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1. Determining the Health Literacy Levels and Attitudes of Individuals in Different Countries Towards Vaccination
2. The Correlation of Tumor Markers, Neutrophil/Lymphocyte Ratio and FDG PET/CT Measures in Pancreatic Cancer
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Determining the Health Literacy Levels and Attitudes of Individuals in Different Countries Towards Vaccination

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A B S T R A C T

Background This research was conducted to determine the health literacy levels and attitudes of individuals in different countries towards vaccination.

Material and Methods This study is cross-sectional, comprised of eight hundred and thirty-eight participants (n=838) drawn from communities in eight different countries; Turkey (Agri), Nigeria (Ibadan), Pakistan (Charsadda), India (Assam), Malaysia (Ipoh), Madagascar (Antananarivo), Indonesia (Bandung), and Nepal (Kathmandu) between September and October 2020.

Results The Health Literacy scale total score mean was 54.92 ± 23.64 . Vaccine Reliability Scale Total Score Means 55.38 ± 12.99 . It was found that there was a statistically significant negative correlation between Health Literacy scale total score mean and Vaccine Reliability Scale Total Score Means and two Vaccine Reliability Scale sub-dimensions; Vaccine Benefit Perception and Trust in Healthcare Professionals.

Conclusions The Health Literacy total score mean was found to be statistically significantly higher among Nepal nationality, male, civil servant and those who do not think the COVID-19 vaccine will be effective and those who do not think they will receive the COVID vaccine if it is free ($p < 0.05$). The vaccine reliability scale total score mean was found to be statistically significantly higher among India nationality, those who receive COVID-19 vaccine, who were not against the COVID-19 vaccine, who think the COVID-19 vaccine will be effective and who will receive the COVID-19 vaccine if it is free ($p < 0.05$). It is recommended to conduct the study in larger groups.

Introduction

The availability of vaccines is regarded as one of the cornerstones of the modern world and one of the most important advances in medicine. Although it is known that smallpox patients were vaccinated for the first time in the 1500s by grinding the scabs of smallpox patients and snorting them; The modern vaccination was carried out by the English doctor Edward Jenner in 1796, when a cattle injected the pus obtained through a smallpox lesion into humans.¹ Pasteur and Koch also contributed greatly to microbiology in the 19th century and vaccination studies gained even more importance.² The World Health Organization initiated the Global Vaccine Action Plan, which was supported by 194 member countries in 2011 for the spread of vaccination services, and by 2020, it aimed to deliver the existing vaccines to all communities equally and to prevent morbidities and deaths that may occur in case of inadequate vaccination.^{3,4}

Today, when it comes to vaccination and immunization, childhood vaccines still come to mind, but it is known that adults can be protected from deaths, disabilities and various diseases thanks to vaccination and immunization.⁵ Although childhood vaccines are closely monitored by family

physicians and offered to the public for free, adult immunization rates are not followed, not offered free of charge to the public, physicians do not update their knowledge on adult vaccination, and the public's knowledge about adult immunization is inadequate. It is stated that the rates are insufficient.⁶ Despite all the known benefits of vaccines, people may exhibit negative attitudes and behavior towards vaccination for reasons such as doubting the safety and efficacy of vaccines, and distrust of governments and healthcare workers.⁷ For this reason, anti-vaccination movements have gained importance in the last 20 years in developed and developing countries, and especially with the spread of the internet, there has been a serious decrease in the number of parents who vaccinate their children.

Insufficient knowledge of parents, who are the main target of anti-vaccine movements, leaves this population vulnerable and open to manipulation.^{8,9} Low level of health literacy (HL), advanced age, being not vaccinated before, and low education level are among the main factors that cause low vaccination knowledge.¹⁰⁻¹² Health literacy, which is the main modifiable factor that will increase the knowledge level of individuals about immunization and provide a positive change in their attitudes and behavior, draws attention here.

It is also thought that individuals with high health literacy levels will be able to get information about vaccination and vaccination from the right sources, and as a result, they can take an important place in the fight against vaccine hesitation and vaccine anti-vaccination.¹³ It is known that health literacy, which means gaining the level of knowledge, personal skills and confidence in taking action to improve individual and community health by changing personal lifestyles and living conditions, is directly related to the general health levels of individuals.¹⁴ In this context, it is obvious that health literacy will play an important role in the maintenance and development of immunization services.

There has been no study in the literature on the health literacy level and attitude towards vaccination of different countries, and it is thought that this study will contribute to literature.

Material and Methods

Study Design

This research used a cross-sectional design to determine the health literacy levels and attitudes of individuals in different countries towards vaccination. The countries included in the study were selected with the convenience sampling method.

Area

This study was conducted in selected communities of eight different countries, the countries and their communities are: Turkey (Agri), Nigeria (Ibadan), Pakistan (Charsadda), India (Assam), Malaysia (Ipoh), Madagascar (Antananarivo), Indonesia (Bandung) and Nepal (Kathmandu).

Population

The universe of the research comprises of individuals living in Turkey (Agri), Nigeria (Ibadan), Pakistan (Charsadda), India (Assam), Malaysia (Ipoh), Madagascar (Antananarivo), Indonesia (Bandung), and Nepal (Kathmandu). Who are of the age of 18 years and above and English speakers. In the power analysis, the required sample size was calculated as 384 people at 95% confidence level and 5% confidence interval. The sample size comprised of eight hundred and thirty eight (n=838) individuals from the indicated community located in the different countries who agreed to participate in the study.

Data Collection Tools

An online google form designed by the researcher was used to gather the primary data. The survey comprises of three forms:

1. Demographic characteristics form: It consists of questions on information that can be used to classify the respondents.

2. Vaccine Reliability Scale

It is an 8-item scale developed by Melissa B. Gilkey.¹⁵ The items are scored between 0 (strongly disagree) and 10 (strongly agree). The scale consists of 3 factors including the benefits of vaccination, the harms of the vaccine, and trust in healthcare providers. The first 4 items are aimed at determining the benefits of the vaccine, Articles 5 and 6 the harms of the vaccine, and Articles 7 and 8 trust in the healthcare worker. A minimum of 0 and a maximum of 80 points can be obtained on the scale. Increasing the total scale score indicates increased confidence in the vaccine. A minimum of 0 and a maximum of 40 points can be obtained from the benefit perception subscale. The higher the score, the higher the perception of benefit. A minimum of 0 and a maximum of 20 points can be obtained from the harm perception subscale. The higher the score, the lower the perception of harm. A minimum of 0 and a maximum of 20 points can be obtained from the trust perception subscale. The higher the score, the higher the trust in healthcare professionals. In our study The Cronbach Alpha value of the scale was found to be 0.78.

3. Health Literacy Scale

Health Literacy Scale, developed by Sorensen (2013).¹⁶ The Cronbach alpha value of the scale is 0.95 and the Cronbach alpha values of the subscales vary between 0.90 and 0.94. The scale consists of 25 items and four sub-dimensions. These four sub-dimensions; Access to Information, Understanding Information, Appraisal/Evaluation, Application/Use. Access to information sub-dimension includes five items (1-5), the minimum score to be obtained from this subscale is 5 and the maximum score is 25. Understanding information sub-dimension contains seven items (6-12), the minimum score to be obtained from this subscale is 7 and the maximum score is 35. The appraisal/evaluation sub-dimension contains eight items (13-20), the minimum score to be obtained from this sub-dimension is 8 and the maximum score is 40. The

application / use sub-dimension contains five items (21-25), the minimum score to be obtained from this subscale is 5, the maximum score is 25. The lowest score that can be obtained from the scale is 25, the highest score is 125. The higher the score, the higher the health literacy level. The scale, has a five-point likert structure. All items of the scale are positive and there are no negative items. In our study the Cronbach Alpha value of the scale was found to be 0.93.

Data Collection Methods

The researcher explained the purpose of the research to the respondents and obtained a verbal consent from the respondents. The online google form prepared by the researchers was then administered to those individuals who agreed to participate in the research.

Limitations

It is a limitation of this study to be conducted only with those who speak English. The vaccine has some different origins. Like the Russian, German, Chinese vaccine. This may affect vaccine diversity and safety. This is a limitation of the study.

Analysis of Data

The data analysis was done using the statistical package for social science (SPSS) software. The Primary data was subjected to descriptive statistics of frequency count, percentage, mean and standard deviation. Kolmogorov – Smirnov test was used to test the distribution normality. Mann-Whitney U test was used for binary groups, and the Kruskal-Wallis test was used for groups more than two. Spearman correlation test was used to determine the linear relationship between variables and severity of the relationship. The p-value<0.05, was accepted as a statistically significant difference.

Ethical Principles

The study was approved by the University Scientific Research Ethics Committee. The study was conducted in accordance with the ethical standards established in the Declaration of Helsinki.

Results

Table 1 showed that the study comprises mostly of citizens of Nigeria, Pakistan and India (12.8% each), 57.5% were male, 67.3%, were single and 59.5% of the respondent completed a tertiary

education. 42.1% of the respondent were student. 56.4% received COVID-19 vaccine, 87.9 % those who do not against the COVID-19 vaccine, 83.7% those who think the COVID-19 vaccine will be effective and 65.6% those who will receive the COVID vaccine if it is free. The table also further revealed that the mean age of the respondent was 29.89±11.41.

Table 2 revealed that the Health Literacy scale total score mean was 54.92±23.64. Access to Information Sub-Dimension 10.76±5.14, Understanding Information Sub-Dimension 15.31±7.03, Value Setting Sub-Dimension 17.98±7.81, Application Sub-Dimension 10.85±5.03, Vaccine Reliability Scale Total Score Means 55.38±12.99, Vaccine Benefit Perception Sub-Dimension 29.86±7.78, Vaccine Harm Perception Sub-Dimension 10.74±4.87, Trust in Healthcare Professionals Sub-Dimension 14.77±4.38.

Table 3 presented the comparison of respondents' demographic characteristics and their Health Literacy total score mean. The Health Literacy total score mean was found to be statistically significantly higher among Nepal nationality, male, civil servant and those who do not think the COVID-19 vaccine will be effective and those who do not think they will receive the COVID vaccine if it is free (p<0.05).

Table 4 presented the comparison of respondents' demographic characteristics and their vaccine reliability scale total score mean. The vaccine reliability scale total score mean was found to be statistically significantly higher among India nationality, those who receive COVID-19 vaccine, who do not the COVID-19 vaccine, who think the COVID-19 vaccine will be effective and who will receive the COVID-19 vaccine if it is free (p<0.05).

It was found that there was a statistically significant positive correlation between Health Literacy scale total score mean and all Health Literacy scale sub dimensions and Vaccine Reliability Scale of sub dimension Vaccine Harm Perception (p<0.05).

It was found that there was a statistically significant negative correlation between Health Literacy scale total score mean and Vaccine Reliability Scale Total Score Means and two Vaccine Reliability Scale sub dimension; Vaccine

Table 1. Showing the Demographic Characteristics of the Respondents' (n=838)

Variables		n	%
Nationality	Turkey	103	12.3
	Nigeria	107	12.8
	Pakistan	107	12.8
	India	107	12.8
	Malaysia	97	11.6
	Nepal	95	11.3
	Indonesia	89	10.6
	Madagascar	133	15.9
Gender	Female	356	42.5
	Male	482	57.5
Marital status	Single	564	67.3
	Married	274	32.7
Education Level	Primary education	34	4.1
	Secondary education	87	10.4
	Tertiary education	499	59.5
	Master	205	24.5
	Doctorate	13	1.6
Occupation	Civil Servant	119	14.2
	Health worker	50	6.0
	Pensioners	28	3.3
	Business owner/trader	82	9.8
	Unemployed	104	12.4
	Student	353	42.1
	Others	102	12.2
Can you receive COVID-19 vaccine?	Yes	473	56.4
	No	365	43.6
Are you against the COVID-19 vaccine?	Yes	101	12.1
	No	737	87.9
Do you think the COVID-19 vaccine will be effective?	Yes	701	83.7
	No	137	16.3
Can you receive the COVID vaccine if it is free?	Yes	550	65.6
	No	288	34.4
		$\bar{X} \pm SD$	
Age (Year)		29.89±11.41 (min. 18, max. 80)	

Source: Online field survey 2020.

Benefit Perception and Trust in Healthcare Professionals.

It was found that there was a statistically significant negative correlation between Vaccine Reliability Scale total score mean and Health Literacy scale total score mean and all sub dimensions ($p < 0.05$).

It was found that there was a statistically significant positive correlation between Vaccine Reliability Scale total score mean and Vaccine Reliability Scale all sub dimensions ($p < 0.05$).

Discussion

In this study, the relationship between health literacy and attitude towards vaccination and the findings regarding the situation in different countries are discussed in the light of the literature.

The total mean scores from the Health Literacy Scale were found to be significantly higher among Nepal's people ($p < 0.05$). Health literacy is affected by many factors, which suggests that the awareness level of the individuals in which the study was

Table 2. Health Literacy and Vaccine Reliability Scale Total Score Means and Sub-Dimension

	$\bar{X} \pm SD$	Min-Max
Health Literacy Scale Total Score Means	54.92±23.64	25.00-125.00
Access to Information Sub-Dimension	10.76±5.14	5.00-25.00
Understanding Information Sub-Dimension	15.31±7.03	7.00-35.00
Value Setting Sub-Dimension	17.98±7.81	8.00-40.00
Application Sub-Dimension	10.85±5.03	5.00-25.00
Vaccine Reliability Scale Total Score Means	55.38±12.99	4.00-80.00
Vaccine Benefit Perception Sub-Dimension	29.86±7.78	0.00-40.00
Vaccine Harm Perception Sub-Dimension	10.74±4.87	0.00-20.00
Trust in Healthcare Professionals Sub-Dimension	14.77±4.38	0.00-20.00

Source: Online field survey 2020.

Table 3. Comparison of Individuals' Demographic Characteristics and Health Literacy Total Score Mean

Variables	n	$\bar{X} \pm SD$	Statistic
Nationality	Turkey	103	51.97±23.12
	Nigeria	107	45.76±20.22
	Pakistan	107	51.95±22.94
	India	107	52.66±24.01
	Malaysia	97	55.55±31.74
	Nepal	95	75.68±8.21
	Indonesia	89	58.66±24.36
	Madagascar	133	50.97±17.87
Gender	Female	356	51.20±23.14
	Male	482	57.66±23.66
Marital status	Single	564	55.10±23.04
	Married	274	54.54±24.87
Education Level	Primary education	34	48.94±27.70
	Secondary education	87	54.49±23.13
	Tertiary education	499	55.85±23.50
	Master	205	53.46±23.45
	Doctorate	13	60.38±23.97
Occupation	Civil Servant	119	62.59±24.68
	Health worker	50	59.72±21.36
	Pensioners	28	47.35±18.48
	Business owner/trader	82	52.96±20.15
	Unemployed	104	49.55±26.46
	Student	353	55.01±23.02
	Others	102	52.40±24.18
Can you receive COVID-19 vaccine?	Yes	473	53.80±22.98
	No	365	56.36±24.43
Are you against the COVID-19 vaccine?	Yes	101	58.31±24.77
	No	737	54.45±23.46
Do you think the COVID-19 vaccine will be effective?	Yes	701	54.00±23.28
	No	137	59.62±24.95
Can you receive the COVID-19 vaccine if it is free?	Yes	550	53.59±24.09
	No	288	57.44±22.58

Source: Online field survey 2020.

Table 4. Comparison of Individuals' Demographic Characteristics and Vaccine Reliability Scale Total Score Mean

Variables		n	$\bar{X} \pm SD$	Statistic
Nationality	Turkey	103	49.72±12.97	KW=90.998 p= 0.000
	Nigeria	107	57.35±11.12	
	Pakistan	107	52.16±20.15	
	India	107	61.72±10.87	
	Malaysia	97	59.82±10.90	
	Nepal	95	54.16±8.71	
	Indonesia	89	57.29±11.13	
	Madagascar	133	52.04±9.93	
Gender	Female	356	56.04±13.17	U=81324.00 p=0.196
	Male	482	54.90±12.85	
Marital status	Single	564	55.35±13.26	U=77072.50 p= 0.953
	Married	274	55.46±12.45	
Education Level	Primary education	34	60.32±13.66	KW=12.871 p= 0.012
	Secondary education	87	58.16±12.55	
	Tertiary education	499	54.66±13.18	
	Master	205	55.05±12.14	
	Doctorate	13	56.76±16.35	
Occupation	Civil Servant	119	54.13±12.79	KW=5.877 p= 0.437
	Health worker	50	55.30±10.67	
	Pensioners	28	52.21±14.35	
	Business owner/trader	82	56.70±11.27	
	Unemployed	104	56.76±12.68	
	Student	353	55.35±13.98	
	Others	102	55.42±11.93	
Can you receive COVID-19 vaccine?	Yes	473	56.84±10.90	U=76454.00 p= 0.004
	No	365	53.50±15.09	
Are you against the COVID-19 vaccine?	Yes	101	51.32±15.06	U=30767.50 p= 0.005
	No	737	55.94±12.59	
Do you think the COVID-19 vaccine will be effective?	Yes	701	56.64±12.33	U=32619.50 p= 0.000
	No	137	48.94±14.36	
Can you receive the COVID vaccine if it is free?	Yes	550	57.24±12.62	U=57700.00 p= 0.000
	No	288	51.85±12.97	

Source: Online field survey 2020.

Table 5. Relationship Between Age, Health Literacy, Vaccine Reliability Scale Total Score Means and Sub-Dimensions

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
Health Literacy Scale Total Score Means (1)	r	-								
	p	-								
Access to Information (2)	r	.892*								
	p	.000								
Understanding Information (3)	r	.941*	.798*							
	p	.000	.000							
Value Setting (4)	r	.956*	.797*	.859*						
	p	.000	.000	.000						
Application (5)	r	.920*	.768*	.837*	.858*					
	p	.000	.000	.000	.000					
Vaccine Reliability Scale Total Score Means (6)	r	-.257*	-.197*	-.229*	-.234*	-.249*				
	p	.000	.000	.000	.000	.000				
Vaccine Benefit Perception (7)	r	-.374*	-.307*	-.340*	-.342*	-.361*	.852*			
	p	.000	.000	.000	.000	.000	.000			
Vaccine Harm Perception (8)	r	.171*	.163*	.155*	.173*	.171*	.527*	.141*		
	p	.000	.000	.000	.000	.000	.000	.000		
Trust in Healthcare Professionals (9)	r	-.409*	-.336*	-.362*	-.399*	-.378*	.747*	.612*	.612*	
	p	.000	.000	.000	.000	.000	.000	.000	.000	
Age (10)	r	-.039	-.055	.003	-.061	-.004	-.025	.023	-.103*	.039
	p	.258	.112	.936	.075	.913	.469	.505	.003	.259

Source: Online field survey 2020.

conducted is higher than in other countries.

The total mean scores from the Health Literacy Scale were found to be significantly higher among men ($p<0.05$). There are similar studies in the literature.^{17,18}

The total mean scores from the Health Literacy Scale were found to be significantly higher among civil servant ($p<0.05$). In the literature, health literacy was found to be higher among those working in an income generating job.^{19,20} In addition, it has been determined that the health personnel have a moderate level of health literacy. This situation suggests that it may be due to the fact that health personnel focus on their work in the unit they are located in and have little interest in other areas.

The total mean scores from the Health Literacy Scale were found to be significantly higher among those who do not think the COVID-19 vaccine will be effective ($p<0.05$). Individuals may think so, since information about the vaccine has not been obtained from the right sources and concrete steps have not yet been taken for the coronavirus vaccine.

The total mean scores from the Health Literacy Scale were found to be significantly higher among those who will not receive the COVID vaccine if it is free ($p<0.05$). Health literacy can also be affected by the economic situation,^{19,20} it is thought that individuals have a negative attitude regardless of their wages.

The total mean scores from the Vaccine Reliability Scale were found to be significantly higher among the Indians ($p<0.05$). This situation suggests that awareness of individuals' attitude towards vaccines has increased due to the fact that India is a very crowded country and the epidemic rate is higher.

The total mean scores from the Vaccine Reliability Scale were found to be significantly higher among those who receive COVID-19 vaccine ($p<0.05$). It is thought that as the attitude towards the vaccine increases, they also take a more positive approach to the coronavirus vaccine.

The total mean scores from the Vaccine Reliability Scale were found to be significantly higher among those who do not against the COVID-19 vaccine ($p<0.05$). As the attitude towards vaccination increases, anti-vaccination decreases and it is thought that the attitude

towards vaccination increases positively.

The total mean scores from the Vaccine Reliability Scale were found to be significantly higher among those who think the COVID-19 vaccine will be effective ($p<0.05$). Individuals who have a positive attitude towards the vaccine can be interpreted as they think the vaccine will be effective.

The total mean scores from the Vaccine Reliability Scale were found to be significantly higher among those who will receive the COVID vaccine if it is free ($p<0.05$). Since the attitude towards the vaccine is positive, it suggests that if the vaccine is produced and free of charge, they will be in high demand.

It was found that there was a statistically significant negative correlation between Health Literacy scale total score mean and Vaccine Reliability Scale Total Score Means and two Vaccine Reliability Scale sub dimensions; Vaccine Benefit Perception and Trust in Healthcare Professionals ($p<0.05$). When we look at the history of vaccines, vaccines have been blamed many times in the period that has passed until today. However, most of the charges are mythologically based. The accusations made with more "medical looking" explanations could not be proven clinically. For example, studies have been carried out on the claim that the mercury in the vaccines causes autism. However, no study has proven this claim. Nevertheless, the US government announced that it removed mercury from vaccines in 2001, fearing that the vaccination rates will decrease.²¹ However, parents believe that there is still mercury in vaccines and that it is associated with autism in the long term. Similarly, he believes that aluminum and other chemicals accumulate in the body and will lead to chronic diseases in the future. There are claims stating that aluminum is a neurotoxin and that vaccines containing aluminum in infants whose brain development is not yet completed may cause neurodevelopmental and autoimmune diseases.²² In laboratory studies, the toxic effects of aluminum and mercury on neuron cell cultures were mentioned, and another study claimed that some sheep developed post-vaccination encephalitis.^{23,24} However, clinically, there are many cases of encephalitis and meningitis prevented by vaccines, as there are no case reports of vaccine-induced encephalitis.

Studies have shown that in the last 20 years, the most measles cases in the United States were seen in 2014, and most of these cases were as a result of individual vaccine rejection.²⁵ Similarly, there was a significant increase in measles case reports in 2011 in Europe, and it was determined that 85% of them were unvaccinated or unregistered.²⁶ Another concern is that vaccines have side effects. In the study of parents who refused vaccines in Venezuela, the side effects of vaccines and the idea that it is unnecessary to give more than one vaccine came to the fore.²⁷ Yes, vaccines and other substances added to increase the effectiveness of vaccines and prevent their deterioration may have many side effects, from simple pain to anaphylaxis. However, the side effects of vaccines are much less frequent and milder compared to the disease itself.²⁸ In addition, knowing that all medical interventions carry risks and informing patients scientifically by healthcare personnel can reduce concerns about this issue. Considering the benefit-harm balance, studies are in favor of vaccination.²⁹ In order to increase the safety and efficacy of vaccines, studies to reduce their side effects may be needed, but considering the benefits, it is beyond the mind and science that this situation leads to vaccine rejection.

Studies have shown that religious beliefs and religious leaders in Africa, Afghanistan and India are effective in vaccination. Jarett et al. According to the WHO 'Vaccine Hesitations Working Group' analysis in 2015, the fact that people describe themselves as more knowledgeable and increased awareness is at the forefront of the trust questions about vaccines, and if we do not count the availability of the vaccine, the guidance of religious and philosophically active people is seen as a problem that requires mutual dialogue that is difficult to solve.³⁰ It is thought that the negative attitude of the group with high health literacy towards vaccination is due to the side effects of the individuals, possible complications and religious philosophical knowledge.

Conclusions

The Health Literacy total score mean was found to be statistically significantly higher among Nepal nationality, male, civil servant and those who do not think the COVID-19 vaccine will be effective

and those who do not think they will receive the COVID vaccine if it is free ($p < 0.05$). The vaccine reliability scale total score mean was found to be statistically significantly higher among India nationality, those who receive COVID-19 vaccine, who do not against the COVID-19 vaccine, who think the COVID-19 vaccine will be effective and who will receive the COVID-19 vaccine if it is free ($p < 0.05$). It is recommended to conduct the study in a larger groups.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Contribution of Authors

Concept – G.O., M.S.Y., M.Y.; Design – M.A.A., Y.S.; Supervision – S.M., A.T., M.T.; Materials – A.U., R.B.K., K.G., A.G.; Data collection &/or processing – M.S.Y., M.Y., S.M., A.T., M.T., A.U., R.B.K., K.G., A.G., N.A.R., A.R.; Analysis and/or interpretation – U.M., M.S.Y., M.Y.; Literature search – D.G., M.Y., M.S.Y. Writing – M.S.Y., M.Y.; Critical review – G.O.

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The Correlation of Tumor Markers, Neutrophil/Lymphocyte Ratio and FDG PET/CT Measures in Pancreatic Cancer

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ABSTRACT

Background This review will outline the correlation of tumor markers and NLR (Neutrophil/lymphocyte ratio) with measures such as MTV (mean total volume), TLG (total lesion glycolysis), and SUV (standard uptake value) in ¹⁸F FDG PET/CT in pancreatic carcinoma with the goal of selection of appropriate treatment modality and decrease rates of treatment failure and recurrences in pancreatic carcinoma by using tumor markers. In this way, we can predict the results of imaging modalities, using easy lab technics such as NLR and tumor markers.

Material and Methods 45 patients newly diagnosed with pancreatic cancer were included in the study. The diagnosis was confirmed by cytology. Their tumor marker levels (CA 19.9, CEA and AFP), NLR and PET/CT measurements (SUVmax, SUVmean, TLG, MTV) were obtained. Patients that were already diagnosed, followed up, or treated by the oncology department, were excluded.

Results When tumor markers were compared with PET/CT measurements (SUVmax, SUVmean, TLG, MTV and tumor size) there were no significant difference between them. Also, total uptake values of organs (liver, spleen, pancreas) were not related with tumor marker levels. However, there were positive significant correlation between tumor size and SUVmax, SUVmean, TLG (p=0.02, r:0.347; p=0.022, r:0.340; p=0.008, r:0.392).

Conclusions Tumor markers may help diagnosing or managing of pancreatic malignities, but we cannot predict PET/CT results according to tumor marker levels. So, tumor markers must be used as an adjunctive method for diagnosing malignities. They cannot be major determiner for malignities. Diagnosing and following up malignities should be supported by other laboratory technics and imaging methods.

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Introduction

Pancreatic cancer is an important health problem because of its aggressive behavior, it causes death in 95% of patients. Five-year overall survival (OS) rate after surgery is only about 10 to 20 percent whereas it is less than for metastatic pancreatic cancer.^{1,2}

Cancer antigen 19.9 (CA 19.9) is a tumor marker present at high levels in some of malignities like bile duct, hepatocellular, colorectal, gastric, esophagus and pancreas cancer. It can be used to confirm the diagnosis of pancreas cancer, to evaluate the response to the treatment and the recurrence of pancreatic cancer.³⁻⁵ Also, it can be elevated in benign conditions such as biliary tract obstruction, cholangitis, acute or chronic pancreatitis, liver cirrhosis, cystic fibrosis, thyroid diseases, inflammatory bowel disease or in normal, healthy population high levels can be detected.⁶ It's known that 5% of population is unable to synthesize CA 19.9 even if there are malign conditions.⁷

Carcinoembryonic antigen (CEA) is a glycoprotein, and it has immunosuppressive and tumor cell adhesion properties, thus it facilitates metastasis and invasion of tumor cells.⁸⁻¹³ In healthy individuals, CEA is present at very low levels in the blood because its production stops before birth. Although it is not tumor specific, its concentrations are raised in some types of cancer.¹⁴⁻¹⁸

Alfa-feto protein (AFP) is also produced during fetal development by the yolk sac and the liver. It plays a major role to screen liver cancer, preoperatively evaluation or postoperative monitoring and it can show advanced disease. Its levels can be raised not only in hepatocellular carcinoma, but also in other benign diseases and malignancies of testes and other germ cells.¹⁹⁻²¹

Neutrophil/lymphocyte ratio (NLR) is an indicator of systemic inflammation. We know that inflammation may play important roles in the development and progression of malignities. The presence of an elevated peripheral NLR has been recognized as a poor prognostic factor in various cancers.

PET/CT (positron emission tomography-computed tomography) is an imaging method that combines functional imaging with anatomical

images. The most common radiotracer on PET is 18F-fluorodeoxyglucose (18F-FDG), which is a glucose analogue. Pancreatic malignities are usually associated with an overexpression of glucose transporter 1 and it causes increased 18F-FDG uptake on PET/CT.²² A main limitation of this imaging modality is the low spatial resolution and possibility of false positive uptake in normal structures or benign diseases, such as inflammatory processes.²³

SUV max (maximum standardized uptake value) is a semi quantitative measure commonly used in 18F-FDG PET/CT. MTV (metabolic tumor volume), is a volumetric measurement of tumor cells with increased 18F-FDG uptake. The MTV on 18F-FDG PET/CT also demonstrates the metabolic activity, thereby it predicts the response to treatment and helps to determine the prognosis in head and neck cancers. In addition to SUVmax and MTV, TLG (total lesion glycolysis) constitutes another measurement derived from FDG PET/CT that can be useful for predicting prognosis in some of malignities.²⁴⁻²⁷

This study will outline the correlation of tumor markers and NLR with measures such as MTV, TLG, and SUV in 18F FDG PET/CT in pancreatic carcinoma to select appropriate treatment modalities and decrease rates of treatment failure and recurrences in pancreatic carcinoma by using tumor markers. In this way, we can predict the results of imaging modalities, using easy laboratory technics such as NLR and tumor markers.

Material and Methods

This cross-sectional study was conducted between April 2016 and December 2018 in internal medicine outpatient clinics of the Afyonkarahisar Health Science University, Turkey. It was approved by the institutional review board of Afyonkarahisar Health Science University with the number 2019/145.

Forty-five patients newly diagnosed with pancreatic cancer were included in the study. The diagnosis was confirmed by cytology. Their tumor marker levels (CA 19.9, CEA and AFP), NLR and PET/CT measurements (SUVmax, SUVmean, TLG, MTV) were obtained. The interval between the FDG-

Table 1. Mean values of tm markers and PET/CT measurements

	Minimum	Maximum	Mean	Std Deviation
Age	36	84	62	10.1
Tumor size (mm)	19	97	41.6	17.4
CA 19.9 (U/mL)	0.60	10.000	1329.7	2923.1
CEA (ng/mL)	0.99	71.29	10.2	14.2
AFP (ng/mL)	0.86	9.48	2.5	1.4
NLR	0.76	27.72	5.56	6.55
SUVmax	3.0	17.2	8.1	3.5
SUVmean	2.0	10.7	4.5	1.9
TLG	14.8	1248	161.3	188.3
MTV	4.5	156	38.3	35.5

NLR: neutrophil/lymphocyte ratio, TLG: total lesion glycolysis, MTV: metabolic tumor volum

PET/CT evaluation and determining tumor markers was no more than one week. Tumor size was obtained by measure of greatest diameter of tumor with computed tomography. Patients that already diagnosed, followed up or treated by oncology department, were excluded. 18F-FDG-PET/CT scans were performed in accordance with a standard whole-body oncological protocol in each institution following the guidelines of the European Association of Nuclear Medicine.

Statistical analysis

The data collected were analyzed by SPSS for IBM, version 23.0 (SPSS, Turkey). Patient characteristics were reported using frequency and descriptive analyses. Tests of normality was determined by Shapiro-Wilk test. Correlation between variables was analyzed with Spearman's test. A p-value of less than 0.05 was considered to statistically significant.

Results

Overall, 45 patients (20 men and 25 women) were included in this study. The mean age of patients was 62 ± 10.1 year. The mean serum levels of tumor markers and NLR and PET/CT measurements are shown in Table 1.

Mean serum levels of CA 19.9 was 1329.7 ± 2923.1 U/mL. 17 of the patients had normal CA 19.9 levels (under 37 U/L). 4 of them had levels above 10,000 U/mL.

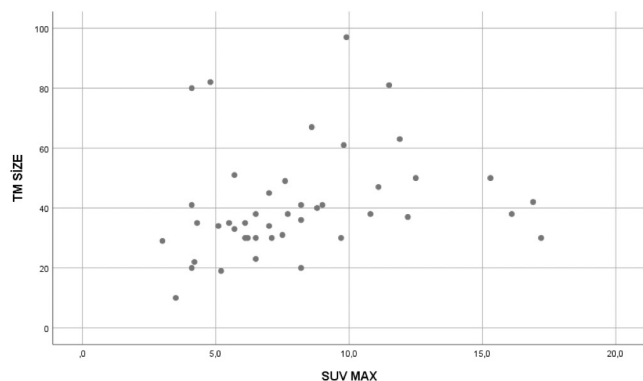
Mean CEA levels were 10.2 ± 14.2 ng/mL and nineteen patients had normal CEA levels (under 5 ng/mL). However, AFP levels of all patients were at normal range (under 10 ng/mL). Mean NLR were 5.56 ± 6.55 . Three patients had very high levels of NLR (above 25) since they had bacterial co-infections.

When tumor markers were compared with PET/CT measurements there were no significant difference between them (Table 2). Also, total uptake values of organs (liver, spleen, pancreas) were not related with tumor marker levels.

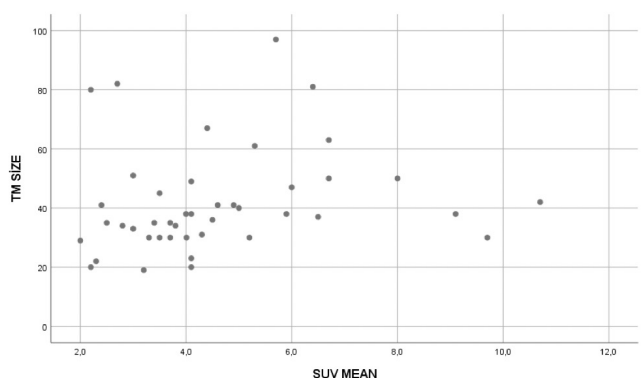
Table 2. P values of correlations between tumor markers, NLR and PET-CT measurements

	SUVmax	SUVmean	TLG	MTV	Tumor Size	Liver	Spleen	Pancreas
CA 19.9	0.503	0.464	0.961	0.845	0.660	0.751	0.439	0.811
CEA	0.322	0.228	0.487	0.379	0.499	0.643	0.319	0.071
AFP	0.854	0.884	0.152	0.166	0.095	0.105	0.498	0.708
NLR	0.315	0.186	0.468	0.478	0.912	0.512	0.252	0.696

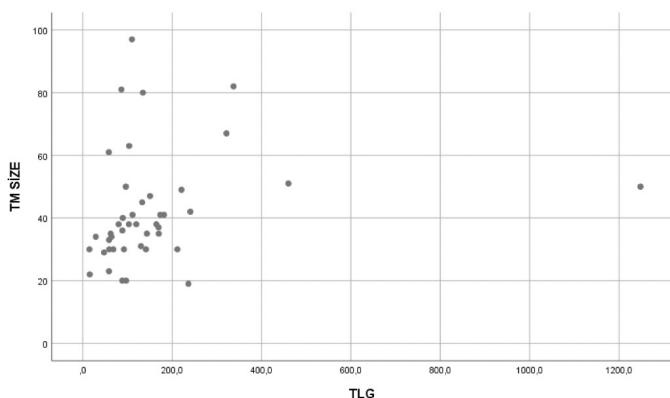
SUVmax: maximum standardized uptake value, SUVmean: Mean standardized uptake value, TLG= total lesion glycolysis, MTV=metabolic tumor volume, NLR= neutrophil lymphocyte ratio (P<0.05 significant)



Graphic 1. Correlation between tumor size and SUVmax



Graphic 2. Correlation between tumor size and SUVmean



Graphic 3. Correlation between tumor size and TLG

Interestingly, we found that a negative correlation between CA 19.9 levels and SUVmax, SUVmean but it was not statistically significance ($p=0.503$, $r:-0.102$; $p=0.464$, $r:-0.112$). Likewise, between CEA levels and TLG, MTV there were negative insignificant correlation ($p=0.487$, $r:-0.106$; $p=0.379$, $r:-0.134$). Negative correlation continued between AFP and TLG, MTV also tumor size. Its level was also negligible ($p=0.152$, $r:-0.217$; $p=0.166$, $r:-0.210$; $p=0.095$, $r:-0.252$).

Between NLR and SUVmax, SUVmean there were negative insignificant correlation ($p=0.315$, $r:-0.153$; $p=0.186$, $r:-0.201$).

As expected, there were positive significant correlation between tumor size and SUVmax, SUVmean, TLG as shown in graphic 1,2 and 3. ($p=0.02$, $r:0.347$; $p=0.022$, $r:0.340$; $p=0.008$, $r:0.392$).

Discussion

Tumor markers are used for detecting, diagnosing, managing certain types of cancer and also determining the progression of disease.

Carbohydrate antigen 19.9 also called cancer antigen 19.9 or sialylated Lewis antigen is a tumor marker that is used firstly in the management of pancreatic cancer.²⁸ But it may be falsely positive in cases of biliary inflammation or obstruction.²⁹ However, CA 19.9 may be undetectable in Lewis antigen-negative individuals even if they have advanced cancer. In our study 17 of patients have normal CA 19.9 value.

As in this study, CA 19.9 serum level of 100 U/mL suggestive of unresectability or metastatic disease.³⁰ Our 4 patients that have distant metastasis, have up to 10,000 U/mL value of CA 19.9.

In pancreatic cancers, levels of CEA may reflect the tumor size, differentiation and metastasis.³¹ Also, its pancreatic juice levels can be used as a tumor marker.^{16,32-34} Preoperatively, high serum levels of CA 19.9 and CEA can be an indication of nonresectability or low chance of survival. While CA19.9 level is increased in both malignant and benign diseases, CEA increases only in malignant diseases.³⁵ In our study mean value of CEA was 10.2 ± 14.2 ng/mL. Only 19 patients' results were under 5 ng/mL, it can be explained by the presence of CEA-related glycoproteins. Unlike the literature, we did not find any correlation between CEA levels and tumor size.

AFP has a high specificity for a hepatocellular carcinoma. It can be used for screening hepatocellular carcinoma and its levels also can be elevated in liver cirrhosis and chronic hepatitis.³⁶ We found that all AFP values were under 10 ng/mL. According to these results, we can predict that in pancreas malignities even if

there is distant metastasis (like liver metastasis), elevated AFP values are not always expected.

It is known that inflammation plays a very significant role in the development of cancer and may affect cancer patients' survival.³⁷ Systemic inflammation supports tumor metastasis and progression.³⁸ Because inflammatory cells and mediators generate a tumor related inflammatory microenvironment which plays vital roles in tumor progression and pathogenesis.³⁹ The previous meta-analyses had showed that the prognostic value of preoperative NLR for patients with cancers, such as epithelial ovarian or upper urothelial tract, hepatocellular carcinoma and all solid tumors.⁴⁰⁻⁴³ In the same way, Li et al.⁴⁴ indicated that high NLR was associated with poor overall survival, disease free survival, recurrence free survival in colorectal cancer. They had defined high NLR as values higher than 5.^{44,45} Also Fujii et al.⁴⁶ found that high NLR were significantly associated with high SUVmax in the primary tumor of breast. They demonstrated that high NLR may be predictive of poor prognosis among patients with breast cancer 46. In our study, the mean value of NLR was 5.56 ± 6.55 . Contrarily, we did not detect any significant relation between NLR and SUVmax, SUVmean.

Sun et al.⁴⁷ showed that SUVmax levels were associated with tumor size in pancreatic cancer patients.⁴⁷ Like them, we also defined relation between tumor size and SUVmax, SUVmean, TLG.

As a result, tumor markers may help diagnosing or managing of pancreatic malignities but we can not predict PET/CT results according to tumor marker levels. So, tumor markers must be used as an adjunctive method for diagnosing malignities. They can not be major determiner for malignities. Diagnosing and following up malignities should be supported by other laboratory technics and imaging methods.

Unfortunately, our study has some limitations. First of all, it is a retrospective study and involves small sample size and all patients were selected from same hospital. Therefore, to say a relation between tumor markers and PET/CT measurements, multi-center, large sample prospective studies are needed.

Conflict of interest

The authors declared that there are no potential conflicts of interest.

Authors' Contribution

Study Conception: MH; Study Design: MH; Supervision: EH, HD; Funding: EB; Materials: ABS, NU, FCH; Data Collection and/or Processing: RK; Statistical Analysis and/or Data Interpretation: RK, EB; Literature Review: EH, HD; Manuscript Preparation: MH; and Critical Review: EH, HD.

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Acoustic Radiation Force Impulse Elastography Findings of Achilles Tendon in Patients with Hypothyroidism

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ABSTRACT

Background The aim of our study was to investigate the effect of thyroid dysfunction on tendons and the contribution of Acoustic Radiation Force Impulse (ARFI) elastography to the diagnosis of tendinopathy.

Material and Methods Eighty Achilles tendons of 40 patients under levothyroxine treatment, who had previously known hypothyroidism but high serum thyroid stimulating hormone levels, and 80 Achilles tendons of 40 healthy individuals were evaluated with ARFI (Virtual Touch Quantification®). 19 of 40 of the patients with hypothyroidism' Achilles tendons were re-evaluated after thyroid stimulating hormone levels reached to normal limits following the adjustments in thyroid hormone replacement therapy. The middle portion of the each Achilles tendon was chosen for the examination. Every examination consisted of three to five independent measurements (shear wave velocity - meters per second). The mean shear wave velocity value was calculated for each tendon, and used for statistical analysis.

Results The stiffness values of both left and right Achilles tendons, represented as shear wave velocity, were similar in patients with hypothyroidism and control group. There was no significant difference between the Achilles tendon shear wave velocity measurements of 19 of 40 hypothyroidism patients who were re-evaluated after the adjustments in thyroid hormone replacement therapy.

Conclusions The lack of significant difference in Achilles tendon stiffness between non-naive hypothyroid patients and the control group may be explained as a positive clinical effect of thyroid hormone replacement therapy.

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Introduction

Thyroid hormones triiodothyronine (T3) and thyroxine (T4) play an important role in the development and regulation of many tissues and organs. As shown in in vitro studies on animals and both in vitro and in vivo studies on humans, thyroid hormones also structurally affect tendons.¹ However, there are very limited number of clinical studies and data on the effect of thyroid dysfunction in hypothyroidism on connective tissue.^{1,2,3} Tendinitis can be the first complaint in hypothyroidism and symptomatic relief can be provided with the appropriate treatment of primary thyroid deficiency.^{2,3}

Achilles tendon, which comprises the tendinous components of gastrocnemius and soleus muscles, is the strongest, largest and thickest tendon in the human body.⁴ Achilles tendon injuries are common among both athletes and general population due to sports-related trauma and excessive use.⁵ In order to prevent achilles tendon rupture and tendon injury from becoming chronic, early diagnosis and treatment of tendinopathy is important. While conventional B-mode ultrasonography (US) detects tendon rupture with a high rate of accuracy, its value in the diagnosis of tendinopathy is controversial.⁵⁻⁷ Unlike classical US, elastography, which has come to use in the recent years, enables the assessment of tissue stiffness. There are studies with the ultrasonographic and elastographic findings of achilles tendon in normal population, the elderly, professional athletes, end-stage renal disease patients, long-term hemodialysis patients, secondary hyperparathyroidism, and smokers.^{5,8,9}

With the initial elastographic methods, tissue stiffness was evaluated subjectively using a color scale. Acoustic radiation force impulse (ARFI) imaging is an elastography technique that provides an objective numerical assessment of tissue stiffness differently from the other elastography techniques. It provides an estimate of tissue elasticity by measuring the propagation of shear waves emitted during induced tissue displacements. The speed of the shear waves can be measured as shear wave velocity (SWV) and it is expressed quantitatively in meters per second (m/s). Stiffer tissues are associated with

a higher SWV.¹⁰ The benefits and usefulness of ARFI imaging has been shown in many clinical conditions. There have been a small number of studies on the evaluation of achilles tendon in different patient groups using ARFI elastography. In these studies, it has been shown that there is softening in Achilles tendon with age, in patients with intermittent claudication, diabetes patients, and chronic kidney disease patients.^{8,11-13} To our knowledge, there are no studies in the literature on ARFI elastography findings of the Achilles tendon in hypothyroidism patients.

The aim of this study was to investigate the effect of thyroid dysfunction on tendons and the contribution of ARFI elastography to the diagnosis of tendinopathy by comparing ARFI elastography findings of the Achilles tendon in hypothyroidism patients and normal individuals.

Material and Methods

Study Population

This prospective study was conducted in the Radiology and Endocrinology department of Baskent University Ankara Hospital, and approved by the medical ethics committee. Informed consent was obtained from all subjects, according to the Edinburgh (2000) revision of the World Medical Association Declaration of Helsinki.

The participants of the patient group were selected from Endocrinology outpatient clinics. Forty patients under levothyroxine treatment, who had previously known hypothyroidism but high serum thyroid stimulating hormone (TSH) levels, were included in this study. Eighty Achilles tendons of 40 patients with non-naive hypothyroidism were evaluated with ARFI. Nineteen of these patients' Achilles tendons were re-evaluated after TSH values reached to normal limits following the adjustments in thyroid hormone replacement therapy. For the control group, 40 age- and gender-matched healthy individuals from the check-up outpatient clinics were included, and 80 Achilles tendons of the volunteers were evaluated. All participants were asymptomatic,

and none had any past operations or history of trauma affecting the Achilles tendons or cruris muscles. None of the individuals had a history of systemic or another endocrinological disease, surgery, intensive exercise, peripheral artery disease or chronic drug use that could be associated with tendinopathy. All patients' clinical records, including their age, sex, TSH and free T4 (fT4) levels were recorded.

Imaging technique

Ultrasonographic studies were performed using a 9–14-MHz linear transducer (Acuson S2000, Siemens Healthcare, Erlangen, Germany) and adequate software for performing elastographic examinations in quantitative ARFI mode (Virtual Touch Quantification®, VTQ). All examinations were performed by the same radiologist with 14 years of experience in US and 6 years of experience in elastography. Each Achilles tendon was examined in axial and longitudinal planes in the prone position with the foot hanging over the examination bed in a relaxed position.⁹ The middle portion of the Achilles tendon, which is nearly 2 to 6 cm proximal to the calcaneus insertion, was chosen for the examination. ARFI (VTQ) mode was performed on the longitudinal plane of Achilles tendon, and the probe was held perpendicular to the tendon to avoid anisotropy. The transducer was gently applied without pressure, together with a sufficient amount of contact gel. Because of the superficial localization of the Achilles tendon, more ultrasonic coupling gel was used. A fixed size of 5×6 mm region of interest (ROI) was used. Every examination consisted of

three to five independent ARFI measurements (SWV - meters per second). The mean SWV value of the three to five SWV measurements was calculated for each tendon, and used for statistical analysis.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, Version 23.0 (SPSS, Chicago, IL, USA). Continuous data were presented as mean±standard deviation or median (minimum–maximum) as appropriate. The level of significance was determined using t-test for values with normal distribution and the Mann–Whitney test for values with non-normal distribution. Categorical variables were compared using Chi-squared test. One-way repeated measures ANOVA was conducted to determine whether there were any statistically significant differences between ARFI measurements of patients in hypothyroid and euthyroid states. P value of <0.05 was considered statistically significant.

Results

Forty hypothyroidism patients and 40 age- and gender-matched healthy controls were included. Table 1 demonstrates the demographic and biochemical characteristics of hypothyroidism group and control group. There was no significant difference between the groups in terms of age and gender. As expected, TSH and sT4 levels were significantly high and low, respectively, in the patient group compared with control group.

Table 1. The demographic and biochemical characteristics of hypothyroidism group and control group

	Patient Group* (n=40)	Control Group (n=40)	P value
Age (year)	47.2±14.0	48.5±9.9	0.053
Sex (F/M)	33 / 7	32 / 8	0.075
TSH levels (mU/L)‡	21.0 (6.5-372.0)	1.6 (0.6-3.1)	<0.0001
fT4 levels (ng/dL)	0.7±0.3	0.9±0.2	0.005

*Group of patients with hypothyroidism, ‡ median (minimum-maximum)
Normal range fT4: 0.7-1.48 ng/dL, TSH: 0.35-4.94 mU/L

Table 2. The shear wave velocity (SWV) measurements of Achilles tendon in patients with hypothyroidism and control group

	Patient group * (n=40)	Control group (n=40)	P value
Right Achilles tendon (m/s)	5.07±1.14	5.36±1.11	0.245
Left Achilles tendon (m/s)	5.09±1.16	5.21±1.11	0.662

*Group of patients with hypothyroidism

Table 3. Achilles tendon shear wave velocity (SWV) measurements of 19 of 40 patients with hypothyroidism, which were obtained before- and after- the adjustments in thyroid hormone replacement therapy

	Before*	After**	P value
Right Achilles tendon (m/s)	5.14±1.45	4.7±1.37	0.269
Left Achilles tendon (m/s)	5.34±1.36	4.7±1.17	0.097

*before-, and **after- the adjustments in thyroid hormone replacement therapy

Table 2 shows the SWV measurements of both left and right Achilles tendon in the groups. The stiffness values of both left and right Achilles tendons, represented as SWV, were similar in patients with hypothyroidism and control group (Table 2).

There was no significant difference between the Achilles tendon SWV measurements of 19 of 40 hypothyroidism patients who were

re-evaluated after the adjustments in thyroid hormone replacement therapy (Table 3, Figure 1). The mean duration of re-evaluation of these patients after therapy adjustment was a mean of 2.6±1.2 months. TSH levels of these 19 patients before- and after- the adjustments in thyroid hormone replacement therapy were 58.7±1.32 mU/L, and 1.5±1.23 mU/L, respectively.

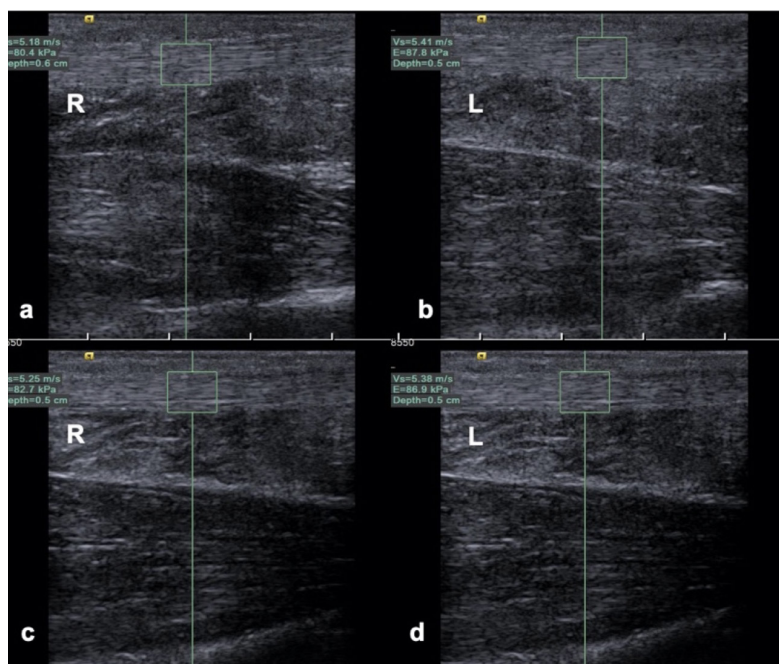


Figure 1. Shear wave velocity (SWV) measurements in the right (a, c) and left (b, d) Achilles tendon of a 42 years old female with hypothyroidism, before (a, b) and after (c, d) the thyroid hormone replacement. The SWV of the tendons were measured with fixed measurement sample dimensions of 5x6 mm. In this patient, the mean SWV of the right and left Achilles tendons were calculated 5.94 m/sn, 5.14 m/sn before the therapy, and 5.32 m/sn, 5.24 m/sn after the therapy, respectively. R: right; L: left

Discussion

Our data indicate that there was no significant difference between non-naive hypothyroidism patients and healthy individuals in terms of Achilles tendon stiffness. Moreover, there was no significant difference between patients who were re-evaluated after the adjustments in thyroid hormone replacement therapy in terms of Achilles tendon stiffness. To the best of our knowledge, this is the first study that evaluates Achilles tendon stiffness using ARFI elastography in patients with and without hypothyroidism.

Elastography is a recently developed noninvasive method that allows for the assessment of tendon elasticity. Several studies confirmed that a normal Achilles tendon was more stiff than an abnormal tendon, as well as a tendon with tendinopathy and a ruptured tendon.^{9,14} Klauser et al.¹⁵ compared the elastography of cadaveric Achilles tendons to histological data and confirmed that elastography could predict signs of histopathologic degeneration in Achilles tendon disorders. Turan et al.¹⁶ demonstrated that elastography was useful for evaluating tendon abnormalities in patients with ankylosing spondylitis. These and similar studies revealed that the elastic properties of the Achilles tendon might improve the diagnosis of early stages of tendon abnormalities. ARFI elastography is an elastography technique that allows for the attainment of numerical results, therefore enabling more clear and objective interpretation of the level of tissue stiffness. This technique has also been used to evaluate tendons, especially the Achilles tendon, which is the largest and thickest tendon in the human body. To our knowledge, there were only a few small scale studies on the elasticity of Achilles tendon using ARFI elastography. Iyidir et al.¹³ demonstrated that diabetic patients with neuropathy had a softer Achilles tendon while the elasticity of Achilles tendon measured using ARFI was similar in diabetic patients without neuropathy and healthy controls. Yilmaz et al.¹¹ showed that the elasticity of Achilles tendons decreased in patients with intermittent claudication. Karatekin et al.¹⁷ demonstrated that there was a decrease in the elasticity value measured using ARFI of the repaired Achilles tendon compared to the non-injured side. Kural Rahatli et al.¹² reported that

Achilles tendons in patients with chronic renal failure and patients receiving hemodialysis were softer than renal transplant patients and control group.

Different soft tissues and bone diseases have been associated with hormone imbalance due to the alteration of biological pathways and the loss of control of cellular homeostasis.¹⁸ In addition, various biomechanical properties of the musculoskeletal system seem to be affected by hormonal diseases.¹⁹ Thyroid hormones play an important role in cell growth and proliferation in a dose-dependent manner, and affect the structural setting of the tendons.^{20,21} In vivo studies underlined that hypothyroidism leads to hypoxia and apoptosis, contributing to musculoskeletal problems in humans.^{22,23} Thyroid symptomatology differs significantly across hypothyroidism spectrum. Restoration of euthyroidism is associated with the reversal of majority of thyroid symptomatology, improves the quality of life and reverses the impairments of cardiovascular, respiratory, and muscle functions at rest and during exercise.^{24,25} Tendinitis can be the presenting complaint in hypothyroidism and symptomatic relief can be obtained by appropriate management of the primary thyroid deficiency.² Several authors have reported complete disappearance, while others have reported only a decrease in symptoms and signs.³ Some studies indicated that the patient's symptoms commonly improved rapidly after levothyroxine was started, and the relief of the musculoskeletal complaints occurs 2 to 8 weeks after the initiation of replacement therapy.^{2,22,26-29} Knopp et al.² concluded that, the dramatic improvement and complete resolution of the symptoms with thyroid replacement therapy after failure with all other medical treatments suggest that normal tendon healing is impaired in hypothyroidism. Unfortunately, to the best of our knowledge, there were no studies in the literature that evaluated tendinitis symptomatology and biochemical parameters of the patients with high serum TSH levels during thyroid hormone replacement therapy. In our study population, all patients had previously known hypothyroidism and all were under levothyroxine treatment. Positive clinical effect of levothyroxine treatment may explain the fact that there was no significant difference between the Achilles

tendon stiffness of non-naive hypothyroidism patients and healthy individuals, and the absence of a significant difference in Achilles tendon stiffness between patients who were re-evaluated after adjustment of thyroid hormone replacement therapy in our study. Furthermore, the duration of hypothyroidism in our patients is not known. Hypothyroidism level and duration is important for the chronic connective tissue changes.³⁰ So as we do not know the duration of hypothyroidism state of these patients, it is hard to make a judgement that hypothyroidism do not effect tissue elasticity measured by ARFI elastography. The short duration of hypothyroidism in our patients may also explain these findings.

The major limitation of this study was the small sample size. In addition, while the study included patients with previously known hypothyroidism under levothyroxine treatment but with high serum TSH levels, patients with naive hypothyroidism were not included. Also, the duration of hypothyroidism of the non-naive patients which may be important for the chronic connective tissue changes, were not known. Another limitation was that a histological analysis was not performed. Since all our patients were asymptomatic, an invasive procedure like biopsy could not be performed. In addition, Achilles tendon was evaluated with ARFI, just the middle portion of the tendon was selected. Thus, the values did not represent the entire tendon. However, most abnormalities of the tendon occur in the middle third or proximal two-thirds.^{14,31} The tendon has a highly anisotropic nature, which requires positioning the ultrasonic beam in a perfectly parallel or perpendicular direction with respect to the fibers. The anatomic position and angle in the proximal third of the Achilles tendon is complex, as it consists of interpenetration and rotation of fibers from the gastrocnemius and soleus muscles. It is relatively easy to achieve the requirements only in the middle portion of the tendon.⁵

In conclusion, there were no significant differences between non-naive hypothyroidism patients, healthy individuals and patients who were re-evaluated after the adjustments in thyroid hormone replacement therapy in terms of the stiffness of Achilles tendon. These findings may be explained as a positive clinical effect of

thyroid hormone replacement therapy. ARFI is a simple, non-invasive and objective method for the assesment of changes in Achilles tendon. This study is important in terms of being a pilot study on a subject that can be considered new for the literature. Further prospective studies with larger sample size, which also include naive clinically overt hypothyroidism patients, are needed to identify the causal relationship between the sonoelastographic changes in Achilles tendon and hypothyroidism. Besides prospective follow-up studies evaluating the effect of thyroid hormone replacements on sonoelastographic measurements in hypothyroid patients can be conducted to clarify the treatment effects on thyroid hormone levels and Achilles tendon elasticity measured by ARFI.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

All authors have contributed the conception and design, or analysis and interpretation of data, the drafting of the article or its critical review for important intellectual content. All authors read the final version of the manuscript. All authors have agreed with the content of the manuscript and approved the submission to the 'Turkish Journal of Internal Medicine'.

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Prevalence of Hepatitis B Virus Serological Groups in Rheumatoid Arthritis and Association of Previous Hepatitis B Virus Infection with Demographic Data and Parenteral Therapies

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ABSTRACT

Background: The aim of this study is to determine the frequency of Hepatitis B virus (HBV) serological groups in Rheumatoid arthritis (RA) and to compare the demographic characteristics and frequency of parenteral therapies between patient groups with and without previous HBV infection.

Material and Methods: Charts of RA patients were examined retrospectively. HBsAg, anti-HBc IgG, and anti-HBs test results were screened. All participants were divided into 3 serological groups (patients naive to HBV infection, previous HBV infection, vaccinated). Those with previous HBV infection were further divided into 3 serological subgroups (naturally immune, anti-HBc IgG positive only, chronic HBV infection). Findings were compared between RA patients with and without previous HBV infection.

Results: Four hundred and fifty-one patients (female/male: 343/108) were included. The prevalence of patients naive to HBV infection, with previous HBV infection and vaccinated were 59.4%, 33.7%, and 6.9%, respectively. The prevalence of patients with naturally immune, anti-HBc IgG positive only, and chronic HBV infection were 25.7%, 4.4%, and 3.5%, respectively. Age in RA patients with and without previous HBV infection was 60.8 ± 12.4 and 56.7 ± 14.2 years, respectively ($p < 0.001$). The frequency of previously administered joint injection, subcutaneous and intravenous therapies in RA patients was not different between the groups ($p = 0.644$, $p = 0.796$, and $p = 0.686$, respectively).

Conclusions: Chronic HBV infection in RA patients is close to the prevalence in the Turkish population. Previous HBV infection is common in RA and this group is older than those without previous HBV infection. Parenteral therapies in RA treatment options do not change the frequency of HBV exposure.

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Introduction

Hepatitis B virus (HBV) continues to be an important public health problem due to the mortality and morbidity it causes worldwide. Although HBV seroprevalence varies between regions, approximately 3% of the world population has chronic HBV disease.^{1,2} The rate of chronic HBV infection and the frequency of being infected with the HBV in Turkey is high. In a multi-center study conducted in Turkey, HBsAg positivity was found to be 4.0% and anti-Hepatitis B core antigen (HBc) IgG positivity was found to be 30.6%.³ Rheumatoid arthritis (RA) is a systemic inflammatory disease of unknown etiology, mainly involving the synovial membranes. Biological drugs such as rituximab and tumor necrosis factor (TNF) α inhibitors, disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, leflunomide, sulfasalazine and bridging drugs such as corticosteroids are frequently and continuously used in the treatment course of RA patients. These immunosuppressive (IS) drugs may cause reactivation in those with previous HBV infection, and the frequency of reactivation varies according to the serological group of HBV occurring in the host following HBV infection.⁴⁻⁷ While reactivation is most common in HBsAg (+) individuals following IS therapy, the frequency of reactivation varies significantly in HBsAg (-)/anti-HBc IgG (+) individuals according to the positive and negative status of antibodies against hepatitis B surface antigen (anti-HBs).^{6,7} Therefore, it is important for clinicians to have information about the frequency of HBV serological groups in RA patients. HBV can be transmitted sexually and parenterally. Parenteral treatments such as subcutaneous treatments and intravenous drugs, as well as interventional procedures such as intra-articular injections are among the treatment options for RA patients. According to the limited data in the literature HBsAg positivity in RA patients in Turkey is close to the frequency in the general population, but we have no information about the prevalence of HBV serological groups of RA patients in Turkey.^{3,8} In addition, we do not have any information on whether these parenteral treatments and interventional procedures, which are frequently used in RA patients, increase transmission.

The aim of this study is to determine the

frequency of HBV serological groups by investigating the seroprevalence of HbsAg, anti-HBc IgG and anti-HBs in RA patients followed up in a single center, and to compare demographic characteristics and frequency of parenteral therapies between patient groups with and without previous HBV infection.

Material and Methods

Study Design

Ethics committee approval of the study was obtained from Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (2011-KAEK-25 2018/11-12). The study was designed as a retrospective study and the charts of 1053 patients who were followed up with the diagnosis of RA in the Rheumatology department were examined. In the preliminary examination, the information recorded in the patients' charts was examined first, and when the investigated data were not found in the charts, the electronic archive records were examined.

Inclusion criteria: Those whose current disease age is over 18, those who were diagnosed with RA by a specialist rheumatologist and had a rheumatology follow-up chart were included.

Exclusion criteria: Patients for whom all HBV serological test results (HBsAg, anti-HBc IgG and anti-HBs) could not be reached from the follow-up charts or electronic archive were excluded.

Examining the Data of the Patients Included in the Study

Demographic information (age and gender), disease duration, auto-antibody tests [Rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP)] were obtained from records of patients whose HBV serological test results were available. In addition, it was investigated whether intra-articular injection, subcutaneous treatments [subcutaneously administered methotrexate and/or insulin and/or biological therapy (etanercept, adalimumab, golimumab, serralizumab)] or intravenous therapy (infliximab, rituximab, tocilizumab or abatasept) were applied before the date of HBV serological tests.

Hepatitis B Serological Subgroups

All participants were divided into 3 serological groups according to their HBV serological test results;

- Patients naive to HBV infection: HBsAg (-), anti-HBc IgG (-), anti-HBs (-)
 - Previous HBV infection: HBsAg (-/+), anti-HBc IgG (+), anti-HBs (-/+)
 - Vaccinated: HBsAg (-), anti-HBc IgG (-), anti-HBs (+)
- Those with previous HBV infection were further divided into 3 subgroups;
- Naturally immune: HBsAg (-), anti-HBc IgG (+), anti-HBs (+)
 - Anti-HBc IgG positive only: HBsAg (-), anti-HBc IgG (+), anti-HBs (-)
 - Chronic HBV infection: HBsAg (+), anti-HBc IgG (+), anti-HBs (-)

Comparisons Between Serological Groups

Demographic data, disease duration, presence of RF and anti-CCP autoantibodies were compared between serological groups of RA patients with and without previous HBV infection. Medical history including intra-articular injection, subcutaneous therapy and intravenous therapy was compared between the groups of patients with and without previous HBV infection.

Statistical Analysis

Descriptive statistical data were given together with mean, standard deviation, median, minimum, maximum values and frequencies. Shapiro-Wilks or Kolmogorov-Smirnov test

was used to determine whether the continuous variables had normal distribution or not. In the comparison of quantitative data between the groups, the Student's t-test was used when there was normal distribution, and the Mann-Whitney-U test was used when there wasn't normal distribution. Fisher's exact test or Chi-square (χ^2) test was used for the comparison of qualitative data between the groups.

Results

HBV Test Results and HBV Serological Groups in the Study Population

Among 1053 patients, 451 patients (343 females and 108 males, mean age 57.7 ± 13.8 years) whose all HBV serological test results could be reached were included in the study. Demographic data, HBV serological test results and HBV serological groups of RA patients included in the study are shown in Table 1. HBsAg positivity was 3.5% and anti-HBc IgG positivity was 33.7%. The frequency of those naive to HBV infection was 59.4%, while the frequency of those vaccinated was 6.9%. Out of 152 patients with previous HBV infection, 116 were positive for anti-HBs antibodies (naturally immune), while 20 were found to be negative for anti-HBs antibodies (Anti-HBc IgG positive only).

Table 1. Demographic data, HBV serological test results and HBV serological subgroups of rheumatoid arthritis patients included in the study.

	(n=451)
Age, mean \pm SD,	57.7 \pm 13.8
Female, n (%)	343 (76.1)
<i>HBV serological test results, n (%)</i>	
HBsAg	16 (3.5)
Anti-HBs	148 (32.8)
Anti-HBc IgG	152 (33.7)
<i>HBV serological groups, n (%)</i>	
Patients naive to HBV infection	268 (59.4)
Previous HBV infection	152 (33.7)
Naturally immune	116 (25.7)
Anti-HBc IgG positive only	20 (4.4)
Chronic HBV infection	16 (3.5)
Vaccinated	31 (6.9)

SD: standard deviation, HBsAg: Hepatitis B surface antigen, HBc: Hepatitis B core antigen, HBV: Hepatitis B virus.

Table 2. Comparison of demographic data, duration of disease, autoantibodies and parenteral treatments between those with and without previous HBV infection among RA patients.

	Previous Hepatitis B infection + n= 152	Previous Hepatitis B infection - n=299	p
Age, mean±SD	60,8±12.4	56.7±14.2	<0.001
Age distribution, n (%)			
Under 30	2 (1.3)	9 (3.0)	
30-40	4 (2.6)	31 (10.4)	
40-50	22 (14.5)	53 (17.7)	
50-60	35 (23.0)	79 (26.4)	
60-70	57 (37.5)	74 (24.7)	
70-80	23 (15.1)	40 (13.4)	
80-90	6 (3.9)	12 (4.0)	
Over 90	3 (2.0)	1 (0.3)	
Gender, n (%)			0.076
Female	108 (71.5)	235 (78.3)	
Male	43 (28.5)	65 (21.7)	
Disease duration, years	5.0 (1-40)	5.0 (1-40)	0.597
Autoantibodies, positive, n (%)			
RF	107 (70.4)	181 (60.7)	0.044
Anti-CCP	90 (59.2)	161 (54.0)	0.295
Parenteral therapies, n (%)			
Subcutaneous treatment	102 (67.1)	197 (65.9)	0.796
IV treatment	9 (5.9)	15 (5.0)	0.686
Intraarticular injection	3 (2.0)	8 (2.7)	0.644

RA: rheumatoid arthritis, SD: standard deviation, min: minimum, max: maximum, RF: rheumatoid factor, Anti-CCP: Antibodies against cyclic citrullinated peptide, IV: intravenous.

Comparison of Data Between the Groups

Comparison of demographic data, duration of disease, autoantibodies and parenteral treatments between those with and without previous HBV infection among RA patients is shown in Table 2. Mean age in RA patients with and without previous HBV infection was 60.8±12.4 and 56.7±14.2 years, respectively ($p<0.001$). While RA patients with previous HBV infection mostly cluster in the age range of 60-70 years (37.5%), RA patients without previous HBV infection mostly cluster between the ages of 50-60 years (26.4%). RA disease duration and gender distribution were not different between the groups. RF positivity was found in 70.4% and 60.7% of RA patients with and without HBV infection, respectively ($p=0.044$). Anti-CCP positivity was not different between the groups ($p=0.295$). The frequency of previously administered parenteral therapies (joint injection, subcutaneous and intravenous therapies) in RA patients was not

different between the groups ($p=0.644$, $p=0.796$ and $p=0.686$, respectively).

Discussion

In this study, HBV seroprevalence was investigated in a cohort of RA patients from a single center in the eastern region of one of the largest cities in Turkey. The prevalence of chronic HBV infection in our RA cohort, was found to be close to the normal population prevalence of chronic HBV in Turkey. It was also found that one third of the RA patients in our cohort had previous HBV infection, most of whom developed anti-HBs. When demographic data were compared between those with and without previous HBV infection, it was found that gender distribution was not different between the groups, but those with previous HBV infection were older. In addition, it was observed that parenteral treatment and interventions were

not different between those with and without previous HBV infection. Although no research has been conducted in our country according to HBV serological groups in RA patients, in the study of Yılmaz et al.⁸ HBsAg seroprevalence was found to be 2.3% in RA patients, and it was found that HBV seroprevalence was most common in the age range of 60-69 years in these patients. Similarly, in the present study, the most common age range in which RA patients with previous HBV infection cluster was found between the ages of 60-70 years, and the HBsAg seroprevalence was found to be close to the frequency of HbsAg positivity in the study conducted by Yılmaz et al.³ In a multicenter study HBsAg positivity was found in 4.0% of the normal population in Turkey. Therefore, we can say that chronic HBV infection in RA patients in our country is at least not higher than the normal population. The fact that the duration of RA disease was not different between those with and without previous HBV infection in the present study is another proof that the presence of RA does not change the risk of HBV infection in our country. However, in order to make a definite comment on this issue, it is necessary to conduct studies comparing the HBsAg seroprevalence between healthy population and RA patients in our country. Already, the data of studies in some other countries contradict our findings. In a study conducted in Israel, by Mahroum et al.⁹ the prevalence of chronic HBV in RA patients was found higher than the control group (1.19% vs 0.63%, $p < 0.001$). And in another study conducted in Belgium, Permin et al. found that 3 of 74 RA patients (4%) were HBsAg positive (10). Although no comparison with the control group was made, the rate they found is much higher than the general chronic HBV prevalence in Belgians (0.67%).¹¹

The current HBV serological group and the immunosuppressive drug to be used are the most important factors affecting whether reactivation occurs after immunosuppressive drugs in patients who have previously had HBV infection. Rituximab and high doses of corticosteroids are the most common causes of reactivation, followed by anti-TNF drugs.¹² The serological group at greatest risk is the group that is HBsAg positive. In the study of Chiu et al.⁵

while the frequency of detecting ALT elevation increased 3 times in HBsAg positive patients compared to non-infected patients in the use of anti-TNF drugs, there was no difference in HBsAg (-)/anti-HBc IgG (+) patients compared to those who were not infected. In the study of Tamori et al.⁶ reactivation was observed in 2 of 5 patients with HBsAg (+), while reactivation was detected in only one of 45 patients with HBsAg (-)/anti-HBc IgG (+) after anti-TNF drug use. In the HBsAg (-)/anti-HBc IgG (+) serological group, the most important factor affecting whether reactivation occurs is the presence of anti-HBs antibody. Chen et al.⁷ investigated the frequency of reactivation in 103 patients with HBsAg (-)/ anti-HBc IgG (+) following rituximab treatment and found the reactivation frequency to be 20% in those with anti-HBs (-) and 4% in those with anti-HBs (+). In the study of Fukuda et al.¹³ as a result of a 4-year follow-up of patients with previous HBV infection and using corticosteroids and synthetic DMARDs, they found that being over 70 years of age and having anti-HBs (-) in this group of patients were independent risk factors for reactivation. In our cohort, 3/4 of those with previous HBV infection were found to have anti-HBs antibodies, and only 1/5 of them were over 70 years old. According to these results we can conclude that many of the patients receiving IS drugs with previous HBV infection in our cohort were not in the risk group for HBV reactivation.

Although HBV has not been found to be an etiological factor in the occurrence of RA in the studies conducted so far, a relationship has been found between HBV infection and autoantibodies especially with RF. When Su et al. evaluated the risk of hepatitis C virus (HCV) and HBV infections to develop RA, they found that while HCV increased the risk of RA, HBV did not (14). Shim et al.¹⁵ found RF positivity as 3.7% in healthy population in Korea, while they found RF positivity as 11.8% in HBsAg positive patients. When Generalli et al.¹⁶ examined a 15-year database, among HBsAg positive patients, they found a relative risk of 5.7 (CI: 1.2-26.3) indicating RA development in those with RF (+), compared to 13.2 (CI: 3.8-46.3) in those with anti-CCP (+). All these results suggest that RF positivity in chronic HBV patients can be seen

independent of the presence of RA. As a matter of fact, in our study, in accordance with the literature data, RF positivity was found with a higher frequency in RA patients with previous HBV infection compared to those who did not have HBV before. The reason why RF was more common in RA patients with previous HBV infection in our study may be related to the increase in the formation of RF autoantibodies induced by HBV.

In our study, the percentage of patients who received neither subcutaneous nor IV treatment was found to be different between RA patients with and without previous HBV infection. In addition, the frequency of intra-articular injection was not different between the groups. These results suggest that parenteral treatment and procedures in RA patients do not affect HBV transmission. Besides, HBsAg seroprevalence was not found to be higher than the country average in the RA cohort in our study. Today, the use of subcutaneous treatments mostly with disposable injectors and the increasing hygiene conditions in our country may be the reasons for the seroprevalence of HBV, which is not seems to be different from the normal population, in RA patients with intensive parenteral treatments.

The data of this study were obtained retrospectively from a single center, which reduces the reliability of the data. Our findings need to be confirmed by multi-center prospective studies. A larger sample size is needed to assess the effects of interventional procedures across the groups. In addition, since the drugs used by the patients were obtained from the records in our study, we may have made insufficient evaluation due to the lack of information such as whether the patients actually used these drugs and how often they used them.

In conclusion, the prevalence of chronic HBV in RA patients in our region is close to the prevalence in normal population. HBV infection has been experienced in a significant part of the RA patients and immunity has occurred in most of them. The percentage of those vaccinated is low and more than half of RA patients are naive to HBV. Because of the majority of patients naive to HBV infection in our RA cohort, more attention should be paid to routine HBV vaccination of these patients. Those with previous HBV infection

are older than those who do not. Interventional applications in RA treatment options do not change the frequency of HBV exposure.

Conflict of Interest

Authors have no conflict of interest to declare.

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Authors' Contribution

Study Conception: KA; Study Design: KA, AA, OO; Supervision: KA, AA; Data Collection and/or Processing: OO, MT, TDH, KA; Statistical Analysis and/or Data Interpretation: KA, MT; Literature Review: KA, TDH; Manuscript Preparation and Critical Review: KA, OO, MT, TDH, AA

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A Possible contributor to Erythropoiesis-Stimulating Agents Requirement in Hemodialysis: Paraoxonase 1 Activity

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ABSTRACT

Background: Anemia is one of the most prevalent complications of chronic kidney disease. In chronic kidney disease-related anemia, circulating erythrocytes have a decreased life span. Paraoxonase-1 activity is one of the essential factors protecting cell membranes, e.g., erythrocytes, from lipid peroxidation under normal conditions. In this study, we investigated Paraoxonase-1 activity in hemodialysis patients with and without erythropoiesis-stimulating agent therapy and the possible relationship of Paraoxonase-1 activity levels with the erythropoiesis-stimulating agent dose required.

Material and Methods: This study is composed of patients undergoing hemodialysis with a minimum dialysis vintage of six months. We excluded cases with an active infection, cardiovascular events and malignancy, hypo- or hyperthyroidism, central venous catheters, iron deficiency, cystic kidney diseases, nephrectomy, and routine C-reactive protein levels higher than reference range within the last six months.

Results: Baseline characteristics, laboratory parameters, oxidative stress, and systemic inflammatory indices were similar between groups. The mean Paraoxonase-1 activity of the erythropoiesis-stimulating agent+group was significantly lower than the erythropoiesis-stimulating agent–group (191.4 ± 118.8 and 488.1 ± 174.9 , respectively; $p < 0.001$). Cumulative erythropoiesis-stimulating agent doses and Paraoxonase-1 activity were significantly and negatively correlated ($R = -0.736$, $p < 0.001$).

Conclusions: The results of this study suggest that lower Paraoxonase-1 activity in hemodialysis patients is associated with the requirement for erythropoiesis-stimulating agent therapy, presumably due to decreased life span of erythrocytes. Further studies examining the relationship between Paraoxonase-1 activity and erythropoiesis-stimulating agent treatment requirements are necessary to reveal new treatment goals for chronic kidney disease-related anemia.

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Introduction

Anemia is one of the most prevalent complications of chronic kidney disease (CKD).^{1,2} In CKD related anemia, circulating erythrocytes have a decreased life span, and compensatory erythropoiesis is decreased.³ In the latter, the most prominent mechanism is the reduction in intrinsic erythropoietin (EPO) secretion. However, the secretion of EPO remains significant even in end-stage renal disease in patients without total nephrectomy.⁴ The primary condition that requires the use of erythropoiesis-stimulating agents (ESA) is patients' blunt response to low hemoglobin (Hb) level.⁵ On the other hand, every patient's need for ESA treatment is not the same, and even some patients persistently have adequate Hb levels without ESA.

The pathophysiological mechanism of decreased erythrocyte life span in CKD patients has not been clarified.⁶ Studies investigating the possible mechanical effects of hemodialysis have failed to reveal significant differences with peritoneal dialysis patients.⁷ The so-called "uremic milieu" in CKD describes numerous pathophysiological mechanisms such as increased uremic toxins, systemic inflammation, and oxidative stress.⁸ On the other hand, there is an inadequacy in the mechanisms that balance these phenomena.

Among the components of the "uremic milieu," one of the significant pathophysiological mechanisms that concern cellular life span is the increased cell membrane lipid peroxidation in chronic renal failure.⁹ Paraoxonase-1 (PON1) activity in high-density lipoprotein (HDL) is one of the essential factors protecting cell membranes, e.g., erythrocytes, from lipid peroxidation under normal conditions.^{10,11} The protective effect of PON1 on the erythrocyte membrane is observed in animal models and human studies.^{12,13}

Studies have shown that patients with CKD have decreased PON1 activity compared to the healthy population, and revealed its adverse outcomes on patient survival.^{14,15} In this study, we investigated PON1 activity in HD patients with and without ESA therapy, excluding cases with total nephrectomy or cystic kidney diseases,

anemia not related to CKD, and factors that may cause ESA resistance. We also analyzed the possible relationship of PON1 activity levels with the ESA dose required.

Material and Methods

Statement of Ethics

The study protocol was approved by an independent research institute's committee on human research.

Study Design, Participants, and Definitions

This cross-sectional study is composed of 50 patients undergoing HD with a minimum dialysis vintage of six months. We excluded cases with an active infection, an active or recent history of any cardiovascular events and malignancy, hypo- or hyperthyroidism, central venous catheters, iron deficiency, prosthetic heart valves, unilateral or bilateral nephrectomy, polycystic kidney disease or acquired kidney cysts, routine C-reactive protein (CRP) levels higher than reference range within the last six months, a calculated erythropoietin resistance index (ERI) of ≥ 5 U/kg/week/g/dL, and a single pool Kt/V of ≤ 1.2 . Informed consent was obtained from all patients for being included in the study.

The ERI was calculated as the weekly recombinant human erythropoietin (rhEPO) dose divided by the body weight and the hemoglobin concentration.¹⁶ Mean weekly and cumulative rhEPO doses applied within the last six months were calculated. Doses of darbepoetin were converted to equivalent doses of epoetin for standardization.¹⁷ Patients with >100 mL/day urine output were considered to have a residual renal function (RRF).¹⁸ Single pool Kt/V calculated by Daugirdas' second-generation formula. Urea reduction ratio (URR) calculated by taking the difference between pre- and post-dialysis urea levels and divided by predialysis urea levels.

All of the patients treated with a standard HD procedure via A-V fistulae, each session lasted 4 hours, three times a week, using bicarbonate-containing dialysate and low-flux polysulfone membrane. The blood flow rate ranged from 300 to 350 mL/min, and the dialysate flow rate was 500 mL/min.

Blood Specimen Collection

Blood specimens were collected at the initiation of a mid-week session. Specimens were allowed to clot at room temperature for 30 minutes. Clot removed by centrifuging samples at 3500 rpm for 10 minutes. The serum immediately transferred into a polypropylene tube and stored at -80°C .

Materials and Measurements

Total oxidant status (TOS) and total antioxidant status (TAS), high sensitive CRP (hsCRP), interleukin-6 (IL-6), and PON1 activity were measured from freshly collected serum. Last (within two weeks) blood urea nitrogen (BUN), creatinine (cre), albumin (alb), hemogram test, and lipid profile results were evaluated retrospectively. The mean value of the last six months was calculated for intact parathormone and ferritin levels. Patients' demographic features such as age, sex, and body mass index were noted.

Biochemical Study

Serum levels of hsCRP were studied by the nephelometric technique using BN II/BN ProSpec (Siemens, Marburg, Germany), and IL-6 were studied by chemiluminescence immunoassay technique using Immulite 2000 (Siemens Diagnostics, Gwynedd, UK).

Total oxidant status (TOS) and total antioxidant status (TAS) levels were measured using commercially available kits (RelAssay Diagnostics, Ankara, Turkey). The ratio of TOS to TAS accepted as the OS index (OSI). For calculation, the unit of TAS converted to $\mu\text{mol/L}$, and the OSI calculated according to the following formula: $\text{OSI (arbitrary unit)} = \text{TOS } (\mu\text{mol H}_2\text{O}_2 \text{ equivalent/L}) / \text{TAS } (\mu\text{mol Trolox equivalent/L})$.

PON1 activity was measured using commercially available kits (RelAssay, Ankara, Turkey). The rate of paraoxon hydrolysis (diethylp-nitrophenylphosphate) was measured by monitoring the increase of absorption at 412 nm at 37°C . The amount of generated p-nitrophenol was calculated from the molar absorption coefficient at pH 8.5, which was $18.290 \text{ M}^{-1} \text{ cm}^{-1}$. PON1 activity was expressed as U/L.

Statistical Methods

Patients were grouped as "ESA+" and "ESA-" according to rhEPO or darbepoetin requirements

within the last six months. Numeric values of the study were shown with mean and standard deviation or medians with ranges, categorical data, frequency, and percentage. For data normally disturbed, Unpaired Student's T-Test is used for comparison between two groups. For abnormal distributed data Kruskal-Wallis test performed. Pearson correlation test was used to find a correlation between continuous variables. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Science (SPSS, Chicago, IL, USA) for personal computers, version 21.0.

Results

Baseline Characteristics

The demographic characteristics, laboratory parameters including hemoglobin, ferritin and HDL, six months cumulative iron doses, dialysis adequacy calculations, HD vintages, and RRFs of patients in the ESA+ and ESA- groups were similar (Table 1).

Systemic Inflammation and Oxidative Stress Indices of the Groups

The mean hsCRP and IL-6 levels of patients in the ESA+ and ESA- groups were similar. Similarly, the TOS, TAS, and calculated OSIs of the groups were similar. The mean PON1 activity of the ESA+ group was significantly lower than the ESA- group (191.4 ± 118.8 and 488.1 ± 174.9 , respectively; $p < 0.001$) (Table 2).

Correlations of PON1 Activity with Patient-Related Factors, Oxidative Stress, and Cumulative ESA Doses

There was no significant correlation between age, BMI, dialysis time, HDL level or OSI, and PON1 activity, as shown in Table 3 and Figure 1. Cumulative ESA doses and PON1 activity were significantly and negatively correlated ($R = -0.736$, $p < 0.001$).

Discussion

The results of our study suggest that the serum PON1 activity is significantly lower in HD patients requiring ESA therapy, and PON1 activity significantly correlates with cumulative

Table 1. Baseline characteristics and laboratory parameters of the groups

	ESA+ (n=32)	ESA- (n=18)	p-value
Female/male (n)	14/18	5/13	0.273
Age mean (SD)	58.6 (±14.7)	55.1 (±16.3)	0.437
BMI, kg/m ² (SD)	23.4 (±4.9)	25.6 (±5.1)	0.150
Smoking, n (%)	6 (18.8%)	4 (22.2%)	0.774
Diabetes, n (%)	7 (21.8%)	5 (27.7%)	0.647
BUN mean, mg/dL (SD)	67.1 (±16.2)	57.6 (±15.7)	0.067
Creatinine mean, mg/dL (SD)	8.4 (±1.7)	8.1 (±2.0)	0.543
Hemoglobin mean, g/dL (SD)	11.3 (±1.2)	11.2 (±2.0)	0.831
Albumin mean, g/dL (SD)	3.8 (±0.3)	3.8 (±0.3)	0.837
iPTH median, pg/mL (min-max)	314.5 (14-1834)	296 (69.2-1401.1)	0.693
Ferritin mean, ng/mL (SD)	568.6 (±174.7)	499.5 (±281.0)	0.289
LDL mean, mg/dL (SD)	107.7 (±42.4)	101.0 (±35.1)	0.570
Triglyceride mean, mg/dL (SD)	204.0 (±140.6)	184.0 (±114.7)	0.626
HDL mean, mg/dL (SD)	38.6 (±8.9)	38.3 (10.8)	0.916
IV iron median, mg (min-max)	600 (0-2200)	600 (0-1200)	0.074
ACEI/ARB use, n (%)	5 (15.6%)	2 (11.1%)	0.303
Kt/V mean (SD)	1.6 (±0.3)	1.6 (±0.4)	0.880
URR (%) mean (SD)	75.2 (±6.2)	74.6 (±7.0)	0.747
HD vintage mean, months (SD)	70.6 (±56.7)	62.8 (±48.3)	0.629
RRF, n (%)	11 (34.3%)	6 (33.3%)	0.942

ESA: erythropoiesis-stimulating agent, BMI: body mass index, BUN: blood urea nitrogen, iPTH: intact parathormone, LDL: low-density lipoprotein, HDL: high-density lipoprotein, ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, URR: urea reduction ratio, HD: hemodialysis, RRF: residual renal function

Table 2. Systemic inflammation and oxidative stress indices of the groups

	ESA+ (n=32)	ESA- (n=18)	p-value
hsCRP mean, mg/L (SD)	5.20 (±2.4)	4.34 (±2.2)	0.223
IL-6 mean, pg/mL (SD)	3.8 (±0.9)	3.7 (±0.9)	0.791
TOS mean, µmol/L (SD)	3.22 (±2.3)	3.14 (±2.5)	0.917
TAS mean, µmol/L (SD)	2.33 (±0.2)	2.31 (±0.3)	0.747
OSI	0.13 (±0.1)	0.14 (±0.1)	0.970
PON1 mean, U/L (SD)	191.4 (±118.8)	488.1 (±174.9)	<0.001

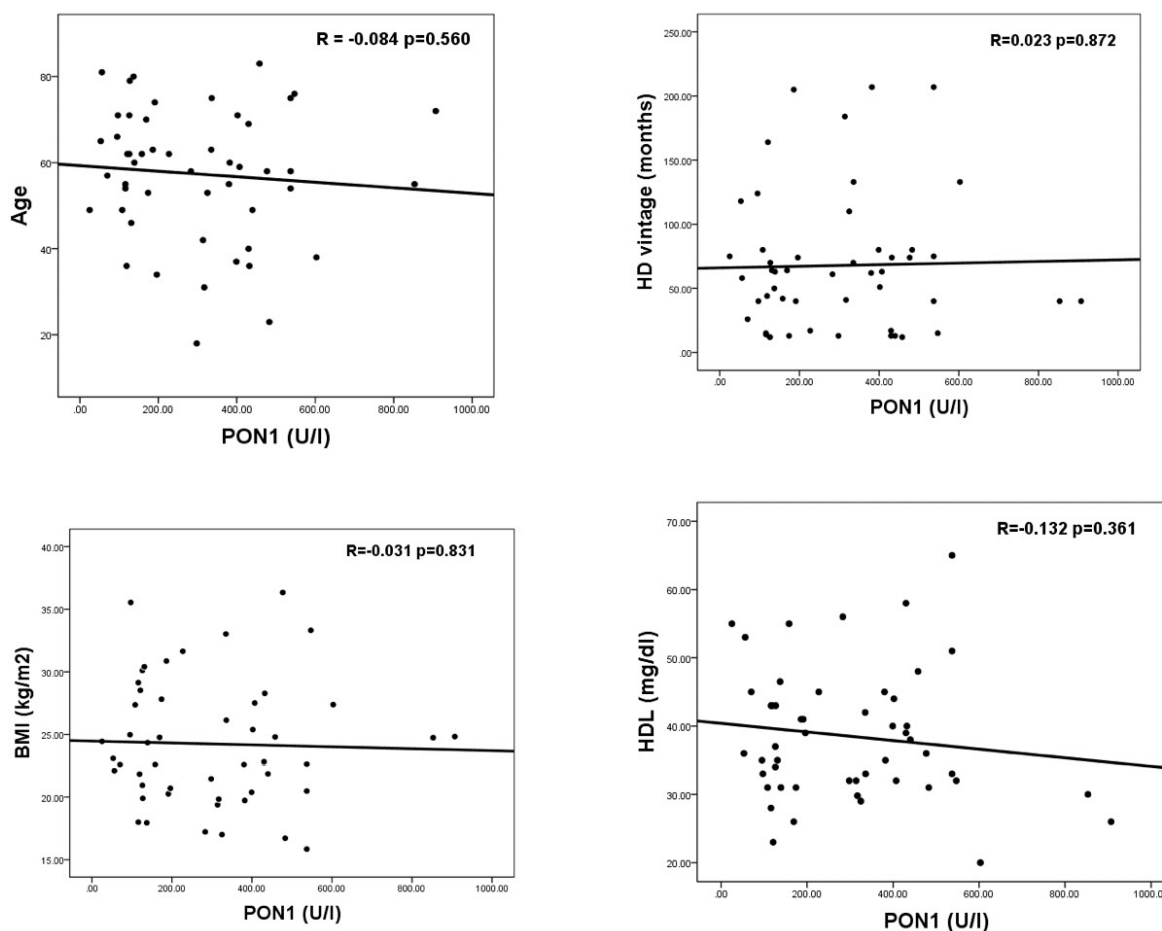
hsCRP: high sensitive C-reactive protein, IL-6:interleukin-6, TOS: total oxidant status, TAS: total antioxidant status, OSI: oxidative stress index, PON1: paraoxonase-1 activity

Table 3. Correlations of PON1 with patient-related factors, oxidative stress, and cumulative ESA doses

	PON1 activity (U/L)	
	R	p-value
Age	-0.084	0.560
BMI, kg/m ²	-0.031	0.831
HD vintage	0.023	0.872
HDL (mg/dL)	-0,132	0.361
OSI	-0.072	0.618
Cumulative ESA dose (U)	-0,736	<0.001

PON1: paraoxonase-1, BMI: body mass index, HD: hemodialysis, HDL: high-density lipoprotein, ESA: erythropoiesis-stimulating agent

Figure 3. Correlations of PON1 with patient-related factors, oxidative stress indices and cumulative ESA doses (PON1: paraoxonase-1, BMI: body mass index, HD: hemodialysis, HDL: high-density lipoprotein, ESA: erythropoiesis-stimulating agent)



ESA doses. PON1 activity is not associated with age, BMI, serum HDL levels, dialysis vintage, and oxidative stress index.

Decreased erythrocyte life span is one of the major determinants of CKD related anemia. Median erythrocyte life span decreased by 20%

in HD patients compared with healthy controls.¹⁹ However, the reason for this significant decrease is not well understood. In one study, IL-6, IL-18, IL-10, and hsCRP levels were compared with the erythrocyte life span, but no association was found.²⁰ On the other hand, in this study,

erythrocyte life span and uric acid were positively correlated. This finding suggests that antioxidant mechanisms may have a role in this subject.

HDL is a lipoprotein that binds high-density cholesterol, takes part in the transport of cholesterol from the periphery to the liver, and is inversely associated with cardiovascular morbidities.²¹ HDL is composed of apolipoprotein A-I and A-II and also many antioxidant proteins, including PON1.²² PON1 is now considered to be more prominent than HDL as the source of positive cardiovascular effects.²³ The human PON1 gene is on chromosome 7 and encodes PON1, PON2, and PON3.²⁴ PON1 is synthesized in the liver and transported to the periphery by HDL to perform hydrolysis of oxidized phospholipids on cellular membranes.²⁵ These uniform features make PON1 one of the future treatment targets.

PON1 activity was found to be lower in HD patients compared to the healthy population and associated with adverse cardiovascular outcomes.²⁶ Although there is no study directly examining the relationship between PON1 activity and anemia, there is evidence suggesting that its lower activity may also be associated with CKD related anemia. Riberio et al. investigated factors associated with PON1 activity level in HD patients and found lower activity in patients with systemic inflammation, longer dialysis vintage, and higher dose ESA therapy.²⁷ Another study suggested that HD patients had increased hemolysis susceptibility of erythrocytes with lower PON1 activity.²⁸

The possible cause of this significant PON1 activity difference in two similar HD groups may be due to PON1 gene polymorphisms. To date, two polymorphisms of PON1 and three polymorphisms of its promoter region was defined.²⁹ However, the results of the studies are controversial in terms of the clinical significance of these polymorphisms. In addition, epigenetic factors have been reported to have an important effect on PON1 activity.³⁰ Further studies are needed to clarify the effect of genetic and epigenetic factors on PON1 expression and activity in the HD population.

We designed our study to be suitable for understanding the relationship between PON1 activity and ESA treatment requirements in HD

patients. To ensure this, we excluded all possible factors that contribute to the development of anemia in CKD patients. However, these strict exclusion criteria may have prevented us from observing factors that may affect PON1 activity levels. In order to confirm the results we obtained in our study, studies designed to directly examine the relationship between PON1 activity and erythrocyte life span in HD patients is needed. Thus, the pathophysiology of CKD-related anemia will be better understood, and new targets for treatment can be introduced.

Conclusions

The results of this study suggest that lower PON1 activity in HD patients may be associated with the requirement for ESA therapy. Further studies examining the relationship between PON1 activity and ESA treatment requirements are necessary to reveal new treatment goals for CKD-related anemia.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Authors' Contribution

Study Conception: BK; Study Design: BK, HY, EBB; Supervision: GG; Fundings: GG; Materials: BK, HY; Data Collection and/or Processing: BK, HY; Statistical Analysis and/or Data Interpretation: BK, HY; Literature Review: BK, HY, EBB, MKD; Manuscript Preparation: BK, HY; Critical Review: MKD, GG; Biochemical Measurements: EBB

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Heart Failure and Aortic Stiffening in Patients with Preserved Ejection Fraction

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ABSTRACT

Background This study aimed to explore a possible relationship between aortic stiffness parameters and diastolic function in patients with asymptomatic or symptomatic diastolic dysfunction, and subsequently, the effect of aortic stiffness parameters on the progression from asymptomatic diastolic dysfunction to clinical diastolic heart failure.

Material and Methods Seventy-five subjects were enrolled in the study of whom 20 had diastolic heart failure with the left ventricle ejection fraction (LVEF) >50%, 20 had asymptomatic diastolic dysfunction, 16 had hypertension with normal diastolic function, and 19 were normotensive healthy subjects. Ascending aorta recordings for measuring aortic strain and distensibility as markers of aortic stiffness were obtained from a spot nearly 3 cm above the aortic valve using 2-D echocardiography under M-mode. Doppler echocardiography and 2-D echocardiographic measurements were used to determine diastolic function.

Results While no statistically significant difference in aortic strain or distensibility values was observed between the asymptomatic group and the diastolic heart failure group; however, E/E' values were higher in the heart failure group [12.1(10.0-17.1) vs. 10.0(6.2-22.5)] (p=0.014). Aortic strain and distensibility values significantly decreased as E/E' values increased (r=-0.416; p<0.001 and r=-0.576; p<0.001, respectively) for pooled data from all groups.

Conclusions Although aortic stiffness parameters did not have a direct effect on the progression from asymptomatic diastolic dysfunction to diastolic heart failure, echocardiographic monitoring of these parameters may be beneficial in identifying patients who would progress to clinical heart failure from diastolic dysfunction.

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Introduction

The adverse effects of cardiovascular risk factors on the heart and vessels have been the subject of many studies. It is known that vessels harden or “stiffen” as the result of structural changes caused in the great vessels by exposure to these risk factors. Aortic stiffness arises from the elastic resistance of the aorta against distension. Aortic stiffness particularly increases with age and also in many pathological conditions such as hypertension, atherosclerosis, diabetes, chronic renal insufficiency or connective tissue diseases. “Stiffness” studies, especially of the great vessels, have demonstrated that this process directly influences cardiovascular morbidity and mortality.¹⁻³

Heart failure (HF) can be defined as a complex clinical syndrome where the heart is unable to pump an adequate amount of blood to meet the metabolic needs of the body. It arises from defects in cardiac input and/or output due to structural or functional cardiac impairment.⁴ Making a diagnosis of HF can be quite difficult, and is based on the demonstration of an underlying cardiac reason. Recently, another type of heart failure has been described, in that, while the ejection fraction is within the normal range, left ventricle (LV) wall thickness and left atrium (LA) size are increased. Such patients show positive evidence of diastolic dysfunction which is considered to cause HF.⁵ Left ventricular diastolic dysfunction may remain asymptomatic for a long time, even while progressing to manifest heart failure from a subclinical myocardial injury. Although the prevalence of diastolic heart failure is increasing, therapeutic options remain limited. Currently, there are no treatments that have convincingly shown a reduction in morbidity or mortality in patients with diastolic HF. Therefore, early diagnosis and prompt treatment of asymptomatic diastolic dysfunction, along with clinical and echocardiographic monitoring of these patients, may delay the development of diastolic HF and thus reduce disease-related morbidity and mortality.^{6,7}

The nature of the relationship between aortic stiffness and cardiac diastolic function has not yet been clearly defined.⁸ Therefore, in the present study, we aimed to investigate whether there is a

relation between aortic stiffness parameters and diastolic function by measuring aortic stiffness and diastolic dysfunction markers in asymptomatic and symptomatic diastolic dysfunction patients. Further, we also wanted to investigate if and how differences in aortic stiffness parameters affected the transition from asymptomatic diastolic dysfunction to clinical diastolic heart failure.

Material and Methods

A total of 75 patients who presented to the cardiology polyclinic between July 2012 and November 2012, requiring echocardiographic testing, and meeting the eligibility criteria were recruited. These patients were divided into four groups as follows.

Heart failure group: Patients were assigned to this group in accordance with the European Guidelines for Cardiovascular Disease Prevention in Clinical Practice (version 2012)⁹ and consisted of 20 patients aged 40-60 years with hypertension (HT), left ventricle hypertrophy (LVH) (wall thickness >1.3 cm) on transthoracic echocardiography (TTE), history of hospitalization due to class IV heart failure (according to New York Heart Association, NYHA) or already presenting with symptoms of class II or III HF (according to NYHA), and with left ventricle ejection fraction (LVEF) >50%.

Asymptomatic group: Consisting of 20 asymptomatic patients with HT aged 40-60 years with LVH and diastolic dysfunction on TTE.

Control group: Consisting of 16 patients with HT aged 40-60 years but without LVH or diabetes and with normal diastolic functions on TTE.

Normal group: Consisting of completely healthy 19 individuals aged 40-50 years.

Prior to echocardiography, a 12-lead electrocardiography was performed on all the patients. Data on height, body weight, body mass index (BMI), body surface area (BSA), systolic and diastolic blood pressures, cardiac risk factors and any medication history were recorded for all participants. Functional classification of the patients was done in accordance with the criteria issued by the NYHA.

Patients with the following conditions were excluded: Acute decompensated heart failure

or with conditions that cause tissue hypoxia (pulmonary disease, acute manifestations of COPD (chronic obstructive pulmonary disease), recent asthma attack, shock, anemia), suspected coronary artery disease (CAD) based on clinical history and/or stress testing, peripheral artery disease, and mild, moderate or serious aortic stenosis, moderate or serious cardiac valve disease, malignancy, serious liver or kidney disease, atrial fibrillation, and an ejection fraction <50%.

The study was conducted in accordance with the Helsinki Declaration after approved by the ethics committee of our hospital. Informed voluntary consent was obtained from all the subjects.

M-mode, 2-D image, and color-flow Doppler recordings of all study participants were done using a GE Vingmed Vivid 7 echocardiography device with transducers set to adjustable frequencies (2.5-3.5 MHz). Examination was done during three cycles at the parasternal long axis and at the apical four-chamber view (according to the criteria recommended by the American Echocardiography Association), and the arithmetic mean of three values was recorded.¹⁰

LVEF was calculated for all the patients. In addition, left ventricle end-systolic diameter, left ventricle end-diastolic diameter, left ventricle posterior wall thickness, inter ventricular septum thickness and left atrium diameter were measured, and left atrium volume index (LAVI) and left ventricle mass (LVM) were calculated. LAVI was calculated according to Nagueh et al (2009).¹¹ LVM was calculated using the following equation developed by Devereux and Reichek, which is based on routinely acquired echocardiographic measurements.¹⁰

$$LVM = 0.8 \times 1.04 ([LVEDD + PWT + IVST]^3 - [LVEDD]^3) + 0.6$$

(LVM: Left ventricle mass, IVST: Interventricular septum thickness, LVEDD: Left ventricle end-diastolic diameter, PWT: Posterior wall thickness)

The patients were placed in a slightly supine position; and ascending aorta recordings were obtained using the M-mode under 2-D guidance at a distance of 3 cm above the aortic valve. Aortic diameters were defined as the distance between the internal margins of the anterior and posterior walls of the aorta during systole or diastole. Systolic

diameter of aorta (AoS) was measured when the aorta was in the completely open position, and diastolic diameter of aorta (AoD) was measured simultaneously with the QRS peak on ECG. Measurements were made during consecutive 5 pulses and their arithmetic mean was calculated.¹⁰ The measurements were individually evaluated for each patient and the following parameters were calculated to assess the elastic characteristics of the aorta.

Pulse Pressure (PP): Systolic Blood Pressure (SBP)–Diastolic Blood Pressure (DBP)

Aortic Strain (%): $[(AoS - AoD) \times 100 / AoD]$

Distensibility: $2(Aortic\ strain) / PP$

A Mitral valve trace was obtained by intermittent placing of the Doppler sample on the tips of mitral valve in line with the flow (<20°) on the apical four-chamber images. The E-wave flow rate, A-wave flow rate and E/A ratio were also obtained. Speed of the mitral annulus was recorded throughout the cardiac cycle using the tissue Doppler technique. Volume samples from the apical four-chamber view were placed onto the annulus near to the point where the mitral valve is attached and recordings were obtained from both the septal (medial) and lateral points. Measurements were done at the end of expiration during three or four consecutive cycles. The arithmetic mean of septal and lateral E' values was calculated and it was divided by the E value to obtain the mean E/E' value. Normal diastolic function was defined as follows: septal E' wave ≥ 8 cm/s, lateral E' wave ≥ 10 cm/s and left atrial volume index <34 mL/m² on TTE, and abnormal diastolic function was defined as an E/E' ratio greater than 15.¹¹

The Kolmogorov-Smirnov test was used to test normal distribution of continuous variables and homogeneity of the variances was tested by the Levene test. Descriptive statistics were represented as mean \pm standard deviation or median (minimum–maximum) for continuous variables and as case number and percentage (%) for categorical variables. Means between groups were analyzed by One Way Analysis of Variance (One-Way ANOVA), whereas medians between groups were analyzed by the Mann Whitney U test for independent two groups or by Kruskal

Wallis test for more than two groups, with post-hoc Tukey's HSD or Conover's nonparametric multiple comparison test. Categorical variables were analyzed by Pearson's chi-square test and correlation between continuous variables was investigated using the Spearman's correlation test.

The combined effects of all potential risk factors that affected or were considered to affect LV mass indices, aortic strain and distensibility during univariate analyses were investigated using Multivariate Linear Regression Analysis, and the regression coefficient and 95% confidence intervals calculated for each variable. As the measurements of Aortic strain and distensibility were not normally distributed, they were log transformed for regression analyses. The results were considered statistically significant at $P < 0.05$, and all analyses were performed using SPSS (version 11.5).

Results

The group-wise demographic characteristics of the participants are listed in Table 1. Patients in the HF group were significantly older compared to the control group ($p = 0.014$) and normal group, and mean age of the asymptomatic group was higher than that of the normal group. BMI and BSA were also higher in the asymptomatic group and the HF group compared to the normal group. There was no difference among these four groups with respect to gender distribution and the prevalence of smoking. Importantly, there was no difference in baseline characteristics between the asymptomatic and HF groups which are the target groups of the study.

Lipid profiles of the subjects in the asymptomatic group and the HF group were not different. Interestingly, however, differences in triglyceride levels were statistically significant between the control group and the normal group ($p = 0.007$), between the asymptomatic group and the normal group ($p < 0.002$), and between the HF group and the normal group ($p < 0.001$). Subjects in the asymptomatic group and the HF group were similar in terms of other co-existing conditions and prescribed medication (Table 1).

LAVI was higher in the asymptomatic and HF groups compared to the control and normal groups, and there was no difference between the control group and the normal group. The HF group had the highest E/E' ratio (Figure 1). While the E/E' ratio was significantly higher in the HF group compared to the asymptomatic group ($p = 0.014$), no such difference in LAVI was observed.

LV MASS index was lower in the control group compared to the asymptomatic and HF groups, but no such difference was determined between the asymptomatic group and the failure group. Distensibility and aortic strain values were lower in the asymptomatic, HF and control group compared to the normal group; and no significant difference was found between the control and asymptomatic groups, the control and HF groups, and the asymptomatic and HF groups. Table 2 compares diastolic dysfunction parameters, LV mass index, aortic strain, distensibility and PP values of the groups and Figure 2 compares LV mass index, aortic strain and distensibility measurements among the groups.

As there were differences among the groups in demographic indices such as age and BMI, correlation coefficients between LV mass index, aortic strain and distensibility and other demographic and clinical measurements were calculated and their level of significance was analyzed. While an increase in age, BMI and BSA was positively correlated with an increase in LV mass index ($r = 0.52$, $p < 0.001$; $r = 0.33$, $p = 0.004$ and $r = 0.25$, $p = 0.030$ respectively); it was negatively correlated with aortic strain and distensibility ($r = -0.42$, $p < 0.001$ and $r = -0.579$, $p < 0.001$). Moreover, an increase in LV mass index coincided with a decrease in aortic strain and distensibility values. Gender and smoking did not seem to affect LV mass index, aortic strain or distensibility ($p > 0.05$).

Evaluation of effects of overall potential risk factors those are likely to influence the changes in LV Mass index, aortic strain and distensibility of the normal group versus the other groups

Using multivariate linear regression analysis we evaluated the effects of overall potential risk factors (age, female factor, BMI, BSA, triglyceride and pulse pressure) that are likely to influence the changes in LV mass index, aortic strain and

Table 1. Distribution of demographic characteristics, comorbidities and lipid profiles of the cases and the drugs being received among the groups

Variables	Asymptomatic n=20	Failure n=20	Control n=16	Normal n=19	p-value
Age, years	55.3±8.9 ^b	57.4±9.7 ^{a,c}	49.2±6.2 ^a	44.6±5.0 ^{b,c}	<0.001
Male n(%)	13 (65.0)	8 (40.0)	8 (50.0)	10(52.6)	P>0.05
Female	7 (35.0)	12 (60.0)	8 (50.0)	9(47.4)	
BMI(kg/m ²)	31.0±4.9 ^b	32.0±4.6 ^c	28.4±4.1	26.1±4.0 ^{b,c}	<0.001
BSA(m ²)	1.99±0.22 ^b	1.96±0.16 ^c	1.86±0.15	1.78±0.17 ^{b,c}	0.002
History of smoking n(%)	7(35.0)	7(35.0)	8 (50.0)	9(47.4)	P>0.05
HT n(%)	2(100%)	20(100%)	16 (100%)	-	P>0.05
DM n(%)	8(40.0%)	5(25.0%)	-	-	P>0.05
Cholesterol(mg/dL)	188.1±42.9	205.1±39.3	211.3±40.8	195.0±19.9	P>0.05
LDL(mg/dL)	111.6±41.3	124.4±37.3	127.1±27.7	126.8±11.9	P>0.05
HDL(mg/dL)	41.5(22-69)	43.5(29-69)	48.5(19-95)	40(35-90)	P>0.05
Triglyceride(mg/dL)	167.5(48-340) ^b	179.5(74-274) ^c	140.5(61-421) ^d	100(60-180) ^{b,c,d}	0.011
Beta Blocker n(%)	5(25.0)	5(25.0)	2(12.5)	-	P>0.05
CCB n(%)	8(40.0)	9(45.0)	5(31.3)	-	P>0.05
ACEI n(%)	10(50.0)	7(35.0)	5(31.3)	-	P>0.05
ARB n(%)	5(25.0)	9(45.0)	8(50.0)	-	P>0.05
Diuretic n(%)	9(45.0)	14(70.0)	8(50.0)	-	P>0.05
Alfa Blocker n(%)	-	2(10.0%)	-	-	P>0.05
Anti-Lipemic n(%)	3(15.0)	7(35.0)	2(12.5)	-	P>0.05

ACEI, angiotensin–converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; BSA, body surface area; CCB, calcium channel blocker; DM, diabetes mellitus; HDL, high density lipoprotein; HT, hypertension; LDL, low density lipoprotein.
^aDifference between the Control group and Failure group was statistically significant (p=0.014),
^bDifference between the Asymptomatic group and normal group was statistically significant (p<0.01),
^cDifference between the Failure Group and Normal group was statistically significant (p<0.05)
^dDifference between the Control group and Normal group was statistically significant (p=0.007)

Table 2. Diastolic function parameters, LV mass index, aortic strain, distensibility and Pulse Pressure values

	Asymptomatic	Failure	Control	Normal	p-value
LV MASS Index	113.1±17.7 ^{a,c}	127.7±26.1 ^{b,d}	77.4±10.5 ^{a,b}	72.2±13.8 ^{c,d}	<0.001
Aortic strain	3.9 (2.4-9.3) ^c	4.1 (2.2-9.0) ^d	3.5 (2.5-10.0) ^c	10.3 (6.4-22.2) ^{c,d,e}	<0.001
Distensibility	0.14 (0.05-0.46) ^c	0.10 (0.06-0.58) ^d	0.16 (0.07-1.00) ^e	0.66 (0.26-12.33) ^{c,d,e}	<0.001
PP	55 (30-100) ^c	70 (30-105) ^{b,d}	52.5 (20-80) ^{b,e}	40 (20-50) ^{c,d,e}	<0.001
LAVI	28.7 (18.0-62.2) ^{a,c}	35.0 (18.8-63.3) ^{b,d}	21.0 (13.4-35.1) ^{a,b}	20.0 (16.0-25.0) ^{c,d}	<0.001
Septal E'	6 (2-8) ^{a,c}	5 (3-7) ^{b,d}	9 (7-11) ^{a,b}	9 (8-12) ^{c,d}	<0.001
Lateral E'	8 (2-13) ^{a,c}	6 (4-10) ^{b,d}	11 (9-16) ^{a,b}	13 (11-15) ^{c,d}	<0.001
E/E'	10.0 (6.2-22.5) ^{a,c,f}	12.1 (10.0-17.1) ^{b,d,f}	7.2 (4.1-8.0) ^{a,b}	6.3 (4.0-7.7) ^{c,d}	<0.001

LAVI, left atrium volume index; LV Mass index, left ventricular mass index; PP, pulse pressure
^aDifference between the Control group and asymptomatic group is statistically significant (p<0.001),
^bDifference between the Control group and Failure group is statistically significant (p<0.01),
^cDifference between the asymptomatic group and normal group is statistically significant (p<0.001),
^dDifference between the failure group and normal group is statistically significant (p<0.001),
^eDifference between the Control group and normal group is statistically significant (p<0.05)
^fDifference between the Asymptomatic group and Failure group is statistically significant (p=0.014).

distensibility values. Distensibility and aortic strain values in the control, asymptomatic and HF groups were lower compared to the normal group and statistically independent of all risk factors only distensibility was influenced by age and gender with lower values seen in females than males regression ([Regression coefficient ; p value] [-0.037 {-0.060 - -0.015}; p<0.001 for age and [-0.582 {-1.041 - -0.123}; p=0.014] for females). Also when adjusted

to other risk factors, the increase in LV mass index in the asymptomatic and HF groups, compared to the normal group, was not influenced by these risk factors, implying that LV mass index is independent of these risk factors.

Aortic strain and distensibility significantly decreased as the E/E' value increased [(r =-0.416 and p<0.001) and (r =-0.576 and p<0.001), respectively], but only in pooled data from all the subjects.

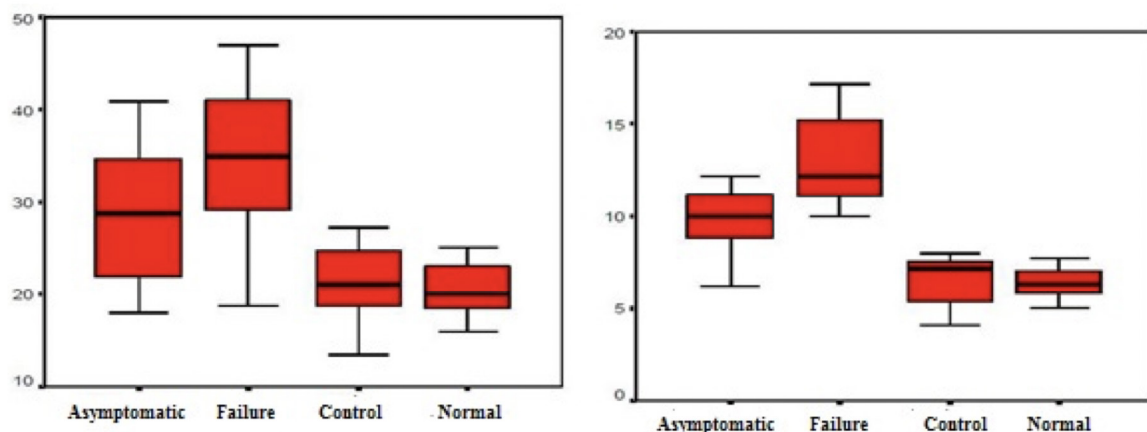


Figure 1. Distribution of E/E' and LVI measurements among groups.

Box plot of E/E' and LVI measurements, data represents percentiles. The horizontal line in the middle of each box indicates median value (50th percentile), the bottom and the top margins of the boxes represent the 25th and 75th percentiles, respectively. The vertical lines extending from the upper and lower margins of the box indicate minimum and maximum values, respectively.

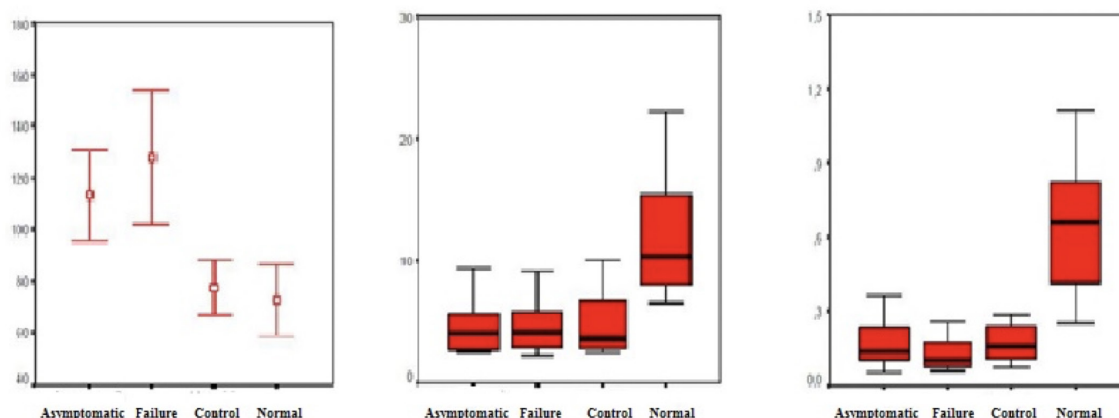


Figure 2. Distribution of LV mass index, aortic strain and distensibility measurements among groups.

Discussion

In the present study, we compared aortic stiffness parameters and diastolic function in asymptomatic and symptomatic diastolic dysfunction patients. While we found no difference between these two groups in terms of aortic stiffness parameters, however, the E/E' ratio, an important and sensitive marker of diastolic dysfunction, was significantly higher in the HF group compared to the asymptomatic group. Furthermore, even though we found that aortic strain and distensibility values significantly decreased as the E/E' ratio increased, we were unable to demonstrate a direct effect of aortic stiffness on the transition from asymptomatic diastolic dysfunction to diastolic heart failure.

It is known that the ventricles and the great vessels become hard or "stiffen", due to structural and functional changes caused by cardiovascular risk factors such as hypertension, diabetes and endothelial dysfunction.¹² Both these processes also directly influence cardiovascular morbidity and mortality.³ Signs and symptoms of heart failure are clearly apparent in patients suffering from Heart Failure with Preserved Systolic Function even though the EF is within normal range.³ The main pathophysiological mechanism responsible for this clinical picture is diastolic dysfunction, which is defined as an impaired pressure-volume relationship resulting from a resistance to ventricular filling.¹⁴ LV relaxation and LV diastolic stiffness are the major indicators of diastolic function.^{15,16} HF with preserved systolic function accounts for 50-55% of all cases of heart failure, and such patients are usually over the age of 65, female, and present with hypertension, obesity and diabetes.¹⁷ A significant relationship between the degree of aortic stiffness and the LV function in prediabetic population has been shown recently.¹⁸ In line with the available literature, we also found diastolic dysfunction in predominantly older and obese subjects, and the ratio of diabetics was similar to that found in literature.

A review of studies that have investigated aortic stiffness shows that pulse wave velocity (PWV), measured either by invasive or noninvasive methods, has been predominantly used as an index of aortic stiffness.¹⁹ While estimating PWV,

it is not possible to accurately measure the distance covered by the pulse wave even though the wave recording is done by Doppler. A superficial measurement method has been suggested for the estimation of this distance but it does not always give a correct result as it requires adjustment for age and factors such as overweight, large breast size, and spinal and thoracic abnormalities can cause errors in measurement. Thus, the correct measurement of this distance requires invasive or angiographic methods, which makes the practical use of PWV difficult. Therefore, aortic strain and aortic distensibility, which can be calculated using echocardiographic aortic diameter and routine blood pressure values, have been suggested as alternate indices of aortic stiffness, and it has been demonstrated that these noninvasively measured parameters are as efficacious as those measured invasively.²⁰

Many studies have investigated the relationship between aortic stiffness and cardiac systolic function. However, few studies on aortic stiffness and cardiac diastolic function have investigated whether there is a cause and effect relationship, and have not grouped patients with diastolic dysfunction according to the presence or absence of symptoms of heart failure.^{8,21} Moreover, to the best of our knowledge, no study has yet investigated the effect of aortic stiffness on the transition from asymptomatic diastolic dysfunction to symptomatic diastolic heart failure. Besides, a majority of such stiffness studies included patients with coronary artery disease and some studies were particularly conducted on patients with coronary artery disease alone.^{22,23} In addition, higher coronary calcium scores were observed more commonly in patients with diastolic dysfunction and found to be strongly correlated with aortic elasticity.²⁴ The fact that aortic elasticity measurement was performed over the ascending aorta in such patients and that this region is likely to be influenced by the nature of coronary blood flow poses restrictions under certain conditions such as coronary ischemia.²⁵ Contrarily, CAD was excluded in the participants of the present study by stress testing, which was performed based on either patient history or the suspicion of CAD. Therefore, the margin of error in measuring aortic elasticity due to altered coronary blood flow was minimized. Moreover, as we also

excluded patients with other diseases which are likely to influence aortic stiffness and diastolic dysfunction such as hypoxic pulmonary diseases, aortic stenosis and chronic renal insufficiency and included only patients with documented hypertension and/or diabetes, we aimed to more clearly define the relationship between aortic stiffness and cardiac diastolic function. However, as the participants in the present study were either hypertensive or both hypertensive and diabetic, a control group was formed with the hypertensive subjects alone, apart from a second control group of healthy individuals without any cardiovascular risk factors.

A study conducted in healthy individuals without any cardiac risk factors observed a positive correlation between brachial pulse wave velocity (baPWV) and the E/E' ratio, and demonstrated that the carotid artery stiffness value was beneficial in the early detection of patients with untreated hypertension who would subsequently develop diastolic dysfunction.²² Further, Xu et al.²⁶ have demonstrated a significant correlation between baPWV and E/A values in healthy individuals with normal LVEF, and another study ascertained that an increase in arterial stiffness in hypertensive patients is a strong predictor of diastolic dysfunction that is independent of other risk factors.²³ Fujiu et al.²⁷ demonstrated that, in hemodialysis patients, aortic arch calcification and increased arterial stiffness play an important role in the later development of left ventricular diastolic dysfunction, and an age-related increase in vascular stiffness values and E/E' ratio was discerned in patients even in the absence of cardiovascular disease.²⁸ Thus, an increase in LV mass index and E/E' ratio along with a decrease in aortic strain and distensibility reported in the present study are consistent with the available data.

Estimation of diastolic function by Doppler echocardiographic methods is not easy because many of the measurements are volume-dependent (preload), show variation with age, and are affected by the time of measurement and by various medications being used by the patient. Therefore, alternative echocardiographic methods or indicators are needed to evaluate diastolic function. Left atrium volume index (LAVI), a parameter independent of volume load, is one

such reliable indicator because an increase in left atrium size is the earliest marker of diastolic dysfunction.¹¹ We used both tissue Doppler and left atrial volume measurement to evaluate diastolic function but found no difference in LAVI values between the control group and the normal group, which is probably due to the absence of diastolic dysfunction in the control group, even though it consisted of subjects with hypertension alone. The fact that among patients with diastolic dysfunction LAVI values were higher in those with heart failure, compared to those without, suggests that there may be factors other than diastolic dysfunction that lead to diastolic heart failure. Furthermore, Kalaycioglu et al.²⁹ supported this suggestion by observing an association between impaired left atrial function and ambulatory arterial stiffness index independent of left ventricular diastolic dysfunction in hypertensive diabetic patients.

Our knowledge of the pathogenesis of diastolic HF is still limited but diabetes and hypertension appear to be the most common causes. Characteristic features of HF with preserved systolic function include myocyte hypertrophy, intramyocardial microangiopathy, fibrosis, vascular and ventricular systolic and diastolic stiffness, and impaired relaxation.³⁰ LVH is present in 90% of patients with hypertension and diastolic dysfunction despite the fact that diastolic dysfunction can occur even in the absence of LVH. An experimental study on rats demonstrated impaired left ventricle compliance/distensibility during the transition from LVH to heart failure with preserved ejection fraction.³¹ Further, patients having HF with preserved systolic function show prolonged isovolumic relaxation time, reduced LV filling and increased diastolic stiffness.¹⁵ Another study reported lower resting systolic myocardial velocity (Mean Sm) and mean early diastolic velocity (Mean Em) in patients with hypertensive LVH or hypertensive diastolic HF compared to healthy control subjects.³² Further, when these two groups were compared with each other, Mean Sm and Mean Em were lower in the hypertensive HF group.³² Similarly, we also show that, among diastolic dysfunction patients, the E/E' value is higher in patients with the HF phenotype.

LV diastolic dysfunction can remain asymptomatic for a long time and until its transition from subclinical myocardial injury to

manifest clinical HF. Studies have demonstrated that moderate to severe asymptomatic diastolic dysfunction is also associated with increased cardiovascular mortality.³³ Nevertheless, the prognosis is considered to be better for patients with asymptomatic diastolic dysfunction compared to those with diastolic HF, and echocardiographic assessment and monitoring of patients in the subclinical stage is important.³⁴ Likewise, we also report high E/E' ratio in patients with clinically manifest diastolic HF. Moreover, although aortic stiffness and distensibility values were not different between asymptomatic group and the HF group, pooled data from all the groups showed that both these parameters significantly decreased as the E/E' increased. This result implies that such a decrease in aortic strain and distensibility values together with increase in E/E' ratio can serve as useful criteria for identifying those patients who will subsequently develop clinically manifest HF.

An important limitation of our study is relatively low number of subjects. Another limitation, similar to other studies, is the fact that diastolic dysfunction diagnosed by echocardiography was not verified by cardiac catheterization. While selecting patients for the diastolic heart failure group diagnosis was made based on patient history and echocardiographic criteria and neither serum BNP nor NT-ProBNP levels were estimated.

Conclusions

Although the prevalence of diastolic HF is gradually increasing, treatment options remain limited. Till date no treatment regimen has been shown to convincingly reduce morbidity and mortality in diastolic HF patients. Although we found no difference in aortic stiffness parameters between asymptomatic and symptomatic diastolic dysfunction patients; however, as aortic strain and distensibility values are decreased with an increase in the E/E' ratio; we suggest that echocardiographic monitoring of asymptomatic patients, which is both easy and readily available, will be beneficial in identifying the patients who would show a transition from diastolic dysfunction to clinically manifest HF. Therefore, studies that investigate the effect of an efficient treatment regimen on the development of diastolic heart failure during the asymptomatic period are needed.

Conflict of interest

All authors declare that they have no conflict of interest.

Authors' Contribution

Study Conception: OK, BS; Study Design: AT, OK; Supervision: BS, OK, AT; Funding: AT; Materials: OK, BS; Data Collection and/or Processing: OK, BS; Statistical Analysis and/or Data interpretation: BS, AT; Literature Review: OK, BS, AT; Manuscript Preparation: OK; and Critical Review: BS, AT.

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The Impact of Health Literacy on the ERCP Process

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ABSTRACT

Background Endoscopic retrograde cholangiopancreatography (ERCP) is an invasive method commonly used for the diagnosis and treatment of hepatopancreaticobiliary diseases. The aim of this study is to assess whether there is a relationship between Health Literacy (HL) levels and the ERCP process.

Material and Methods The study prospectively evaluated the HL data of 72 patients who had ERCP in our hospital between July-November 2020. The Turkish version of the 47-item European Health Literacy Survey Questionnaire (HLS-EU-Q47) was used to assess health literacy. The patients' demographic characteristics, duration of referral to hospital, duration of the ERCP procedure, white blood cells (WBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), and total-direct bilirubin levels and HLS-EU-Q47 results were recorded and evaluated.

Results In our study, 77.7% of the patients had insufficient HL levels. The median body mass index (BMI) was statistically higher in patients with an insufficient HL level ($p=0.046$). GGT, total and direct bilirubin levels were higher in patients with a low HL level ($p=0.009$, $p=0.031$, $p=0.008$, respectively). The assessment of the duration of referral for ERCP revealed that the median duration of referral was statistically significantly longer in patients with an insufficient HL level ($p<0.001$). The median duration of cannulation during ERCP was statistically higher in patients with an insufficient HL level ($p=0.002$).

Conclusions The level of Health Literacy affects the early diagnosis and the success of the procedure in hepatopancreaticobiliary diseases that require ERCP.

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Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a commonly used method for the diagnosis and treatment of benign and malignant hepatopancreaticobiliary diseases.¹ The most common ERCP indications are benign (such as bile duct stones or strictures, biliary pancreatitis and parasitic diseases of the biliary tract) and malignant diseases of the periampullary region, biliary or pancreatic ductal system.² Although it was widely used for diagnostic purposes in the early years, it is now used mostly for therapeutic purposes because of the development of non-invasive diagnostic methods such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS).³ The most important factors affecting the success of ERCP include the experience of the endoscopist, the duration of the patient's referral, severity of the disease, and anatomical variations.³

Health Literacy (HL) was defined by the WHO (World Health Organization) in 1998 as cognitive and social skills that determine the ability of individuals to access, understand and use information to promote and maintain their health.⁴ Parallel to the increase in Health Literacy levels, it has been found that an individual's duration of referral to healthcare services is shorter and health outcomes can be improved by making active decisions for treatment and initiating early treatment.^{5,6} Studies have shown that there is a relationship between HL levels and patients' referral process for treatment.⁷⁻¹⁰ Our knowledge regarding the effect of HL levels on referral prior to ERCP and the procedure is limited. The aim of our study is to determine the relationship between HL levels and the ERCP process.

Material and Methods

Study Design

The study prospectively recorded and evaluated the data of 72 patients who had ERCP in the endoscopy unit of our hospital between July 2020 and November 2020. The patients were given detailed information and provided their written informed consent prior to the study. The study was conducted in accordance with the

principles of the Declaration of Helsinki. The local ethics committee approved the study (2011-KAEK-25 2019/10-18).

Sampling

An ERCP procedure was performed on patients who had elevated total and direct bilirubin (T. Bil, D. Bil), alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) levels as biochemical parameters and obstructed or dilated intra-extrahepatic bile ducts on MRCP for diagnostic and therapeutic purposes. The study included outpatients aged from 18 to 80 years, who would have ERCP under sedoanalgesia for the first time and who were competent to fill in the health literacy questionnaire. Patients who previously had undergone ERCP, who did not accept to fill in the questionnaire or who failed to complete it, and who were healthcare personnel, were excluded.

Data Collection

The Turkish version of the European Health Literacy Survey Questionnaire (HLS-EU-Q47) was used in the study.¹¹ Patients with indications for ERCP were administered the HLS-EU-Q47 before the procedure. The questionnaire is comprised of 47 items, and the patients were asked to choose one of the four options (very difficult, difficult, easy and very easy) for each item. The questionnaire items were divided into three subgroups: items 1–16, health care; items 17–31, disease prevention; and items 32–47, health promotion. The indices were standardized as indicated in the formula below, with 0 indicating the lowest health literacy level and 50 the highest health literacy level on a scale from 0 to 50. Formula $\text{Index} = (M - 1) * (50 / 3)$, where the Index is specific index calculated, M is the mean of all participating items for each individual, 1 is the minimal possible value of the mean, 3 is the range of the mean and 50 is the chosen maximum value of the new metric.¹¹ Health literacy was considered insufficient for scores of 0–33 and sufficient for scores of 33–50.

The patients' hemogram and biochemical parameters were analyzed before and after ERCP. ERCP procedures were conducted under sedation anesthesia in the prone position in the endoscopy

unit under the control of an anesthesiologist. All procedures were performed by the same endoscopist. The pre-cut technique was used for cannulation in patients with failed cannulation using an ERCP catheter or sphincterotome.

Demographic characteristics, duration of referral to hospital, duration of the ERCP procedure, preoperative and postoperative levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALP, GGT, white blood cells (WBC), amylase, lipase, T. Bil, and D. Bil. and HLS-EU-Q47 results of the patients undergoing ERCP were recorded and evaluated.

Statistical Analysis

The Shapiro-Wilk test was used to test the concordance of the data to normal distribution. Continuous and discrete variables are expressed with median and interquartile range values, while categorical variables are reported with frequency and corresponding percentage values. The Mann-Whitney U test was used to compare the continuous and discrete variables between adequate and inadequate health literacy groups. In contrast, the chi-square test and Fisher’s exact test were used to analyze categorical variables. Risk factors that are thought to be effective on inadequate health literacy levels were examined by logistic regression analysis. Internal consistency of the Health Literacy Scale was examined by Cronbach alpha coefficient. SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) software was used for performing statistical analysis, and $p < 0.05$ was set for statistical significance.

Results

The study included 72 patients who had ERCP for the first time. Cannulation was successful in 86.1% of the patients. Complications developed in 15.2% of the patients. Of the patients, 8.3% developed moderate pancreatitis and were treated medically. Transient hyperamylasemia occurred in 6.9% of the patients and these patients were followed up conservatively. There was no mortality in this series of patients.

Our study identified insufficient HL levels in 77.7%, and sufficient HL levels in 22.3% of the patients undergoing ERCP (*Table 1*).

A comparison was made of Health Literacy levels and patient demographic characteristics (*Table 2*). There was no statistically significant relationship between age and gender and HL levels ($p=0.64$, $p=0.949$). Health literacy was found to be insufficient in 78.1% of male and 77.5% of female participants. The median body mass index (BMI) was statistically higher in patients with an insufficient HL level ($p=0.046$).

The relationship between clinical variables and HL was examined (*Table 3*). There was no statistically significant relationship between the presence of comorbidity and the American Society of Anesthesiologists (ASA) scores and HL levels ($p=0.431$, $p=0.617$). The examination according to the duration of referral for ERCP revealed that the median duration of referral was statistically significantly longer in patients with an insufficient HL level ($p<0.001$). There was no statistically significant difference in HL levels between patients with and without bile duct dilatation ($p>0.99$). AST and ALP levels were not significantly related with HL scores ($p>0.005$), while ALT and GGT levels were statistically significantly

Table 1. Health Literacy Levels of Study Participants

	Insufficient HL	Problematic HL	Sufficient HL	Excellent HL	Cronbach’s alpha (α)
Overall HL	31.90%	45.80%	16.70%	5.60%	0.898
Healthcare HL	26.40%	43.10%	23.60%	6.90%	0.881
Disease prevention HL	40.30%	34.70%	19.40%	5.60%	0.909
Health Promotion HL	40.30%	34.70%	16.70%	8.30%	0.954

HL: Health Literacy

Table 2. Comparison of Demographic Characteristics Between Health Literacy Groups

	Health Literacy Level		p-value
	Sufficient (n=16)	Insufficient (n=56)	
Age (years)	53.50(19.50)	58(19)	0.640 ^a
Gender			
<i>Female</i>	9(22.50%)	31(77.50%)	0.949 ^b
<i>Male</i>	7(21.90%)	25(78.10%)	
BMI (kg/m ²)	23.55(3.23%)	26.35(5.18%)	0.046 ^a

Data are presented as median (interquartile range).

BMI: Body Mass Index

a: Mann-Whitney U-test, b: Chi-square Test

higher in patients with an insufficient HL level ($p=0.028$, $p=0.009$, respectively). Amylase and lipase levels were not significantly related with HL ($p>0.05$), while T. Bil and D. Bil levels were statistically significantly higher in patients with an insufficient HL level ($p=0.031$, $p=0.008$, respectively). There was no significant relationship between WBC and HL levels ($p>0.05$). The median duration of cannulation during ERCP was statistically higher in patients with an insufficient HL level ($p=0.002$).

HL levels were not statistically significantly related with the following conditions: papillary localization, success of pancreatic cannulation, necessity to perform pre-cut, presence of malignancies, development of complications and complications that need treatment in the ERCP process ($p>0.05$).

Discussion

ERCP is used for diagnostic and therapeutic purposes in hepatopancreaticobiliary diseases. The most common indications for ERCP include bile duct stones that cause biliary obstruction, and malignant biliary obstructions.¹² Early diagnosis and treatment have an important role in the success of the ERCP procedure performed for benign and malignant pathologies.¹³ The success rate of the procedure increases with early intervention in the treatment of benign biliary obstructions.¹³ In malignant biliary diseases, in turn, early diagnosis shortens the

time to initiate treatment, and biliary stenting shortens the time to initiate chemotherapy in patients who are not eligible for surgery.¹³ Cannulation and treatment success rates have been reported to increase with early consultation to the physician in patients with ERCP indications.¹⁴ It has been reported that HL levels affect healthcare solutions in individuals, and decreased levels of HL have an adverse effect on the duration of referral to healthcare institutions, and diagnostic and therapeutic processes.¹⁵

Health literacy levels are found to be higher in men, particularly those who are young and single.¹⁶ Another study reported lower HL levels in the elderly.¹⁷ In Turkey, the rate of low HL levels was found to be 68.9% in a study conducted by the Ministry of Health.¹⁸ A study involving eight European Union countries found this rate to be 47.6%.¹⁸ According to the national adult literacy study in the United States of America (USA), in turn, this rate was 36%.¹⁸ The present study established that the HL level was inversely proportional to the duration of referral for ERCP and the duration of cannulation. It was found that patients with a high HL level in decision-making about health had an earlier referral for ERCP. In addition, it is thought that the duration of cannulation at these patients would be short at ERCP.

One of the most important factors that affect cannulation success in ERCP is virgin papilla.¹⁴ Since the patient history of ERCP would affect the results, we only included patients who

Table 3. Comparison of Clinical Characteristics Between Health Literacy Groups

	Health Literacy Level		p-value
	Sufficient (n=16)	Insufficient (n=56)	
Comorbidity	0 (1)	1 (3)	0.431 ^a
ASA			
I	9(27.30%)	24(72.70%)	
II	6(18.80%)	26(81.20%)	0.617 ^b
III	1(14.30%)	6(85.70%)	
Duration of Referral (Days)	10(5)	20(7.50)	<0.001 ^a
Bile Duct Dilatation	12(22.20%)	42(77.80%)	>0.99 ^c
AST (U/L)	41(102)	44(56)	0.807 ^a
ALT (U/L)	27(43)	47(67)	0.028 ^a
ALP (U/L)	98(119)	132(94)	0.336 ^a
GGT (U/L)	127(81)	189(213)	0.009 ^a
Amylase (U/L)	56(106)	47(58)	0.386 ^a
Lipase (U/L)	54(197)	45(46)	0.420 ^a
T.Bil (mg/dL)	1.50(0.70)	2.50(2.70)	0.031 ^a
D.Bil (mg/dL)	1.10(0.60)	2.20(2.60)	0.008 ^a
WBC (10 ³ /uL)	5.10(4.20)	5.70(4)	0.684 ^a
Duration of Cannulation (min)	3(3)	5(2)	0.002 ^a
Papillary Status			
Abnormal Localization	2(16.70%)	10(83.30%)	
Normal	14(23.30%)	46(76.70%)	>0.99 ^c
Pancreatic Cannulation			
Yes	2(13.30%)	13(86.70%)	
No	14(24.60%)	43(75.40%)	0.495 ^c
Pre-cut			
Yes	1(16.70%)	5(83.30%)	
No	15(22.70%)	51(77.30%)	>0.99 ^c
Successful cannulation	15(24.20%)	47(75.80%)	0.440 ^c
Malignancy			
Yes	0	5(100%)	
No	16(23.90%)	57(76.10%)	0.580 ^c
Complications			
Yes	2(18.20%)	9(81.80%)	
No	14(23%)	47(77%)	>0.99 ^c
Therapy for Complications			
Yes	2(18.20%)	9(81.80%)	
No	14(23%)	47(77%)	>0.99 ^c

Data are presented as median (interquartile range).

ASA: American Society of Anesthesiologists, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferase, T.Bil: Total bilirubin, D.Bil: Direct bilirubin, WBC: White blood cell, a: Mann-Whitney U-test, b: Chi-square test, c: Fisher's Exact test

would have an ERCP for the first time. There was no significant relationship between HL levels and cannulation success in our patients.

Our study established that the low HL group presented with high cholestasis enzymes (T. Bil, D. Bil, ALT, GGT) ($p < 0.05$). Factors that affect ERCP success are the presence of chronic pancreatitis or the number (>3) and size (>1 cm) of stones in the common bile duct.¹⁹ Factors such as alcohol, genetics and hyperlipidemia cause chronic pancreatitis, secondary to pancreatic inflammation.²⁰ Likewise, the time to develop multiple and large common bile duct stones is longer compared to single and small common bile duct stones.²¹ It was thought that patients with a low HL level referred late for ERCP and consequently were found to have higher values in liver function tests. However, AST and ALP levels were not associated with HL levels. We attribute this result to the cross-sectional design of our study and to the low patient number included in our study.

There are studies showing that there is no significant relationship between HL and BMI or that patients with a low HL level have a higher BMI.^{22,23} Our study established higher BMI values also in patients with a low HL level ($p = 0.046$).

Our study has some limitations due to the relatively small number of cases, single-center study design and variability in health literacy levels in different countries.

Conclusions

Our study is the first research on the relationship between Health Literacy and the ERCP process. HL levels have inversely proportional effect on the referral process for diagnostic and therapeutic ERCP procedure. We believe that the improvement of health literacy would increase the success rates of diagnosis and treatment in patients who require ERCP.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' Contribution

Study Conception: UA, HMC; Study Design: UA, HMC; Supervision: UA, HMC; Funding: UA, HMC; Materials: UA, HMC; Data Collection and/or Processing: UA; Statistical Analysis and/or Data interpretation: UA; Literature Review: UA; Manuscript Preparation: UA; and Critical Review: HMC.

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Chest Pain in A Patient with Polyarteritis Nodosa and Behcet's Disease: Myocardial Infarction or Aortic Dissection?

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ABSTRACT

Aortic diseases have high mortality and are usually late or misdiagnosed. Especially in patients with inflammatory vasculitis, diagnosis is often confused with other causes of chest pain and this causes a delay in diagnosis. Vascular complications are the most important predictors of mortality and morbidity in Behcet's disease and also polyarteritis nodosa. The diagnosis of aortitis is usually obtained by vascular imaging, but partly made only by biopsy on occasion of an operation. Here we present a case of pathologically proven fatal aortitis and aortic dissection in a patient with Polyarteritis nodosa and Behcet's disease.

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Keywords: Aortic dissection, vasculitis, polyarteritis nodosa, Behcet's disease.

Introduction

Vasculitis develops reactive damage that causes inflammation in the vascular wall. They cause bleeding and ischemia as a result of damage to the vascular lumen and impaired vascular permeability.

They are usually classified according to the size, type, and location of the affected vessel. Although it involves specifically according to the vessel size, there are also forms with a wide variety of vascular involvement. Organ structures affected are also important in the diagnosis of vasculitis.

Vasculitis is serious diseases that can sometimes be fatal. Therefore, early diagnosis and treatment are crucial. Aortic dissection is one of the most fatal cases of vasculitis. Aortic dissection associated with polyarteritis nodosa has been reported in the literature only in a few cases, but cases of aortic dissection associated with Behcet's disease have been reported.

It is difficult to diagnose because of diseases that mimic vasculitis. Systemic lupus erythematosus, atherosclerotic diseases and drug reactions can be given as examples.



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Case Report

A 44-year-old man was admitted to our hospital with chest pain that started 2 hours before admission. His medical history had celiac disease, hypertension, Behcet's disease, Polyarteritis nodosa, hepatitis B. His medications were 40 mg prednisolone once a day and azathioprine 50 mg three times in a day. ECG was normal and the cardiac troponin value at the time of admission was 38.3 ng/mL (0-17.5 ng/mL), while it was 110.6 ng/mL after 6 hours of admission. Transthoracic echocardiography demonstrated with mild hypokinesis of the anterior wall and an ejection

fraction was around 50%. In accordance with these results, the patient was diagnosed with acute non-ST-segment elevation myocardial infarction (NSTEMI) and decided to perform a coronary angiography.

As a result of coronary angiography slow flow was observed in the LAD and several attempts to identify the right coronary artery (RCA) ostium failed. Injection of contrast medium didn't show any coronary artery originating from right coronary cusp. An aortogram revealed an ascending aortic dissection flap and real lumen early opacification and then the false lumen opacified. (Figure 1A, 1B) The patient was transferred to

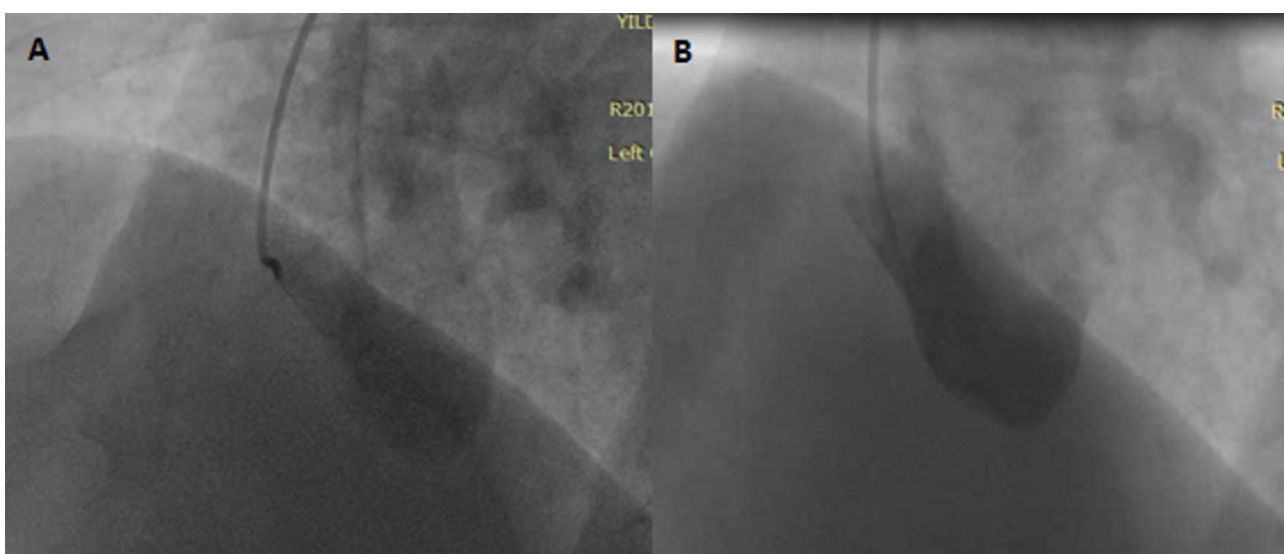


Figure 1A. Aortic dissection flap is seen in aortography with right Judkins catheter; **Figure 1B.** Early opacification of the real lumen is observed.

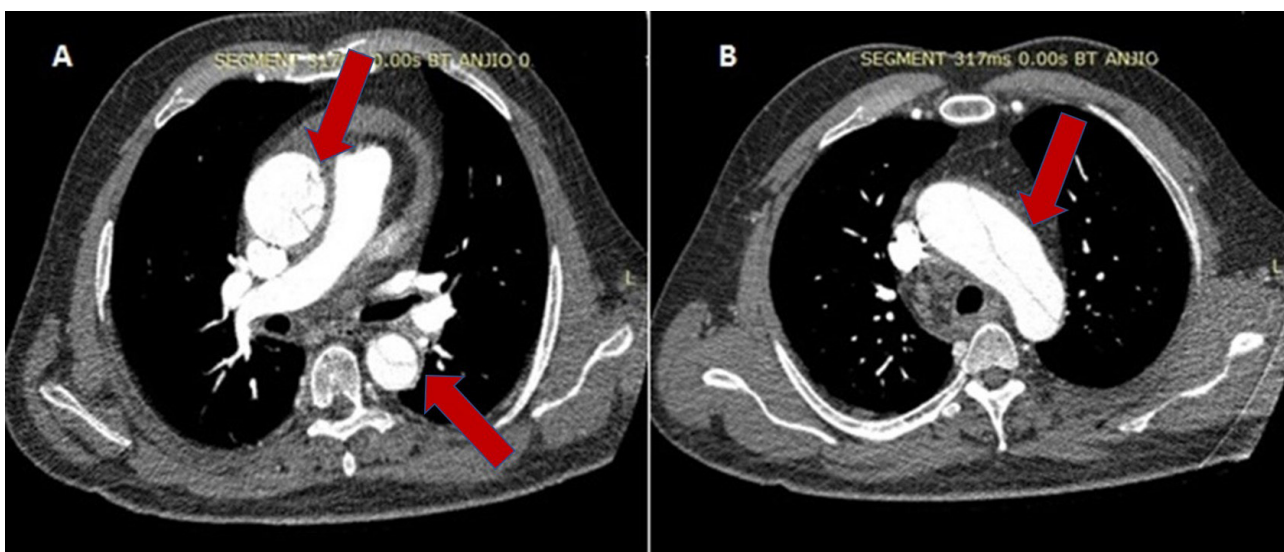


Figure 2A and Figure 2B. Aortic dissection images with multi-slice computerized tomographic angiography.

an intensive care unit and urgent cardiovascular surgeon consultation was requested. The infusions of esmolol and nitroprusside were up-titrated and the so that the patient's blood pressures could be closely monitored. Hydromorphone and fentanyl were initiated for a pain control.

An emergent contrast-enhanced computed tomography angiography scan was obtained and revealed aortic dissection of Stanford A and DeBakey type 1. (Figure 2A, 2B) The origin of the intimal tear was detected just distal to the coronary sinus. The dissection reached the abdominal aorta and pervaded both external iliac arteries. The celiac trunk, superior mesenteric artery and right renal artery originated from the true lumen. The left renal artery and inferior mesenteric artery originated from the false lumen.

The patient was transferred for cardiac surgery. The surgical repair consisted of graft replacement of the ascending aorta with the reconstruction of the left brachiocephalic and left common carotid artery. Despite the successful implementation of the procedure bleeding control was not achieved and the patient died. Histopathological examination of the resected specimen was revealed cystic medial degeneration and dissection at the medial layer, active and chronic inflammation and vasculitic process in the adventitia. (Figure 3A, 3B)

Discussion

Behcet's Disease is a chronic multisystemic immune-mediated disorder characterized by recurrent oral and/or genital ulcers, arthritis, skin manifestations, and ocular, vascular, neurological, or intestinal involvements. Vascular involvement

may be seen in 25–50% of Behcet's disease patients.¹ Four types of vascular lesions were described: arterial occlusion, aneurysms, venous occlusion, and thrombophlebitis or thrombosis. Venous manifestations are more common than arterial involvement (88% vs. 12%).¹ Arterial lesions are frequently localized in the aorta, cerebral, carotid, subclavian, brachial, ulnar, renal, and popliteal arteries.² Sporadic cases of endocarditis, myocarditis, pericarditis, acute myocardial infarction, aortic aneurysm, ventricular thrombosis, congestive cardiomyopathy, and valvular dysfunction have been reported.^{3,4} In patients with Behcet's disease, the vasculitis may damage the aortic wall and may predispose to dissection and development of aneurysms.

Polyarteritis Nodosa is characterized by a necrotizing inflammation of the entire vascular wall which develops in a segmental pattern. Fibrinoid necrosis is frequently observed in active lesions, and neutrophils are more frequently present in vessels with fibrinoid necrosis.⁵ Approximately, 20% of polyarteritis nodosa may be associated with chronic viral hepatitis caused by the Hepatitis B virus infection.⁶ Cardiac involvement is stated to occur in up to 35% of patients with polyarteritis nodosa and carries prognostic significance.⁶

Polyarteritis nodosa is a vasculitis of medium-sized and small vessels, small arteries may be involved, but small vessels, including arterioles, capillaries, and venules, are not, and therefore involvement of the ascending aorta is not expected.⁶ The most common cardiac involvement of is myocardial infarction due to coronary artery involvement.^{7,8} Lino T described a 59-year-old woman with polyarteritis nodosa with hepatitis

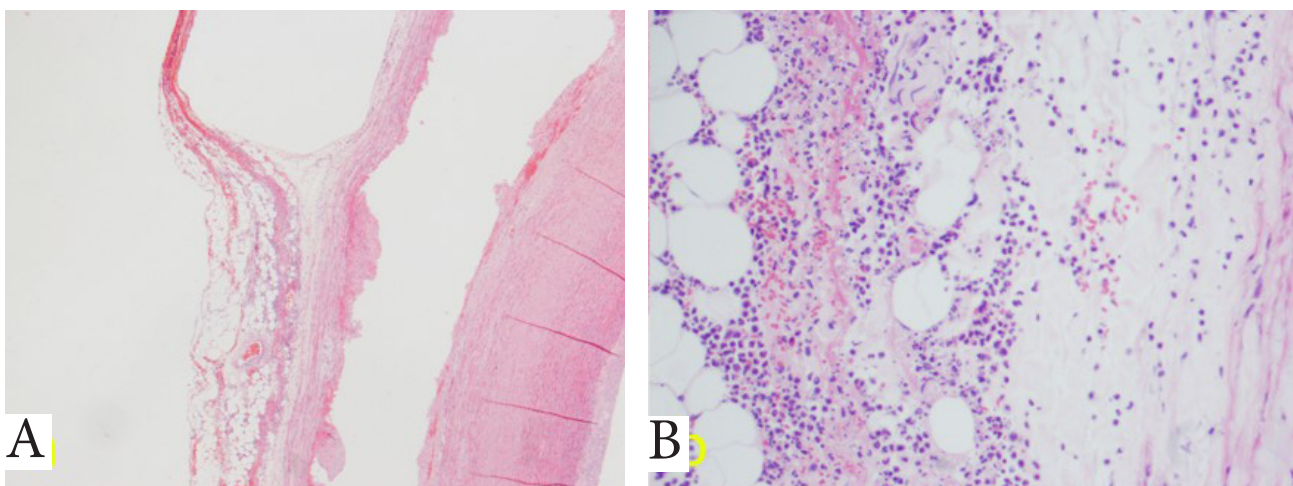


Figure 3A and Figure 3B

B admitted acute onset of chest pain. After developing the acute attack of severe chest pain, she died suddenly. At autopsy, a DeBakey type I aortic dissection was found and the immediate cause of death was found to be cardiac tamponade secondary to rupture of the aortic dissection.⁹

In these types of inflammatory diseases, when complications such as aortic dissection and aneurysm develop, mortality is high. Therefore, we should be careful about such complications that may be lethal in this patient group and we should follow up the symptoms of patients like chest pain and shortness of breath. When the diagnosis of aortitis is suspected on the basis of clinical presentation, expedient imaging of the entire aorta with an appropriate modality is critical to establish the diagnosis. Modern imaging tools for the aorta include computed tomography angiography (CT), magnetic resonance angiography (MRA), and ultrasonography. Positron emission tomography (PET) scanning has emerged for targeted imaging of vascular inflammation and may be particularly useful when combined with traditional cross-sectional imaging modalities.¹⁰

An immunosuppressive therapy is the primary treatment of non-infectious aortitis due to vasculitis, and patients are ideally managed by a multidisciplinary team that includes a rheumatologist and medical and surgical cardiovascular specialists.¹¹

In our patient's pathological examination; there was no fibrinoid necrosis on vascular involvement. So we think that the vascular inflammatory disease causing the aortic dissection of the patient is Behçet's disease. However, overlap syndromes and disease interactions should be considered in patients with diffuse vasculitic involvement in which multiple inflammatory diseases coexist as well as in our patients.

Conclusion

In conclusion, vascular complications are the most important predictors of mortality and morbidity in Behçet's disease and also polyarteritis nodosa. Early detection of vasculitis and the need

for aggressive treatment are essential for the optimal care of these patients. At the same time, aortic dissection should be kept in mind when these patients are referred to with chest pain.

Conflict of Interests

Authors declare that there are none.

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