,00	12,00	6,24±1,71	3,00	8,00
Analysis	**KW= 7,108; p=0,000**			KW= 1,227; p=0,297			**KW= 4,518; p=0,001**		
Working status									
not working	9,15±1,83	3,00	13,00	8,14±2,50	2,00	14,00	5,87±2,03	1,00	10,00
Retired	9,84±1,46	7,00	13,00	8,14±1,76	4,00	11,00	5,93±1,96	2,00	8,00
working	8,13±1,92	3,00	13,00	7,70±2,19	2,00	11,00	4,53±1,89	1,00	8,00
Analysis	**KW= 10,773; p=0,000**			KW= 0,674; p=0,511			**KW= 8,626; p=0,000**		
Smoking									
Yes	8,78±1,89	3,00	13,00	8,11±2,31	2,00	13,00	5,42±2,05	1,00	9,00
No	9,31±1,81	3,00	13,00	7,99±2,29	2,00	14,00	5,75±2,05	1,00	10,00
Analysis	**MW=4,560; p=0,034**			MW=0,162; p=0,688			MW=1,370; p=0,243		
Number of pregnancies									
1 time	8,48±1,95	5,00	13,00	8,67±2,50	2,00	14,00	4,81±2,09	1,00	8,00
2 times	8,91±2,03	3,00	13,00	8,30±1,79	5,00	12,00	5,33±2,23	1,00	10,00
3 times	8,69±2,05	3,00	13,00	7,65±2,45	2,00	12,00	5,60±2,05	1,00	9,00
4 times	9,00±1,71	6,00	13,00	7,49±2,29	2,00	12,00	5,69±2,00	2,00	10,00
5 times	9,88±1,45	7,00	13,00	8,00±2,24	4,00	13,00	5,77±1,95	2,00	10,00
6 and above	10,04±1,11	8,00	12,00	8,88±2,39	4,00	13,00	6,54±1,65	4,00	9,00
Analysis	**KW= 3,649; p=0,003**			KW= 2,113; p=0,065			KW= 2,135; p=0,062		
Continuous drug use									
Yes	9,47±1,69	3,00	13,00	8,27±2,10	2,00	13,00	5,98±1,86	2,00	10,00
No	7,79±1,80	3,00	11,00	7,48±2,73	2,00	14,00	4,44±2,27	1,00	8,00
Analysis	**MW=17,696; p=0,000**			**MW=3,017; p=0,047**			**MW=11,789; p=0,000**		
Path to menopause									
naturally	8,93±1,92	3,00	13,00	7,81±2,28	2,00	14,00	5,51±2,04	1,00	10,00
surgically	9,67±1,43	6,00	13,00	9,10±2,13	5,00	13,00	6,00±2,06	2,00	10,00
Analysis	**MW= 5,205; p=0,023**			**MW= 10,574; p=0,001**			MW= 1,846; p=0,176		
Going to the doctor for menopause									
Yes	9,12±2,01	3,00	13,00	8,67±2,13	2,00	14,00	5,84±2,01	1,00	10,00
No	9,00±1,67	3,00	12,00	7,33±2,29	2,00	12,00	5,31±2,06	1,00	10,00
Analysis	MW= 0,216; p=0,643			**MW= 20,272; p=0,000**			MW= 3,758; p=0,054		
Receiving information about menopause									
Yes	9,08±1,89	3,00	13,00	8,24±2,27	2,00	14,00	5,56±2,04	1,00	10,00
No	9,05±1,80	3,00	12,00	7,66±2,31	2,00	12,00	5,67±2,09	1,00	10,00
Analysis	MW= 0,010; p=0,921			MW= 3,158; p=0,077			MW= 0,146; p=0,703		

[SS] Standard deviation, Mann Whitney U test, Kruskal Wallis test, independent samples t test

Table 3. (Continued) Examination of the Differentiation of Women's Descriptive Characteristics According to the Menopause Symptoms Evaluation Scale

Variable	somatic complaints			psychological complaints			Urogenital complaints		
Number of Living Children									
None	8,77±1,09	7,00	10,00	8,77±1,85	5,00	11,00	5,44±2,06	3,00	8,00
one	8,29±2,23	4,00	13,00	8,54±2,73	2,00	14,00	4,91±2,20	1,00	8,00
2	8,79±1,94	3,00	13,00	7,97±2,14	2,00	12,00	5,40±2,18	1,00	10,00
3	8,97±1,51	3,00	13,00	7,51±2,30	2,00	12,00	5,30±1,84	2,00	10,00
4	9,76±1,51	7,00	13,00	8,28±2,20	3,00	12,00	6,10±1,72	2,00	9,00
5 and above	10,29±1,04	8,00	12,00	8,88±2,44	4,00	13,00	7,47±1,73	4,00	10,00
Analysis	**KW= 3,992; p=0,002**			KW= 1,701; p=1,136			**KW= 4,551; p=0,001**		
Number of Miscarriages									
None	9,05±1,93	3,00	13,00	8,02±2,27	2,00	14,00	5,54±2,22	1,00	10,00
one	9,00±1,78	4,00	13,00	7,96±2,37	4,00	13,00	5,73±1,62	1,00	9,00
2	9,38±1,61	4,00	12,00	8,38±2,40	5,00	12,00	5,27±1,87	2,00	9,00
3	9,25±1,70	7,00	11,00	8,50±2,51	5,00	11,00	7,25±1,50	5,00	8,00
Analysis	KW= 0,215; p=0,886			KW= 0,209; p=0,890			KW= 1,132; p=0,337		
Number of Abortions									
None	9,05±1,89	3,00	13,00	8,10±2,23	2,00	14,00	5,58±2,04	1,00	10,00
one	9,22±1,68	6,00	13,00	7,67±2,71	2,00	13,00	5,74±2,19	2,00	10,00
2	1,0±8,00	8,00	8,00	8,00±	8,00	8,00	5,00±	5,00	5,00
Analysis	KW= 0,280; p=0,756			KW= 0,468; p=0,627			KW= 0,124; p=0,884		
Getting HRT from the doctor									
I did not take	9,00±1,87	3,00	13,00	7,75±2,41	2,00	14,00	5,72±2,00	1,00	10,00
I'm still taking it	8,17±1,62	5,00	12,00	7,89±2,12	4,00	12,00	4,20±1,98	1,00	8,00
I bought it first, it's not there now	9,52±1,81	3,00	13,00	8,58±2,10	2,00	13,00	5,94±1,96	1,00	10,00
Analysis	**KW= 5,906; p=0,003**			KW= 3,047; p=0,050			**KW= 8,468; p=0,000**		

[SS] Standard deviation, Mann Whitney U test, Kruskal Wallis test, independent samples t test

While the difference between the educational status of women in the sub-dimensions of the scale, Somatic Complaints (p=0.000) and Urogenital Complaints (P=0.001), was found to be statistically significant, the difference in Psychological Complaints (P=0.297) was found to be insignificant (p>0.05). Similarly, while the difference in women's employment status in terms of somatic and urogenital complaints was found to be significant (p<0.05), the difference in psychological complaints was found to be insignificant (p>0.05).

While the difference in women's smoking status according to the somatic complaints sub-dimension was found to be statistically significant (p=.034), the difference in the psychological and urogenital complaints sub-dimension was found to be statistically insignificant (p>0.05). Similarly, the number of pregnancies differs significantly with the somatic sub-dimension (p<0.05), while the difference with the psychological and urogenital complaints sub-dimension seems insignificant (p>0.05).

As can be seen in Table 4, it was observed that the somatic symptoms dimension of the GHQ-28 subscale had a positive and strong relationship with all statements except heart diseases, which is the second of the statements in MSDS. It has been determined that the anxiety and sleep problems dimension has a positive and strong relationship with all of the statements in MSDS except heart diseases. It was observed that the impairment in social functions dimension had a positive and strong relationship with all expressions except hot flashes and sweating, while the depression dimension had a positive and strong relationship with all expressions except sexual problems in the scale, and it had a moderate positive relationship with the expression sexual problems. In addition, while the entire GHQ-28 scale was found to have a positive and strong relationship with the statements other than heart diseases in the MSDS scale and the sub-dimension formed by these statements, it was found to have a positive and moderate relationship with the statement of heart diseases.

Table 4. Effect of MSDS on Sub-Dimensions of GHQ-28 Scale

	GHQ-28				
	Somatic symptoms	Anxiety-sleep disorders	Social Function Corruption	Depression	GHQ-28
MSDS	r	r	r	r	r
1. Hot flashes, sweats	,326**	,380**	,086	,158*	,276**
2.Heart disorders	,069	-,015	,234**	,248**	,159*
3.Sleep problems	,567**	,614**	,541**	,289**	,605**
4. State of malaise	,398**	,409**	,328**	,478**	,471**
5. Irritability	,430**	,605**	,330**	,456**	,535**
6.Worry/Anxiety	,549**	,642**	,478**	,561**	,656**
7. Phys. and mental fatigue	,534**	,539**	,475**	,455**	,592**
8. Sexual problems	,347**	,306**	,326**	,132*	,335**
9. Urinary problems	,359**	,197**	,460**	,313**	,398**
10. Dryness in the vagina	,419**	,279**	,417**	,307**	,423**
11.Joint and muscle disorders	,420**	,343**	,418**	,269**	,434**
MSDS Sub-dimensions					
somatic	,514**	,486**	,502**	,378**	,560**
Psychological	,589**	,681**	,496**	,606**	,697**
urogenital	,489**	,346**	,521**	,318**	,501**
MSDS whole	,688**	,661**	,653**	,571**	,763**

*: Correlation at 0.05 level; **Correlation is at 0.01 level

Simple enrichment analysis was used in the comparisons in this table

DISCUSSION

The distribution of the women participating in the study was examined according to some descriptive characteristics. As a result of this analysis, 26.9% of the participants were between the ages of 56-60, 69.1% were married, 26.9% had primary school education, 59.2% were not working, 53.8% were not working. It was determined that 80.3% of them did not smoke and 80.3% did not drink alcohol.

The average age of the 223 women who participated in our study was found to be 55.85. Contrary to the results of our study, the average age of women was found to be 50.4 ± 3.6 years in Gözüyeşil and Başer's (2016) study.

n our study, it was found that 69.1% of postmenopausal women were married. In other studies, the rate of being married was found to be high in postmenopausal women (Özgen and Saka, 2022; Özdemir and Kavak Budak, 2021; Tümer and Kartal, 2018). The results of our study are similar to the literature.

In the study, it was determined that 26.9% of the participants were primary school graduates and 7.6% did not receive any education. In Alparslan's (2018) study, it was found that 56.4% of the participants were high school and university graduates, and in Kurt and Arslan's study, 55.4% of the women were primary school graduates. The

reason for the high level of education in our study is that as social conditions improve, women's education level increases, the importance of women's education increases and the importance of participation in working life increases.

n our study, it was found that 59.2% of postmenopausal women were not working. Similar to the results of this study, it has been found in various studies that postmenopausal women generally do not work in an income-generating job (Özgen and Saka, 2022; Özdemir and Kavak Budak, 2021).

In the study, the average MSDS score of women was determined as 22.72±4.82. In the study conducted by Kurt and Arslan (2020), the average MSDS score of women was found to be 17.6±8.8. In Alparslan's (2018) study, the mean total score of the scale was reported as 16.11±10.34. Our study differs from the literature.

In our study, the most common menopausal symptoms are somatic complaints, followed by psychological and urogenital complaints. In the study conducted by Tümer and Kartal (2018), it was found that women mostly complained of psychological symptoms. In the study conducted by Gümüşay and Erbil (2019), it was found that women mostly experienced physical complaints, followed by sexual, vasomotor and psychosocial complaints. The reason

for different results from different studies is that women's sociocultural characteristics, socio-demographic status and other lifestyle differences affect the severity and frequency of menopausal complaints.

In our study, it was revealed that the top 3 major complaints were physical and mental fatigue at a rate of 57.0%, heat and sweating at a rate of 55.6%, and sleep disorders at a rate of 51.1%, and our study is similar to some studies in the literature. In the study conducted by Khatoon et al. (2018) to determine women's menopausal symptoms, it was found that women experienced problems such as muscle and joint pain, malaise, heart diseases, fatigue, sleep problems, hot flashes, sweating and irritability at the highest rate. In the study conducted by Vaccaro et al. (2021), it was determined that the participants most frequently experienced muscle and hot flash problems. In line with the results of the study, although the studies were conducted in different regions and different cultures, it is evaluated that the effect of hormonal changes experienced during this period causes similar complaints in most women. According to the results of our study, it is evaluated that the reason for the differences in the severity of menopausal symptoms experienced by menopausal women is related to cultural factors, sociodemographic characteristics and age.

The somatic domain scores of women between the ages of 45-50 were found to be lower than the somatic domain scores of women between the ages of 51-65. Urogenital area scores of women between the ages of 45-50 were found to be lower than the urogenital area scores of women between the ages of 56-65. It has been determined that complaints in the urogenital and somatic areas increase with increasing age.

While the difference between women's marital status and the somatic complaints and psychological complaints dimensions, which are sub-dimensions of the scale, was deemed insignificant, the difference with the urogenital complaints dimension was found to be statistically significant. It was found that married women had higher uregenital area scores.

In the study of Özpınar and Çevik (2016), it was found that all mean scores of married people were

significantly higher. In Iran, Ghazanfarpour et al. In a study conducted by, it was determined that there was a significant relationship between marital status and sexual symptoms (change in sexual desire, vaginal dryness, avoidance of sexual intercourse), and that single people had fewer sexual symptoms.

In our study, it was determined that the somatic and urinary field scores of unemployed women were higher than those who were employed. There are studies with similar results in the literature (Kurt and Aslan, 2020).

Ergin (2016) study, it was found that somatic and psychological symptoms were more common in non-working women.

These results may suggest that women who experience fewer problems and complaints about menopause may experience fewer complaints about menopause by engaging in an occupation for themselves, diverting their attention to other directions, and being in social environments.

In our study, the somatic complaints domain score of non-smoking women was found to be higher. In their study by Im et al. (2014), it was reported that women who had smoked before experienced menopausal symptoms more frequently than women who had never smoked.

Since estrogen levels in women who smoke are low before menopause, this may be one of the reasons why there is no sudden decrease in estrogen levels during the menopausal period and there is no significant difference in menopausal symptoms between smokers and non-smokers.

In our study, the number of pregnancies differs significantly with the somatic complaints sub-dimension, and the difference with the psychological and urogenital complaints sub-dimension seems insignificant. In our study, it was found that women with 4 or more pregnancies had higher somatic domain scores. Similar to the findings of our study, the study conducted by Çelik and Pasinlioğlu (2014) found that women with 6 or more pregnancies experienced menopausal symptoms at a higher rate than other women.

In our study, it was determined that the entire GHQ-28 scale had a positive and strong relationship with the other expressions in the MSDS scale, except

heart diseases, and the sub-dimensions in which these expressions were formed.

In our study, the anxiety and sleep disorders subscale of GHQ-28 has a strong positive relationship with all of the statements in MSDS except heart diseases. Similar to the results of our study, it is thought that the changing hormonal balance during menopause affects the central nervous system and causes changes in mood and behavior. It is very important to follow women during the menopause transition period in order to detect and prevent mental disorders that may occur over time (Erbil, 2018). When the studies conducted in the postmenopausal period are examined, Kalhan et al. (2020) in their study investigating the effect of menopausal symptoms on the quality of life between the ages of 40-60, found that the frequency of menopausal symptoms was 87.7%, the frequency of anxiety was 80%, fatigue was 71.5%, sleep problems was 71.5%. 61.2% and 70.8% reported a deterioration in quality of life.

Similar to the results of our study, Kim et al. (2018) showed in their study that the changes that occur after menopause negatively affect the person's quality of life and sleep.

In our study, the depression dimension from the GHQ-28 subscale has a strong positive relationship with all of the statements in the MSDS except sexual problems. Similar to the findings of our study, in an urban-centered study by Ahlawat et al. (2019), they stated that 58.4% of postmenopausal women had no depressive symptoms, 38.3% had mild depression, and 3.3% had moderate depression.

CONCLUSION

The study found a positive and strong association between menopausal symptoms and overall post-menopausal health.

Women who come to the family health center should be informed about their level of knowledge about menopause, training should be planned for women who do not have knowledge about menopause and menopause problems, and exercise should be done at regular intervals. The number of places where women in menopause can easily reach and receive continuing education and consultancy services should be increased. One of the most

important factors affecting the overall health of women is menopause symptoms. Therefore, first of all, the symptoms of menopause in women should be carefully determined and treatment measures should be planned for each symptom.

Conflict of Interest

Examining the effect of menopausal symptoms on general health status in postmenopausal women onflict of Interest text There is no financial conflict of interest with any institution, organization or person regarding our article and the authors There is no conflict of interest between them.

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Experimental Preliminary Study for Production of Recombinant Subtilisin Enzyme by pET28b Cloning Vector

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ABSTRACT:
Purpose: The purpose of this study is to enable the efficient production of the industrial enzyme subtilisin, a serine protease with extensive applications in various industries such as detergents, food processing, textiles, and pharmaceuticals. By leveraging recombinant DNA technology to produce subtilisin locally, the study aims to decrease reliance on foreign imports and enhance the sustainability of enzyme supply chains. This initiative seeks not only to meet the growing demand for subtilisin but also to promote economic independence, reduce costs, and foster innovation within the local biotechnology sector.
Material and Methods: Following bioinformatic calculations and processes for pET28 and subtilisin, the enzyme was produced.
Results: The results confirm successful cloning and expression of the subtilisin gene in the pET28b vector, creating the recombinant construct pET28b-subt. Agarose gel electrophoresis verified the transformation, showing distinct bands for the pET28b backbone and subtilisin insert. The recombinant subtilisin was purified from lysed *E. coli* using Ni-NTA affinity chromatography, with SDS-PAGE analysis revealing a molecular mass of 41,646.82 Da (Figure 5, Figure 6). These findings demonstrate successful production of subtilisin, though further optimization is needed for industrial applications.
Conclusion: Production has been carried out and the sds-page result supports this. After this, it was seen that it was necessary to focus on activity studies.
Keywords: Recombinant Protein; Subtilisin; pET28b

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INTRODUCTION

Enzymes are biological catalysts that catalyze chemical reactions in the cells of living organisms, which are in the form of proteins. As such, they work under the conditions that the metabolic requirements of a widely diversity of cell types. In general, these metabolic requirements can be described as ▪ Chemical reactions must happen under the conditions of the media of the organism, ▪ Specifity by each enzyme, ▪ High-level reaction rates (Damhus et al, 2008)

Enzyme-catalysed processes are replaced chemical processes in industry (Figure 1) for several areas. Enzymes have all the features of actual catalysts. In

the presence of a suitable enzyme, a chemical reaction takes place at a much high level but the enzyme is not depleted by the reaction. Their ability to officiate quite specific biotransformations has made them gainly popular in industries where less likely specific chemical processes bring out undesired by products. Simplicity and predictability are confidential significance in food industry where by products may be harmful or affect flavour and due to their specifity, pharmaceutical manufacturer favour biotransformations in the improving of new therapeutic agents. The greatest challenge is a research and improving program for matching an enzyme with a process. Increasingly, new organisms

are found out that survive in unsual habitats and these prove a great source of varied enzymes (Saul, 2010).

Recombinant DNA (rDNA) technologies give chance the production of wide range of polipeptides from naturally nonproducing living being. Firstly, pharmaceutical products were but nowadays many proteins are obtained by this way for various applications especially industrial enzymes (Porro et. al, 2005).

The requirement for enzymes and microorganisms in the industrial field has improved "Genetic Engineering and rDNA technology". The technology enables genetic regulation of microorganisms to generate the needed enzyme. Protein engineering job is finding out the structure of enzymes and

modifying them full benefit. Studies focus on improving and producing of functional enzyme. Therefore, biotechnology becomes more attractive than chemical processes. The main advantages provided by enzymes; they are produced from natural resources and they are not harmful for environment etc (Hasan et. al, 2010). For example, biotech origin cleaning materials harmful for environment. Besides having specific activity, they can show this activity at lower temperatures. Their wastes are with lower chemical oxygen demand and not corrosive for nature. Enzyme based cleaning materials are increasingly preferred in the food industry compared to caustic and acidic cleaning agents (D'Souza & Mawson, 2005).
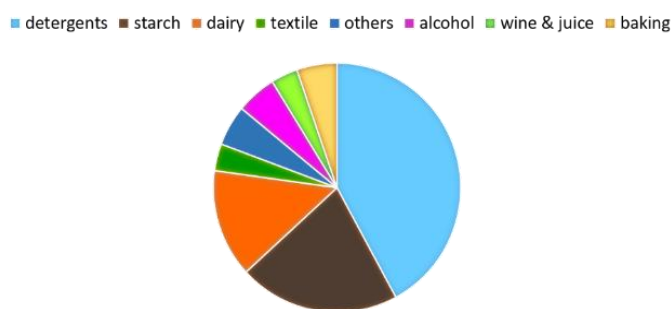

Figure.1. Distribution of industrial enzyme sales according to sectors (Falch, 1991)

Proteinases are one of the most substantial industrial enzymes, accounting for nearly 60% of total worldwide enzyme sales (Ward, 1985; Kalisz, 1988; Outtrup & Boyce, 1990). Since microorganisms can be fermented in a short time and in large quantities, they are the most preferred protease sources. Microbial based alkaline proteinases command the world market with the ratio of 2/3 of detergent industry (Gupta et. al, 2002; Mienda et. al, 2014).

Microbial peptides are long-lasting without loss activity as long as they are stored appropriate conditions. They are extracellular and can directly express in the medium of fermentation. Therefore, they have simplicity for producing that they are preferred than their counterparts in plants and animals. Microbial sources for commercial utilization

are not toxic and not pathogenic that decided as safe (Gupta et. al, 2002).

Genus *Bacillus* is the most popular source for producing alkaline peptidases. Various species can live in different environments, which have ability for producing proteases. A large number of microorganisms produce alkaline peptidases of the serine type that they belong to bacteria, fungi (Kumar & Takagi, 1999).

Subtilisins (EC 3.4.21.62) are a family of subtilase super family, very important enzyme for industry that one of the serine proteases, which are, produced the largest amount by the *Bacillus spp*. They are used in laundry, dishwashing detergents and contact lens cleaning applications (Rao et. al, 1998; Bryan, 2000; Yang et. al, 2000; Saeki, 2007; Anonymous, 2020a).

Subtilisin has highly antimicrobial activity especially for gram-positive bacteria so that they have a broad usage such as food conversation, detergent industry, etc (Okeley et. al, 2003).

There is a significant demand for subtilisin in various industrial sectors, creating a substantial global market that attracts considerable interest. This study aims to produce an enzyme utilizing our own resources to meet this growing demand.

MATERIAL and METHODS

Bacterial Strains and Plasmid Construction

The gene sequence for subtilisin from Bacillus subtilisin (Accession number: HQ699519.1) was retrieved from the NCBI database following a comprehensive literature review and bioinformatics analysis. The pET28b vector (Figure 2) was selected as the cloning vector for this study. Additionally, codon optimization of the subtilisin gene was conducted using bioinformatics tools to enhance expression in the Escherichia coli K12 strain. In codon optimization studies, codons in the nucleotide sequence of the subtilisin gene and expressed at low frequency in *E. coli* K12 microorganism were replaced with codons expressed at higher frequency. For codon optimization, "JCat" codon optimization program was used (http://www.jcat.de/) and DNA alignment was performed using the "CLUSTAL Omega (1.2.1) Multiple Sequence Alignment" program.
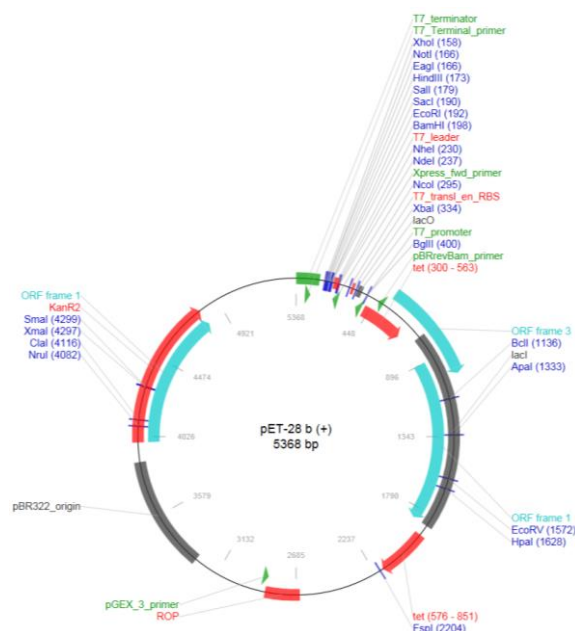

Figure 2. pET28b plasmid map (Anonymous, 2020b)

For the double cut 100 % cutting enzyme pairs (*NcoI & XhoI*) were created in the same buffer which was checked at the "NEB cutter" site for the recognition of these enzymes in the gene. These enzymes were placed at the beginning and end of the gene. Convenience in the purification was provided by adding six His-tag (Figure 3). At the end, the sequence was synthesized by "BIOMATIK Company".

Protein expression

BL21 (DE3) pLysE (*Novagen*), which is a strain of *E. coli* was used as host cell for expressing subtilisin protein. The strain was transformed by recombinant pET28b-subt plasmid (Hanahan, 1985). Transformed cells were spread on LB (Luria Bertani) agar plates which containing 100 µM.mL^{-1} kanamycin. Then all cells were grown at 37°C for a night. A colony of recombinant cell was taken and transferred in to 3 mL LB medium for growing at 37°C and shaking (250 rpm) for 16 hours. Then overnight culture was inoculated into 600 mL of LB [containing kanamycin (1:10) & chloramphenicol (1:1)] and incubated until

the OD$_{600}$= 0.6 and was induced by isopropyl ß-D-1-thiogalactopyranoside (IPTG). Then the culture was incubated for 3 hours. The culture was collected by centrifugation and the cell pellets were resuspended in buffer A (100mM Tris – HCl *-pH= 7-*, containing 1 g.L^{-1} lysozyme, 1 mM PMSF and 1 mM benzamidine). The cells were lysed with a vibra cell processor (sonics VCX130) and centrifuged (Vision VS-30000i) at 30000 rpm for one hour at 4°C. After centrifugation soluble and insoluble fractions were seperated. All samples were analyzed by 12% SDS-PAGE and dyed by commassie brillant blue (Laemmli, 1970).

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ggtgggggatctctggttccgcgcggatccatgcgttctaaaaaactgtggatctctctg
 G  G  G  S  L  V  P  R  G  S  M  R  S  K  K  L  W  I  S  L
ctgttcgctctgaccctgatcttcacgatggctttctctaacatgtctgctcaggctgct
 L  F  A  L  T  L  I  F  T  M  A  F  S  N  M  S  A  Q  A  A
ggtaaatcttctaccgaaaaaaaatacatcgttggtttcaaacagaccatgtctgctatg
 G  K  S  S  T  E  K  K  Y  I  V  G  F  K  Q  T  M  S  A  M
tcttctgctaaaaaaaaagacgttatctctgaaaaaggtggtaaagttcagaaacagttc
 S  S  A  K  K  K  D  V  I  S  E  K  G  G  K  V  Q  K  Q  F
aaatacgttaacgctgctgctgctaccctggacgctaaagctgttaaagaactgaaacag
 K  Y  V  N  A  A  A  A  T  L  D  A  K  A  V  K  E  L  K  Q
gaccgtctgttgcttacgttgaagaagaccacatcgctcaccagtacgctcagtctgtt
 D  P  S  V  A  Y  V  E  E  D  H  I  A  H  Q  Y  A  Q  S  V
ccgtacggtatctctcagatcaaagctccgggtctgcactctcagggttacaccggttct
 P  Y  G  I  S  Q  I  K  A  P  A  L  H  S  Q  G  Y  T  G  S
aacgttaaagttgctgttatcgactctggtatcgactcttctcaccccggacctgaacgtt
 N  V  K  V  A  V  I  D  S  G  I  D  S  S  H  P  D  L  N  V
cgtggtggtgcttctttcgttccgtctgaaaccaaccgtaccaggacggttcttctcac
 R  G  G  A  S  F  V  P  S  E  T  N  P  Y  Q  D  G  S  S  H
ggcacccacgttgctggcaccgttgctgctctgaacaactctatcggtgttctgggtgtt
 G  T  H  V  A  G  T  V  A  A  L  N  N  S  I  G  V  L  G  V
gctccgaacgcttctctgtacgctgttaaagttctggactctaccggtaacggtcagtac
 A  P  N  A  S  L  Y  A  V  K  V  L  D  S  T  G  N  G  Q  Y
tcttggatcatcaacggtatcgaatgggctatctctaacaaaatggacgttatcaacatg
 S  W  I  I  N  G  I  E  W  A  I  S  N  K  M  D  V  I  N  M
tctctgggtggtccgtctggttctaccgctctgaaatctgttgttgaccgtgctgttgct
 S  L  G  G  P  S  G  S  T  A  L  K  S  V  V  D  R  A  V  A
tctggtatcgttgttgttgctgctgctggtaacgaaggcacctctggttcttcttctacc
 S  G  I  V  V  V  A  A  A  G  N  E  G  T  S  G  S  S  S  T
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 I  G  Y  P  A  K  Y  P  S  T  I  A  V  G  A  V  N  S  S  N
cagcgtggttcttttctcttctgttggtccggaactggacgttatggctccgggtgtttct
 Q  R  G  S  F  S  S  V  G  P  E  L  D  V  M  A  P  G  V  S
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 I  Q  S  T  L  P  G  G  T  Y  G  A  Y  N  G  T  S  M  A  T
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 P  H  V  A  G  A  A  A  L  I  L  S  K  H  P  T  W  T  N  A
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 Q  V  R  D  R  L  E  S  T  T  T  Y  L  G  N  S  F  Y  Y  G
aaaggtctgatcaacgttcaggctgctgctcagagccaccaccaccaccaccactaaggt
 K  G  L  I  N  V  Q  A  A  A  Q  S  H  H  H  H  H  H  -  G
acctgatgaacgcgt
 T  -  -  T  R
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Figure 3. Gene sequence of recombinant subtilisin which synthesized after bioinformatics calculations

RESULTS

In this study, the XhoI-NcoI fragment containing the subtilisin gene was successfully cloned into the pET28b plasmid, resulting in the recombinant construct pET28b-subt Figure 4.. The process involved molecular techniques and bioinformatics analyses to ensure the accuracy of the inserted gene. Assessments on the subtilisin sequence included analysis of its structure and potential post-translational modifications, along with comparisons to entries in databases like NCBI and UniProt. The selection of restriction sites was crucial for effective ligation, and after digesting the vector and insert, competent E. coli cells were transformed with the recombinant plasmid. Verification of successful insertion was achieved through colony PCR and restriction digestion analysis, followed by IPTG induction for protein expression. Characterization of the protein was performed using SDS-PAGE to confirm the expected molecular weight, and tools like ProtScale and the SOLpro server were utilized to predict expression levels and solubility, aiding in the optimization of purification conditions. Overall, this work demonstrates the feasibility of producing subtilisin in a bacterial system and lays the groundwork for future functional studies.
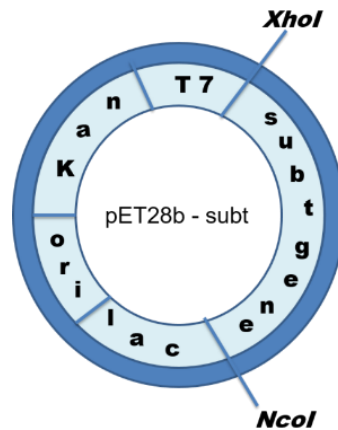
Figure 4. Map of pET28b-subt which subtilisin gene transferred to pET28b (+) vector
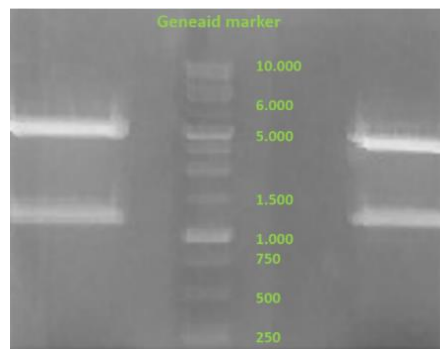

Figure 5. Verification of recombinant pet28b-subt by restriction enzyme digestion
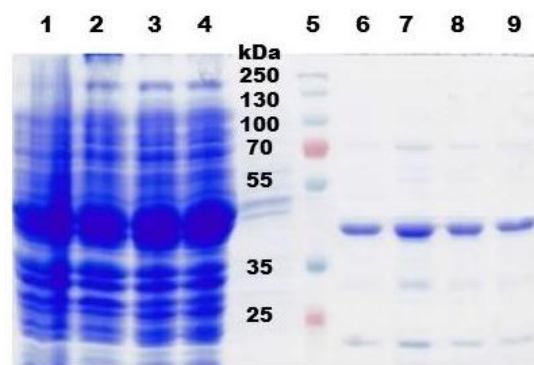

Figure 6. *1, 2, 3* ve *4*: *E. coli* lysate induced with IPTG. *5:* PageRuler Plus Prestained Protein Ladder. *6, 7, 8*, ve *9:* The eluates were collected from Ni-NTA agarose affinity column after washing with imidazole

Production has been carried out effectively, and the results from agarose electrophoresis (Fig. 5) and SDS-PAGE (Fig. 6) provide clear evidence for this outcome. Agarose electrophoresis enabled the visualization of nucleic acid fragments, confirming the presence and integrity of the cloned subtilisin gene. Meanwhile, the SDS-PAGE analysis confirmed the expression of the recombinant subtilisin protein, showing distinct bands that align with the expected molecular weight. Together, these analytical techniques illustrate that the recombinant protein was expressed as intended and substantiate the overall production process.

DISCUSSION

The analysis of the restriction enzymes NcoI and XhoI was conducted on agarose gel containing the "Geneaid" marker for the purified plasmid DNA (pET28b-subt) after the transformation process (Figure 5). he observed size of the pET28b vector, which falls within the 5000-6000 bp range, alongside the 1146 bp fragment corresponding to subtilisin, positioned in the 1000-1500 bp range, provides clear evidence of proper transformation and accurate insertion of the target gene. This ligation confirms that the plasmid retains the functional elements required for expression in *E. coli*. Amplification of the subtilisin gene from *Bacillus subtilis* was conducted using standard polymerase chain reaction (PCR) techniques to ensure the fidelity of the gene fragment. After amplification, the fragment was cloned into the pET28 vector with NcoI and XhoI restriction endonucleases. This new recombinant system, named "pET28b-subt," serves as a key platform for further studies on protein expression.

Following cloning, the recombinant subtilisin protein was purified using Ni-NTA affinity chromatography, taking advantage of the 6xHis tag that allows for selective binding to the resin. This purification method effectively isolates His-tagged proteins, achieving the necessary purity for subsequent applications. Analysis of the eluted samples via Sodium Dodecyl Sulfate–Polyacrylamide Gel Electrophoresis (SDS-PAGE) revealed that the purified subtilisin migrated within the expected molecular weight range of 35,000-55,000 Da (Figure 6). The molecular mass calculated at 41,646.82 Da, determined using ExPASy ProtParam tools, closely aligns with the experimental results, further supporting the methods used for expression and purification.

Although the cloning and purification of subtilisin are important outcomes, further optimization is essential to improve enzymatic efficiency and activity. Existing literature highlights that achieving high enzymatic performance often requires meticulous preliminary studies (Billman-Jacobe et al., 1995; Ghasemi et al., 2012; Joshi & Satyanarayana, 2013). Variables such as expression conditions, including temperature and IPTG concentration, as well as purification strategies, can significantly affect the enzyme's yield and functionality.

Future research should focus on optimizing these parameters, potentially exploring different growth media, induction times, and post-harvest processing methods. Such optimizations are vital for maximizing the yield and stability of recombinant subtilisin, facilitating its application in biocatalysis and other industrial processes. Moreover, the work involving the cloning, expression, and purification of subtilisin lays a solid groundwork for further research. The methodologies developed in this investigation offer valuable insights into producing recombinant proteins in E. coli, highlighting the potential of subtilisin in various biotechnological applications. Continued optimization will be critical to fully harness the capabilities of this enzyme in practical scenarios.

CONCLUSION

This preliminary study on the production of recombinant subtilisin using the pET28b cloning vector has yielded promising results. Confirmation of the successful insertion of the subtilisin gene from *Bacillus subtilis* into the pET28b vector was achieved through molecular techniques, including agarose gel electrophoresis and SDS-PAGE analysis. The recombinant subtilisin protein migrated within the expected molecular weight range, with a calculated mass of approximately 41,646.82 Da, demonstrating the effectiveness of the expression system.

While the production of subtilisin has been successfully established, further optimization is essential to enhance its enzymatic efficiency and activity for industrial applications. Focus should be directed toward refining expression conditions and purification strategies to maximize yield and functionality. These efforts will not only improve the enzyme's performance but also expand its applicability across various sectors, including detergents, food processing, and pharmaceuticals.

The methodologies and findings from this study provide a solid foundation for ongoing research in enzyme production. Future investigations can explore a broader range of optimization parameters, ultimately facilitating sustainable and efficient production of subtilisin and potentially other

industrial enzymes. This initiative represents a significant step toward reducing dependency on external sources and fostering innovation within the local biotechnology landscape.

Acknowledgment

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A Pharmacoeconomic Evaluation of Type 2 Diabetes Drugs in Central Pharmacies in Sivas Province

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ABSTRACT:

Purpose: In this study, prescriptions of 391 patients with type 2 diabetes mellitus selected from pharmacies in Sivas city center by mass sampling method were analyzed and the aim was to investigate the pharmacoeconomic suitability of these drugs considering the chronic complications associated with diabetes.

Material and Methods: This study is characterized as a descriptive cost analysis in which retrospective analysis was conducted on 391 prescriptions issued to Type-2 Diabetes Patients after obtaining the required permissions, including approval from the Ethics Committee. Patient prescription data were collected from pharmacies comprising the sample group over a three-month period in Sivas Province. The demographic features such as age and gender of the patients and the medications prescribed for Type 2 Diabetes were analyzed, and the costs associated with these prescription drugs were calculated. In addition, additional diseases of Type 2 Diabetes patients were also scrutinized within the scope of the study.

Results: According to the data obtained, the drugs prescribed to diabetic patients with chronic diseases were found to be appropriate. However, when all diabetic patients were examined, it was determined that the prescribed amount of insulin preparations was high and not pharmaceutically appropriate. It was revealed that the cost of type 2 diabetes medications for 391 patients was 77.852,79₺, and the prescription price was 199.11₺.

Conclusion: Type 2 diabetes is characterized by insulin resistance in tissues such as liver, muscle and fat as a result of detectable damage to pancreatic beta cells. The disease is also associated with genetics, environmental factors and lifestyle. In our country, 22.6% of the health budget is allocated to the treatment of diabetes and its complications. Due to the increasing frequency of patients with type 2 diabetes, effective and rational treatments to reduce the burden of the disease on the health budget have become an important issue for both payers and policy makers, but it needs to be emphasized and examined from a pharmacoeconomic perspective in future studies.

Keywords: Drug Cost; Insulin; Pharmacoeconomics; Type 2 Diabetes

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INTRODUCTION

Type 2 diabetes mellitus (DM) is a disease characterized by insulin resistance in tissues such as the liver, muscle, and fat, resulting from detectable damage to pancreatic beta cells. Other complications associated with this steadily increasing disease and a rise in mortality rates due to diabetes are becoming more prevalent. According to a study conducted by the International Diabetes Federation (IDF), the cost of treating type 2 diabetes patients was estimated to be $850 billion in 2017, and this number is expected to increase by 8% by 2045 (Eray and Balcı 2005; Tanrıverdi et al., 2013).

In our country, 22.6% of the health budget is allocated to the treatment of diabetes and its complications. In 2012, a budget of approximately 10 billion₺. was allotted to type 2 diabetes patients in Turkey and due to the increasing prevalence of

diabetes, the Turkish government initiated a diabetes management program in 2015 (Yaman, 2019). The expenses associated with diabetes may rise and deteriorate as inexpensive medications for diabetes fail to adequately treat the patient and result in adverse effects, highlighting the importance of cost-effective treatments with favorable side effects to alleviate the health burden. In this study, the prescriptions of 391 Type-2 diabetes patients from pharmacies were selected by mass sampling method in Sivas Province to investigate the pharmacoeconomic appropriateness of these drugs by considering chronic complications related to diabetes. To address this issue, the prescriptions of 391 individuals with Type-2 diabetes were examined from pharmacies selected through mass sampling in the Sivas Province center. The study investigated the pharmacoeconomic appropriateness of these medications by considering the chronic complications associated with diabetes.

Pharmacoeconomics

Healthcare costs are constantly increasing worldwide, especially in newly developing countries. In many countries, this increase even prevents the economic growth of the countries. The primary drivers of economic growth typically stem from technological innovations and the importation of products. For this reason, countries find it appropriate to reduce their expenditures in this field and to follow certain policies. Pharmacoeconomics is the scientific discipline best suited for conducting thorough evaluations and providing guidance in this particular field (Güven, 2016; Karuranga et al, 2017). Pharmacoeconomics has garnered increasing attention globally and in Turkey, particularly in recent times. With the introduction of numerous drugs into the healthcare sector and advancements in technology, there has been an increase in drug costs and concerns regarding risks and side effects, leading to a growing demand for medical economics expertise in the multidisciplinary realm. In essence, pharmacoeconomics involves assessing the benefits of healthcare treatments and allocating costs accordingly (Çetin, 2010).

It is necessary to increase the number of people with knowledge and support in pharmacoeconomics,

including pharmacoeconomics evaluations in drug license applications, to establish hospital formulations in a hospital or national context, to support their use, to compare existing drugs with new formulations and marketed drugs, to compare them in terms of cost and to determine whether they replace SSIs. The inclusion of pharmacoeconomic methods in the determination of drug use is also essential in terms of rational drug use. Prioritizing only drug costs in reimbursement is a false workaround (Acar, 2005). Pharmacoeconomics is a scientific discipline focused on examining, comparing, and evaluating pharmaceutical products and services. Pharmacoeconomic analyses employ various methods such as cost-benefit, cost-effectiveness, cost-minimization, and cost-utilization to assess different aspects of pharmaceutical interventions (Acar, 2005; Çetin, 2010)

Pharmacoeconomics in terms of Health Economics

Health economics is a discipline that aims to protect the health of individuals in society, enable people to live independently of others, increase the welfare of public health, and utilize the opportunities of economics to achieve this goal (Güven, 2016). In addition, health economics is the application of economics to all relevant areas of the health industry. Therefore, health economics aims to provide the highest service with the most appropriate budget in all areas that use and require the financial resources of the field. The most critical problem in health economics is the scarcity of resources. Health economics also works to develop and improve this issue. It aims to use limited resources most efficiently. The primary purpose of health expenditures is to reduce diseases and significantly promote economic development in the future by protecting the labor force, saving health costs, and providing sustainable health services (İlbars, 2008).

Pharmacoeconomics, considered a sub-branch of health economics, is a discipline that compares different products, treatments, surgical procedures, and even medical services using specific analytical methods (Acar and Yeğenoğlu, 2006).

Development of Pharmacoeconomics

Although pharmacoeconomics has remained in the

background for many years, from the recent past to the present, it emphasizes the importance of health costs and budgets allocated to pharmaceutical products and services every year. Medical economics was initially created as a sub-branch of health economics. The priorities of general economics are almost the same as those of medical and health economics. The basic idea of economics is the efficient use of limited resources (Acar and Yeğenoğlu, 2006; İlbars, 2008; Özsarı, 2014).

During the 1960s, pharmacy gained increasing importance and was recognized within academic literature as a clinical discipline. The most important foundations of pharmacoeconomics were laid in the 1970s. The first pharmacoeconomics book in the literature was written in 1973, and the first article was written in 1978. The main point of this published article is the determination of costs, which is the nature of utility and efficiency analysis (Acar and Yeğenoğlu, 2006; İlbars, 2008; Özsarı, 2014). Pharmacoeconomic analyses started to receive more attention, especially after the 1980s. A continuous growth can be observed in its development due to its pharmaceutical and economic benefits to the environment and the alternatives it offers in practice.

MATERIALS AND METHODS
Type of Research
This study is characterized as a descriptive cost analysis in which retrospective analysis was conducted on 391 prescriptions issued to Type-2 Diabetes Patients after obtaining the required permissions, including approval from the Ethics Committee. Patient prescription data were collected from pharmacies comprising the sample group over a three-month period in Sivas Province. The demographic features such as age and gender of the patients and the medications prescribed for Type 2 Diabetes were analyzed, and the costs associated with these prescription drugs were calculated. In addition, additional diseases of Type 2 Diabetes patients were also scrutinized within the scope of the study.

Population of the Study
The population of the research consists of

pharmacies in the borders of Sivas Province Central district.

Sample of the Study
The cluster sampling method was used as the sampling method. The sample consisted of treatment prescriptions for type 2 diabetes among patients aged 18 and older, collected over a three-month period in the city center of Sivas. The pharmacies included in the sample of the study were randomly determined by evaluating them as a cluster. Demographic characteristics, drugs in the prescriptions, and prescription drug costs were calculated based on the patient prescription information between the specified periods.

Dependent and Independent Variables of the Study
In the study, diagnoses and prescription costs of Type 2 Diabetes disease constitute the dependent variable of the research. Age, gender and additional disease diagnoses constitute the independent variable.

Tools and Materials Used in the Study
For this study, prescriptions for Type 2 diabetes were obtained from pharmacy records in Sivas through the medulla systems, forming the sample. This process adhered to the guidelines set by the ethics committee at the University and was conducted with the necessary permissions obtained from the Sivas Pharmacists' Chamber. Following the collection of prescriptions, a database was created utilizing the SPSS (Statistical Package for Social Sciences) software version 22 for Windows. Subsequently, statistical analyses were conducted on this database

Implementation of the Research
The research was carried out on adult patients over 18 who received Type 2 diabetes medications with their prescriptions between 01/09/2020 and 31/12/2020 in pharmacies located in the central district of Sivas province and constituting the sample. For this purpose, in accordance with the permission obtained from the Sivas Chamber of Pharmacists, the pharmacies comprising the sample were informed that prescription analysis would be carried out in line with the research.

Data Analysis

SPSS 22 statistical package program was used for data analysis. Mean ± standard deviation, minimum, and maximum scores were used for continuous variables, and frequency (f) and percentage (%) were used for categorical variables. The normal distribution of continuous variables (drug costs and age) was analyzed by the Kolmogorov-Smirnov (K-S) test, skewness, and kurtosis coefficients. Spearman-Brown Rank Difference Correlation Coefficient was calculated to explore the relationship between continuous variables. The Mann-Whitney U test was employed to assess the differences between the means of the two groups. A significance level of 0.05 was utilized for statistical analysis, indicating the threshold for determining whether any observed differences were statistically significant.

Ethical Aspects of the Study

The study adhered to ethical standards by obtaining approval from the Ethics Committee, and it followed both national and international guidelines of Good Clinical Practice, as outlined in the Declaration of Helsinki. All submitted studies underwent an in-depth ethical and scientific inspection in a timely, comprehensive, and independent manner to ensure compliance with ethical principles and standards.

Findings Related to Prescription Records

In the study, there were prescription records of 391 patients. Of the 391 patients analyzed, 236 (60.4%) were female and 155 (39.6%) were male. The mean age was 62.51 ± 12.49 years.

The classification of prescribed Type 2 Diabetes medicines is presented in Table 1.

Table 1 indicates that 146 (37.3%) of the prescribed drugs were oral antidiabetics, 152 (38.9%) insulinomimetic drugs, 161 (41.2%) insulin preparations and 69 (17.6%) SGLT inhibitors. The categorization of Type 2 Diabetes drugs with respect to gender and age is presented in Table 2.
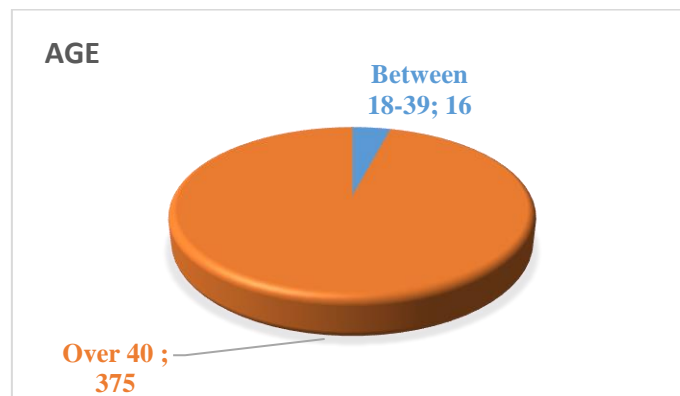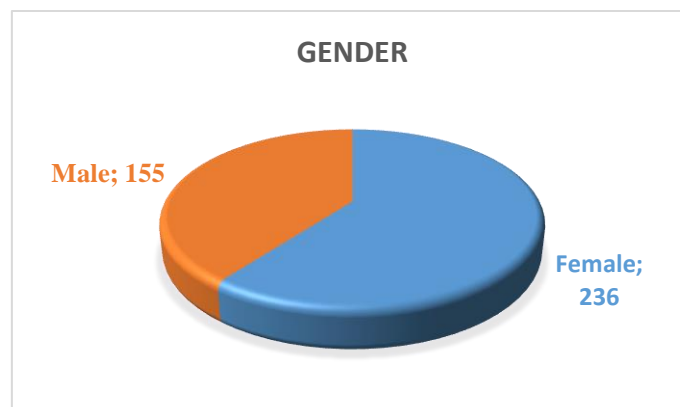

Figure 1. Participants by Age

Figure 2. Participants by Gender

Table 1. Classification of Type 2 Diabetes Drugs

		F	%
1.	Oral Antidiabetic Drugs	146	37.3
2.	Insulinomimetic Drugs	152	38.9
3.	Insulin Preparations	161	41.2
4.	SGLT (Sodium–glucose cotransporter) Inhibitors	69	17.6

Table 2. Classification of Type 2 Diabetes Drugs by Gender and Age

		Female f (%)	Male f (%)	Total f (%)
1.	Oral Antidiabetic Drugs	83 (56.8)	63 (43.2)	146 (100)
2.	Insulinomimetic Drugs	88 (57.9)	64 (42.1)	152 (100)
3.	Insulin Preparations	101 (62.7)	69 (37.3)	161 (100)
4.	SGLT Inhibitors	45 (65.2)	24 (34.8)	69 (100)
		18-39 f (%)	**40 or more f (%)**	**Total f (%)**
1.	Oral Antidiabetic Drugs	4 (2.7)	142 (97.3)	146 (100)
2.	Insulinomimetic Drugs	2 (1.3)	150 (98.7)	152 (100)
3.	Insulin Preparations	12 (7.5)	149 (92.5)	161 (100)
4.	SGLT Inhibitors	2 (2.9)	67 (97.1)	69 (100)

Table 3. The Most Prescribed Oral Antidiabetic Drugs, Insulinomimetic Drugs, Insulin Preparations, SGLT Inhibitors

	F	%
Glifor	78	19.9
Betanorm	19	4.9
Diaformin	16	4.1
GalvusMet	62	15.9
Janumet	46	11.8
Trajenta	17	4.3
Lantus	65	16.6
Novorapid	58	14.8
Novomix	24	6.1
Lantus	65	16.6
Novorapid	58	14.8
Novomix	24	6.1

Upon analysis of Table 2, it is observed that there is no change in the ranking of drug groups used by both women and men. While insulin preparations are in first place both in women and men, SGLT inhibitors hold the last place. The classification of Type 2 Diabetes drugs according to age is illustrated in Table 2. The analysis of table 2 and 3 demonstrates that insulin preparations were prescribed the most, whereas SGLT inhibitors were the least in the age groups of 18-39 and over 40 years.

In Table 3, the first three most prescribed oral antidiabetic drugs for type 2 diabetes patients can be seen as Glifor, Betanorm and Diaformin, respectively. According to Table 3, GalvusMet, Janumet and Trajenta can be regarded as the top three most prescribed insulinomimetics for type 2 diabetes patients. In the following, the most prescribed three insulin preparations. An analysis of Table 3 indicates that the top three most prescribed insulin preparations for type 2 diabetes patients can be seen as Lantus, Novorapid and Novomix, respectively. The most prescribed SGLT inhibitors are given in Table 3. In Table 3, it is evident that SGLT inhibitors Forziga and Jardiance were prescribed to patients with type 2 diabetes, respectively. Moreover, the distribution of type 2 diabetes drugs prescribed for the top 3 most common comorbidities (hypertension, cholesterol, antiaggregants, diabetic neuropathy) is illustrated in Figure 3.

A review of Table 10 indicates that prescriptions with one drug for each prescription make up 34.8% of the

total, prescriptions with two drugs per prescription constitute 40.4% of the total, prescriptions with three drugs per prescription account for 17.6% of the total, and prescriptions with four or more drugs per prescription comprises 7.2% of the total prescriptions for Type 2 diabetes patients.
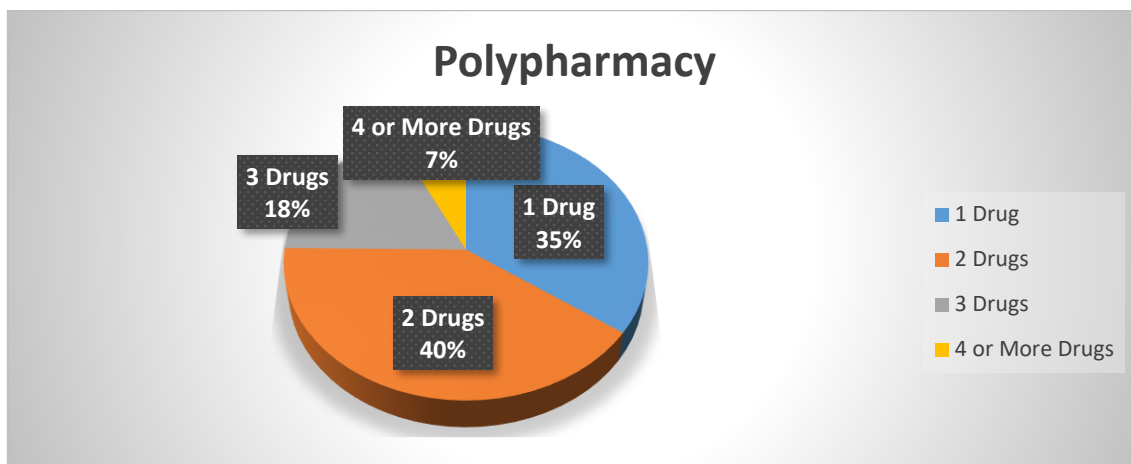

Figure 3. The Distribution of the Number of Medicines Per Prescription

Cost-related Findings

The total drug costs for 391 patients are presented in Table 4.

Table 4 displays that the cost of Type 2 diabetes medication for 391 patients was found to be 77,852.79₺. Besides, the drug cost per prescription was calculated as 199.11₺. A comparison of the drug costs per box of the Type 2 diabetes drug group is also presented in Table 5 below.

When the costs of type 2 diabetes drug groups are analyzed in Table 5, it can be observed that the drugs with the highest cost are 250.51+ 1,103.02 insulin preparations. The lowest-cost drugs are oral antidiabetic drugs, with 34.57+21.63. Type 2 diabetes might be considered a costly disease. It has

a significant cost, together with other complications. Expenses related to type 2 diabetes and accompanying problems due to diabetes were calculated in a diabetology center in Italy. The average annual cost per person was computed as €1909.67. Most of these costs are due to medication, followed by hospitalization and investigations.

Furthermore, it was noted that the cost increased in correlation with the severity of complications. With the escalation of diabetes complications, the cost per individual surged to €3141. Consequently, mitigating diabetes complications can also lead to long-term cost reduction (American College of Clinical Pharmacy, 2008; Zozaya et al., 2019).

Table 4. Findings Related to the Cost

	N	Average Drug Cost per Prescription (TRY)	Total Prescription Cost (TRY)
All Prescriptions	391	199.11	77.852,79

Table 5. The Comparison of Drug Costs per Box According to the Classification of Type 2 Diabetes Drugs (TRY)

	N	Mean $\pm$ SD	Min. – Max.
1. Oral Antidiabetic Drugs	146	34.57 $\pm$ 21.63	10.12 $-$ 188.18
2. Insulinomimetic Drugs	152	140.29 $\pm$ 54.62	29.06 $-$ 359.49
3. Insulin Preparations	161	250.51 $\pm$ 103.02	53.78 $-$ 539.38
4. SGLT Inhibitors	69	161.56 $\pm$ 4.97	157.84 $-$ 168.12

According to the diabetes prevention program, $15,700 was saved for each diabetes prevented. With the emergence of new alternative therapeutic choices in type 2 diabetes, decision-making has become even more difficult, but economic considerations may assist to ease the complexity. However, alternative options might offer greater effectiveness at a higher cost. Consequently, determining the most pharmacoeconomically feasible option has become challenging. For this reason, the literature was systematically reviewed. The economic evaluations of the studies were compared (American College of Clinical Pharmacy, 2008; Zozaya et al., 2019).

DISCUSSION

Diabetes is a disease that is constantly increasing all over the world and in our country. Along with the increasing number of diseases, their cost to our country is also proliferating (Cosentino, 2020; T.C. Sağlık Bakanlığı, 2015). Therefore, this study aimed to investigate the pharmacoeconomic aspects of the drugs used by the patients. For this purpose, individuals were randomly and impartially selected, and their age, gender, and other chronic conditions were also considered. The drugs used by the patients for three months were analyzed, and the cost of their prescriptions was calculated.

Within the scope of the research, the data obtained from 27 pharmacies with the cluster sampling method from 133 pharmacies in Sivas province center, the data of 391 people were examined within the scope of prescription analysis, and approximately 60% of these people are female and 40% are male patients. These data show that the majority of patients with diabetes are women. Type 2 diabetes is a condition typically associated with obesity, which serves as a significant risk factor in determining an individual's probability of developing diabetes. While obesity prevalence differs across societies, it tends to be 2 to 3 times higher in women compared to men, primarily due to increased weight gain with advancing age. According to the Turkish Heart Disease Risk Factors in Adults study, the prevalence of obesity among individuals aged 30 years and older was 25.2% in men and 44.2% in women. This finding aligns with similar studies,

including this study (Özdoğan et al., 2015).

According to the TURDEP II study, diabetes in men was found to be lower than in women. Starting from the 40-44 age group, at least 10% of the population was found to have diabetes (Gümüş et al, 2020). When the drugs used by these patients with type 2 diabetes were analyzed, it was observed that insulin preparations were the most commonly used drug group, followed by oral antidiabetics with a slight difference. When analyzed according to gender, it was observed that men preferred oral antidiabetics more.

In another study conducted at Pamukkale University, when the treatment types of 317 diabetes patients were analyzed, it was determined that 12% of the patients used oral antidiabetic drugs, and 74.8% received insulin treatment. In this study, insulin treatment was found to be the most frequently prescribed. It appears that newly developed insulin formulations, utilizing advancing technologies, are given preference in treatment selection (Akan, 2019).

During patient examination, concurrent medication use for other conditions was also assessed. It is noteworthy to mention that hypertension, high cholesterol, antiplatelet agents, and diabetic neuropathy were among the most prevalent conditions observed in patients with Type 2 diabetes.

Moreover, it was determined that diabetes accounted for three-quarters of cardiovascular deaths due to an increased risk of coronary artery disease (CAD). Özdoğan et al. also observed a negative impact on lipid profiles in diabetic patients, with elevated LDL (Low Density Lipoprotein) levels and decreased HDL (Hıgh Density Lipoprotein) levels, indicating a predisposition towards CAD development. This finding supports the high prevalence of hypertension and cholesterol disorders among diabetic patients (Özdoğan et al., 2015). Additionally, findings from the TURDEP II studies revealed that the most common chronic conditions accompanying diabetes included cardiovascular disorders, diabetic foot complications, nephropathy, and neuropathy (Gümüş et al., 2020). These findings are consistent with the results of our research. Furthermore, the

drug Galvus-met, which combines metformin (a biguanide drug increasing insulin sensitivity) and vildagliptin (a DPP-4 inhibitor), was found to be the most preferred among individuals with diabetes. Physicians who did not prescribe Galvus-met opted for insulin preparations such as Lantus and Novorapid instead. Upon analyzing prescription contents, it was observed that Glifor, containing metformin, was the most commonly prescribed oral antidiabetic medication, followed by Lantus, an insulin preparation with prolonged release.

When the polypharmacy rate in the prescriptions of patients with type 2 diabetes was analyzed, it was observed that physicians mostly preferred dual combinations and did not prefer or rarely preferred the use of two or more multiple drugs. Regarding the economic analysis of prescriptions, the cost per prescription for 391 patients was 199.11₺, while the total revenue was 77,852.79₺. It was found that generic oral antidiabetic and insulinomimetic drugs with the same active ingredient had the same price, and there was no price difference.

When the drug groups used in type 2 diabetes were evaluated pharmacoeconomically, it was found out that the lowest cost was oral antidiabetic drugs, and the highest cost drugs were insulin preparations. In this perspective, upon conducting a pharmacoeconomic assessment, it was concluded that insulin preparations were not suitable for cost-benefit analysis, one of the methods employed in pharmacoeconomic evaluation. This determination was based on the observation that insulin preparations were the most favored drug group and were associated with high costs. Upon comparing the drug costs of male and female patients included in the prescriptions, it was observed that there was no significant difference, with a p-value greater than 0.05.

In 2009, a systematic review of the economic evaluation of medicines marketed in Spain was conducted. According to this review, it was concluded that metformin was the most cost-effective treatment. It was concluded that 2nd generation oral antidiabetics should be used as a complement rather than an alternative to metformin (Ramos et al, 2019, Gomes et al, 2019). It needs to be updated to adapt to the development of new therapies and to include economic values. The first-line treatment for patients with type 2 diabetes is usually metformin. Second-line therapies are usually metformin, sulfonylurea, or DPP-4 inhibitors (Ramos et al, 2019, Gomes et al, 2019). Nevertheless, according to some studies of high quality, seven studies compared SGLT2 inhibitors with dipeptidyl peptidase-4 inhibitors, three studies compared SGLT2 inhibitors with sulfonylureas, and three studies compared SGLT2 inhibitors with glucagon-like peptide-1 receptor agonists (GLP-1 RA) (Chin et al., 2019; Yoshida et al., 2020).

3 studies compared SGLT2 with thiazolidinediones, alpha-glucosidase inhibitors, and other antidiabetic drugs, and two compared SGLT2 with metformin. The results showed that SGLT2 was less costly than other treatment options except for GLP-1 RA (Glucagon-like peptide-1 receptor agonists) (Chin et al., 2019; Yoshida et al., 2020). Literature reviews have shown that SGLT2 may be cost-effective compared to many antidiabetic treatments) (Chin et al., 2019; Yoshida et al., 2020). In another study, evidence from phase 3 randomized clinical trials has emerged regarding the direct cardiovascular advantages of SGLT2 inhibitors in patients with type 2 diabetes recently. These findings revealed that patients treated with SGLT2 inhibitors experienced reduced cardiovascular risk. Furthermore, when combined with metformin, SGLT2 inhibitors led to faster achievement of glycemic indices. Although metformin is typically prescribed as a first-line treatment, SGLT2 inhibitors are now recommended as second or third-line treatment options. This study was the first to evaluate the efficacy of metformin and dapagliflozin compared to 'delayed' combination therapy. This combination was found to be more cost-effective than the combination of metformin and other glucose-lowering drugs in reducing diabetes-related complications. It was more cost-effective than sulfonylureas and DPP+i in patients with type 2 diabetes not adequately controlled with metformin (Chin et al., 2019; Yoshida et al., 2020). Regarding cost-utility, SGLT2 can be considered the only alternative with unambiguously positive results.

The application of more intensive therapies in the early stages of type 2 diabetes has been

controversial. Randomized clinical trials have shown that intensive treatment significantly reduces cardiovascular disease, the biggest problem compared to glycemic control. SGLT2 inhibitors constitute the only oral antihyperglycemic drugs with proven direct cardiovascular benefits. Therefore, initiating first-line treatment with dapagliflozin and metformin has been of interest (Huzur, 2018). It is important to be attentive when assessing the results of these studies for several reasons. Firstly, these studies have been conducted since 2009, indicating a significant time span for data collection and analysis. Secondly, there is notable heterogeneity in the methodologies employed across studies evaluating the efficacy of these drugs, making it challenging to compare and interpret the results accurately. Additionally, economic evaluations have inherent limitations. Efficacy data often require supplementation or completion, and such data are typically derived from clinical trials conducted within specific patient groups (Huzur, 2018).

With the development of technology, new technologies are coming to the field of health. These technologies create an economic burden on countries. The aging of the population is another reason for the increase in health costs (Acar and Yeğenoğlu, 2006). In OECD countries, the average human life expectancy has increased with the increase in drug efficacy, education level, and welfare. In Turkey, life expectancy was 48.3 years in the 1960s and has reached 71.6 years in recent years. This shows the increase in health expenditures of our country with the rise in life expectancy (Acar and Yeğenoğlu, 2006; Güven, 2016). The reason why drug costs are the highest in health expenditures is because other health expenses cannot be fully calculated. When Turkey is compared in terms of private-public health expenditures, it might be claimed that although Turkey was in the last three in the 2000s, it has been in the last place in recent years (Güven, 2016). Although Turkey is below other countries in health expenditures, it is at a tolerable level compared to its income. However, considering the continuous increase in health expenditures, effective and rational use of drugs will have a significant impact on the health economy.

From these insights, pharmacoeconomics can be undeniably regarded as an essential field of study. The insufficiency of the studies indicates that more research in this field should be conducted. The fact that there are so few pharmacoeconomic studies is because pharmacoeconomics is not compulsory in our country. Making such studies obligatory will bring positive results to our country both economically and in terms of patient benefit (Acar and Yeğenoğlu, 2006).

CONCLUSION AND SUGGESTIONS

Diabetes Mellitus is gradually spreading in our country and increasing in terms of cost. To alleviate this economic burden, regular control of Hb1Ac levels in patients plays an essential role in early diagnosis and diagnosis. Thus, the economic burden of the country will be alleviated, and unnecessary drug use of patients will be prevented. Some patients can even be kept under control with diet and exercise. The increasing number of DM patients has paved the way for researchers to explore new methods and technologies. In addition to the possibilities of developing technology, products that have been used for a long time should also be evaluated (Gümüş et al., 2020).

Based on the findings and results obtained within the scope of the study, it has been observed that physicians prefer insulin preparations the most. Still, they are not suitable from a pharmacoeconomic point of view since they are the most expensive drug in terms of cost. However, it is essential to consider the principle of utility in this context to thoroughly assess pharmacoeconomics. When type 2 diabetes drugs were compared in terms of pharmacoeconomics, oral antidiabetics were found to be the most appropriate drugs according to the pharmacoeconomic decision matrix. As a result, it is more appropriate for physicians to give oral antidiabetics to patients first from a pharmacoeconomic point of view regarding both cost and benefit. In terms of cost-effectiveness, which is one of the most reliable methods used in the health sector, the choice of drugs with low cost and high effectiveness will be more accurate. If there is no benefit from oral antidiabetic drugs, using insulinomimetics, which are pharmacoeconomically

cheaper, or combined use will be more appropriate. When other drug groups were analyzed, it was found that insulinomimetics were the third most preferred drug group and SGLT inhibitors were among the last preferred drug groups, not preferred or less preferred.

When patient profiles are examined, it is evident that the DPP-4 inhibitor vildagliptin, often the primary choice for patients with high cholesterol, and metformin hydrochloride, a medication from the biguanide group, hold the top positions in prescription preferences. DPP-4 inhibitors are more effective and have lower side effect profiles than SU's. In addition, Metformin prevents hyperlipidemia, decreases LDL and VLDL levels, and increases HDL levels (Thiazolidinedione group drugs possess this effect; however, they are not preferred due to their tendency to cause weight gain and edema. Nonetheless, in instances where the patient has kidney disease, this group of drugs should be considered as the first choice). Given its classification as an oral antidiabetic medication, it stands as the first-choice drug from a pharmacoeconomic point of view. Moreover, physicians in the central district of Sivas province agree that patients with high cholesterol levels should be prescribed this combination of drugs as the primary treatment option. Upon analysis of patients with hypertension, it is observed that the initially preferred drug group consists of medications containing metformin, an active substance derived from biguanide. This drug, considered cost-effective from a pharmacoeconomically, may display interactions with certain blood pressure medications and diuretics when used concomitantly. It may increase the effects of metformin by interacting with blood pressure patients using ACE inhibitors or patients using blood pressure-lowering agents such as nifedipine and furosemide. Since there may be an increased risk of angioedema with side effects such as lactic acidosis, hypoglycemia, etc., physicians should prescribe this drug, taking into account the chronic diseases and medications used by the patients. In antiaggregant and diabetic neuropathy patients, the first choice was again the combination of vildagliptin, a DPP-4 inhibitor, and metformin hydrochloride from the biguanide group. The reason why SUs was not preferred originated from their hypoglycemic effect and other side effects, particularly when used in conjunction with antiplatelet agents. On the other hand, the DPP-4 inhibitor vildagliptin was favored due to its lack of known side effects. Additionally, in these patient groups, insulin preparations were selected as the second-line treatment option if oral antidiabetic drugs failed to achieve the desired effect.

In light of this information, it appears that the drugs prescribed by physicians in the Central district of Sivas province for patient groups with chronic diseases are pharmacoeconomically suitable within the scope of the analysis. However, when considering the total prescription of diabetes drugs, insulin preparations rank first. Therefore, it is recommended to reanalyze diabetes patients without chronic conditions in terms of pharmacoeconomics. In addition, according to recent studies, patients treated with SGLT-2 had more favorable results. Therefore, if metformin is insufficient after first-line treatment, treatment should be supported with SGLT-2 inhibitors.

Through pharmacoeconomic analysis, the patient will receive the best treatment suitable for them, while the institution that covers health costs will favor paying less. While pharmacoeconomics does not solely focus on selecting the cheapest treatment, choosing the most appropriate treatment method for the patient can ultimately lead to reduced healthcare costs. The primary objective is to ensure that the treatment provided is effective for the patient's needs. Achieving this goal requires collaboration among pharmacists, physicians, and healthcare institutions. As a result, patients with type 2 diabetes should be treated to improve their respective glucose and insulin indices. Then appropriate hypoglycemic drugs should be selected based on their economic status and family history to enhance appropriate treatment (Yaman, 2019). To perform pharmacoeconomic analyses, patient's records and data entries should be obtained entirely. For this purpose, healthcare professionals should be informed, and pharmacoeconomic training should be organized. Pharmacoeconomics should be compulsory in undergraduate and graduate programs (Acar and Yeğenoğlu, 2006).

Conflict of Interest

No conflict of interest

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