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Aurum Journal of Health Sciences (AJHS – A. J. Health Sci.) is an international open access platform for basic, applied, theoretical and clinical studies in health sciences. AJHS publishes double blind peer-reviewed re- search articles, short reports, case reports, invited reviews and letters to the editor. AJHS is published trian- nually both in printed and electronic version. AJHS is a multidisciplinary journal on health sciences and ac- cepts manuscripts on dental, medical, health services and pharmaceutical studies. The manuscripts linking different disciplines of health sciences will be given a priority in the journal.

E-mail and web-sites
e-mail: ajhs@altinbas.edu.tr
web: https://aurum.altinbas.edu.tr/en/journal-of-health-sciences

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Tel: (0212) 709 45 28

Publication Frequency
April-July-December

Language
English

Guide for Contributors
https://dergipark.org.tr/en/pub/ajesa/writing-rules

Typesetting
Sultan Özer

Print
Sena Ofset

Date of Publication
July 2022

AURUM
Journal of Health Sciences (A. J. Health Sci.)
Volume 4 No 2
ISSN: 2651-2815

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aurum Volume: 4 | No: 2
July 2022

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Editorial

In issue 4 (2) of Aurum Journal of Health Sciences, two original research articles and two reviews are presented. Research articles are "Determination Of Radiation Exposure Of Students During Their Internships Using Osl Dosimeter" and "A Descriptive Study To Determine The Relationship Between Health Literacy Level And Catching Covid-19", which emphasizes the importance of workplace safety of healthcare students and health literacy of the general population.

Two review articles are "Nano Formulations As Drug Delivery Systems" and "Diagnosis And Treatment Methods of Autoimmune Myasthenia Gravis: A Systematic Review" which are very important and hot-topics in their disciplines.

All articles in this issue have been reviewed after careful review processes. We would like to thank all authors, reviewers and editorial board members for their valuable contributions.

Prof. Dr. Osman Nuri Uçan
Editor-in-Chief, Aurum Journal of Health Sciences

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JOURNAL OF HEALTH SCIENCES
A. J. Health Sci.

Volume 4, No 2 | Summer 2022, 66-74

RESEARCH ARTICLE

DETERMINATION OF RADIATION EXPOSURE OF STUDENTS DURING THEIR INTERNSHIPS USING OSL DOSIMETER

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RECEIVED DATE: 06.06.2021, ACCEPTED DATE: 19.07.2022

Abstract

To keep the radiation exposure under control is the golden rule for radiation protection. The internal structure of the human body could be visible thanks to radiology and nuclear medicine for the aim of diagnosis, and it was possible to destroy tumor cells with external radiation thanks to radiation oncology for the aim of therapy. Radiation dose monitoring is performed for radiation workers however no dose follow-up has for students. So, in this study it was aimed to determine the level of radiation exposure of students who trained in medical imaging techniques program. This work is assessed the radiation exposure of 132 students during their internships in the department of radiology, nuclear medicine and oncology with the aid of optically stimulated luminescence (OSL) dosimeters between the years of 2019-2017. The OSL dosimeters were sent to the RADKOR Personnel Dosimeter Systems Laboratory (Ankara, Turkey) for measurement. Exposed OSL dosimeters were read according to the laboratory specific method based on IEC 62387. Equivalent doses are defined as for body Hp(10) and skin Hp(0,07). Also Hp(10) and Hp(0,07) are defined in the body of each person considered, their values vary from one person to another and also depend on the location on the body where the dosemeter is worn. For the students in the roles of trainers, maximum accumulated equivalent doses were found to be 2.07 and 2.14 mSv for body Hp(10) and skin Hp(0.07), respectively. The minimum accumulated equivalent dose was 0.00 mSv for 112 students both body and skin. The mean Hp(10) and Hp(0,07) for the 1st, 2nd, 3rd and 4th periods were calculated as 0.23±0.38mSv and 0.20±0.35mSv, 0.27±0.42mSv and 0.23±0.34mSv, 0.18±0.37mSv and 0.12±0.30mSv, 0.22±0.63mSv and 0.04±0.34mSv, respectively. The

results were evaluated with reference to the Radiation Safety Regulation reported by IAEA. According to the regulation, the effective dose for radiation officers cannot exceed 20 mSv for the whole five consecutive years, and 50 mSv for any year. The annual equivalent dose limit for hand and foot or skin is 500 mSv and 150 mSv for the eyepiece. Therefore, it was determined that all absorbed doses found under the radiation safety regulations. However, it was seen that some students whose absorbed dose were found a little bit high acted more courageous with the self-confidence.

Keywords: Radiation exposure, OSL, absorbed dose, whole body exposure, skin exposure, radiation safety

1. INTRODUCTION

Medical imaging and treatment with ionizing radiation has been used all over the world since 1931 (Reed, 2011). The internal structure of the human body could be visible thanks to radiology and nuclear medicine for the aim of diagnosis, and it was possible to destroy tumor cells with external radiation thanks to radiation oncology for the aim of therapy. Radiology has basically used four methods as X-ray device, computed tomography (CT), magnetic resonance (MR), ultrasonography (US) and angiography devices such as fluoroscopy for imaging via external radiation. Nuclear medicine is defined a science where radioisotopes are applied to patients for diagnosis generally and for treatment rarely. In scintigraphic applications called diagnostic images in nuclear medicine, there is a need for a bioactive agent that will allow the radioisotope to be transported to the desired organ in the body. The molecule formed by combining radioisotope and bioactive agent is called radiopharmaceutical. Nuclear medicine has included four methods as Gamma camera, Single Photon Emission Computerized Tomography (SPECT) and Positron Emission Tomography (PET) or their combined version with CT or MR as PET/CT, SPECT/CT, PET/MRI for imaging via internal radiation. Radiation oncology, as a anticipant of personalized clinical oncology, has improved individualized therapies based on anatomical information combined with clinical parameters (Bernier, 2004), (Verellen, 2007). The goal of curative radiotherapy is to sift all cancer stem cells (defined here as recurrent tumor cells) in the primary tumor and regional lymph nodes (Baumann, 2008), or in oligometastatic disease (Weichselbaum, 2011), while limiting damage to normal tissues. For this aim, oncology has used some devices such as LINAC, Cyber-knife, gamma knife, TrueBeam STx and Tomotherapy for therapy via external radiation.

All these applications benefit from the destruction caused by ionizing radiation in the cell, however, as a result of this, the probility of radiation damage to healthy tissues and organs or determination of level of radiation exposure to workers and patients comes into question. For this reason, radiation dosimetry is a main need in all medical applications of radiation. At this point, some dosimeters have been developed and they have proved to be a very significant tool in radiology, nuclear medicine and oncology for monitoring of personnel and environmental ionizing radiation (Loya, 2016).

Personal dosimeters are needed to measure exposure levels of workers working in a radiation environment. Thermoluminescence dosimetry (TLD) and optically stimulated luminescence dosımetry

(OSL) are widely used as personal dosimetry (Gilvin, 2015), (Botter-Jensen et. al., 2003) When dosimetry type is preferred, stable radiation sensitivity, resistance to external factors, tissue compatibility, ergonomic properties, cost and reading procedures are taken into consideration (Fellinger, 1984), (McKeever, 2001). Reusability, accurate dose reading, low effect from external factors and local stimulation are the advantages of OSL dosimeter (Sommer, 2006). Especially, beryllium oxide material stands out due to its near tissue equivalence (Zeff = 7.14) (Sommer, 2006) (Jahn, 2010), energy response, high sensitivity and low cost (Sommer, 2006). In view of these advantages, OSL dosimeters with beryllium oxide were preferred generally. The OSL dosimeter ensures a very high degree of sensitivity by giving an true reading as low as 1 mrem for ionising photons with energies between 5 keV and more than 40 MeV (Statkiewicz-Sherer, 2018).

In this study it was aimed to determine and evaluate the level of radiation exposure of students who trained in medical imaging techniques program.

2. MATERIAL AND METHODS

In the study, total number of 132 students (90 Female, 42 Male) who were educated in Altınbaş University Medical Imaging Techniques Program between 2019-2017 were included. The average age of the students was 18.50 (range between 25-17). Students were assigned to do internships in radiation oncology (132/23), nuclear medicine (132/6) and radiology (132/103). To estimate the equivalent dose from external exposure, all students had OSL dosimeters with BeO crystal. OSL dosimeters were given to the students for 1 period consists of 2 months. Equivalent doses are defined as for body Hp(10) and skin Hp(0,07). Also Hp(10) and Hp(0,07) are defined in the body of each person considered, their values vary from one person to another and also depend on the location on the body where the dosemeter is worn (Dietze, 2000). The study included Hp(10) whole body and Hp(0,07) skin dose measurements (mSv) of 52 students for just 1 period, 37 students for 2 periods, 33 students for 3 periods and 10 students for 4 periods. 1st, 2nd, 3rd and 4th periods were consisted of number of 43 ,80 ,132 and 10 students, respectively.

2.1. Usage of OSL

All students were given guidelines on the use of OSL dosimeters before the internship. OSL dosimeters were usually affixed on the outside of clothing, around the chest or torso. The OSL dosimeter was worn under the lead apron only when a student used a lead apron. OSL dosimeters were never tried to open and not removed from its sleeve. Outside the daily working hours, OSL dosimeters were kept away from radiation, not exposed to heat, humidity and pressure. At the end of the internship, the dosimeters were collected from the students.

2.2. Conditions of Departments

The number of 23 students doing internship in radiation oncology participated in chemotherapy

practices. They also participated in the treatment practice with the CIRUS 60Co teletherapy machine. The number of 6 students who interned in the nuclear medicine department participated in scintigraphic imaging procedures performed with the 99mTc radioisotope. They worked as observers in patient preparation and radioactivity injection practices. The students alternately participated in the practice in the PET room, which contained high energy isotopes as 18F. The number of 103 students, who were doing their internships in the radiology department, completed their internships in the X-ray and tomography rooms.

2.3. Dose Reading of OSL

The OSL dosimeters were sent to the RADKOR Personnel Dosimeter Systems Laboratory (Ankara, Turkey) for measurement. Exposed OSL dosimeters were read according to the laboratory specific method based on IEC 62387 (International Electrotechnical Commission, 2007).

2.4. Evaluation of Doses

The results were evaluated with reference to the Radiation Safety Regulation reported by IAEA (IAEA, 1999). According to the regulation, the effective dose for radiation officers cannot exceed 20 mSv for the whole five consecutive years, and 50 mSv for any year. The annual equivalent dose limit for hand and foot or skin is 500 mSv and 150 mSv for the eyepiece.

3. RESULTS

It was determined that 4 out of 132 students in the 1st period, 41 out of 80 students in the 2nd period, 14 out of 43 students in the 3rd period and 2 out of 10 students in the 4th period were used their OSL dosimeters regularly.

Exposed OSL dosimeters with different doses of X-rays and gamma radiation caused by radiology via X-ray machine and tomography shots, by nuclear medicine via SPECT and PET shots using radioactive sources such as 99mTc, 18F, by radiation oncology via 60Co teletherapy system were placed in the OSL reader to obtain their response in relation to radiation dose. The results of exposed OSL dosimeters for all students were shown detailed in Table 1.

Table 1: The whole body Hp (10) and skin Hp (0,07) doses for all students.

		1st period		2nd period		3rd period		4th period	
Number	*Department of Internship*	*Hp (10) (mSv)*	*Hp (0,07) (mSv)*	*Hp (10) (mSv)*	*Hp (0,07) (mSv)*	*Hp (10) (mSv)*	*Hp (0,07) (mSv)*	*Hp (10) (mSv)*	*Hp (0,07) (mSv)*
#1	R	0.28	0.30	0.32	*0.35	0.32	0.38		
#2	R	0.33	0.31	0.36	*0.35				
#3	R	0.34	*0.37	*0.73	*0.37				
#4	R	0.37	0.35	*0.48	0.24				
#5	R	0.29	0.30	*0.68	0.29				
#6	R	0.26	0.28	*0.46	0.30				
#7	R	0.30	0.33	*0.94	*0.38				
#8	R	0.31	0.34	0.00	0.00	0.24	0.25		
#9	R	0.21	0.25	0.00	0.00				
#10	R	0.27	0.27	*0.61	0.32				
#11	R	0.33	0.33	0.00	0.00				
#12	R	0.28	0.30	0.00	0.00				
#13	R	0.31	0.33	0.00	0.00	*0.43	*0.56		
#14	R	0.32	0.34	0.00	0.00				
#15	R	0.32	0.34	0.00	0.00				
#16	R	0.37	*0.39	0.00	0.00	0.32	*0.37		
#17	R	0.33	*0.36	0.00	0.00	0.25	*0.35		
#18	R	0.34	0.33	0.30	0.30	0.00	0.00	0.32	*0.36
#19	R	0.29	0.32	0.00	0.11	0.21	0.25		
#20	R	0.32	0.35	0.00	0.00	0.37	*0.41		
#21	R	0.34	0.34	0.29	0.30	0.00	0.00	0.30	*0.36
#22	R	*0.4	*0.39	0.34	*0.43				
#23	R	0.29	0.30	0.29	0.32				
#24	R	0.30	0.34	0.26	0.26	0.30	*0.34		
#25	R	0.38	*0.42	0.00	0.00	0.12	0.11		
#26	O	0.35	*0.36	0.00	0.00	0.00	0.00		
#27	O	0.28	0.30	0.00	0.00	0.00	0.00		
#28	O	*0.39	*0.39	0.30	0.31	0.00	0.00	0.00	0.00
#29	O	*0.40	*0.41	0.33	0.34	0.00	0.00	*0.72	*0.41
#30	R	0.35	*0.38	0.25	0.31				
#31	NM	0.28	0.30	0.00	0.00				
#32	O	0.26	0.27	0.00	0.00	0.07	0.07		
#33	NM	*0.41	*0.44	0.05	0.05				
#34	NM	*1.22	*1.26	0.00	0.00	0.34	*0.38		
#35	O	0.32	0.33	0.36	*0.37	0.00	0.00	0.00	0.00
#36	O	*2.07	*2.14	0.00	0.00				
#37	O	0.35	*0.38	0.30	0.31	0.25	0.29		
#38	O	0.29	0.30	0.00	0.00				
#39	O	0.29	0.32	0.28	0.31				
#40	R	0.32	0.33	0.00	0.00				
#41	R	0.30	0.33	0.00	0.00				
#42	O	0.36	*0.37	0.32	0.33	*0.59	*0.38		
#43	O	0.36	*0.37	*0.98	0.27				
#44	R	0.33	0.35	*0.65	0.30				
#45	R	0.33	*0.36	0.27	0.28	0.30	*0.35		
#46	R	0.30	0.32	0.39	*0.40	0.00	0.00	*0.85	0.33
#47	R	0.30	0.33	0.00	0.00	*0.60	*0.35		
#48	R	0.34	*0.38	0.32	*0.35	*0.56	*0.43		
#49	R	*0.53	*0.61	0.00	0.00				
#50	R	0.33	0.32	0.34	*0.37	*0.48	0.25		
#51	R	*0.39	*0.37	0.28	0.33	*0.65	*0.39		
#52	R	0.33	0.35	*0.59	*0.39				
#53	O	0.28	0.31	0.00	0.00	0.00	0.00		
#54	R	0.34	*0.37	0.00	0.00	*0.63	0.3		
#55	R	0.35	*0.37	0.32	0.33	0.00	0.00	0.55	0.29
#56	R	0.32	0.34	*1.25	*0.36				
#57	R	0.27	0.30	0.00	0.00				
#58	R	0.33	0.35	0.00	0.00				
#59	R	0.36	*0.39	0.00	0.00	*0.67	*0.39		
#60	R	0.29	0.30	0.00	0.00	0.06	0.05		
#61	R	0.29	0.31	*0.43	*0.48	*0.50	*0.34		
#62	R	0.29	0.30	0.28	0.27	*0.40	0.24		
#63	R	0.30	0.33	0.00	0.00				
#64	R	0.24	0.32	0.00	0.00				

#65	R	0.31	0.35	0.30	0.31	0.00	0.00	*0.87	0.32
#66	R	0.28	0.29	0.26	0.28	0.00	0.00	*0.83	0.31
#67	R	0.37	0.35	0.00	0.00				
#68	O	0.27	0.31	0.25	0.26	0.00	0.00	0.56	0.32
#69	O	0.32	0.34	0.00	0.00				
#70	O	0.30	0.34	0.00	0.00	0.00	0.00		
#71	NM	0.36	*0.37	0.00	0.00	0.09	0.08		
#72	NM	0.36	0.32	0.00	0.00				
#73	NM	0.36	*0.37	0.00	0.00				
#74	O	0.36	*0.39	0.36	*0.39	*0.63	*0.37		
#75	R	*0.40	*0.40	0.40	*0.39	*0.55	*0.31		
#76	R	*0.46	*0.48	0.07	0.06	0.16	0.15		
#77	R	0.33	*0.36	0.00	0.00	*0.43	0.27		
#78	R	0.37	*0.38	0.00	0.00	0.22	0.25		
#79	R	0.31	0.34						
#80	R	0.32	0.33						
#81	R	0.29	0.32						
#82	R	0.32	0.34	1.22	*1.72				
#83	O	0.33	0.35						
#84	R	*0.39	*0.38						
#85	R	0.35	*0.36						
#86	R	0.35	*0.37						
#87	R	0.00	0.00						
#88	R	0.00	0.00						
#89	R	0.00	0.00	0.06	0.05				
#90	R	*0.55	0.27						
#91	R	*0.94	*0.82						
#92	R	*0.48	0.32						
#93	R	*0.53	0.33						
#94	R	*1.10	0.34						
#95	R	*0.43	0.32						
#96	R	*0.51	0.34						
#97	R	*0.56	0.35						
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#99	R	*0.44	0.28						
#100	R	*0.62	*0.37						
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#115	R	0.28	0.30						
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#118	R	0.05	0.05						
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#121	O	0.05	0.05						
#122	O	0.08	0.07						
#123	O	0.09	0.09						
#124	R	0.06	0.05						
#125	R	*0.57	0.33						
#126	R	0.27	0.32						
#127	R	0.25	0.29						
#128	R	0.30	*0.37						
#129	R	*0.41	0.29						
#130	R	*0.50	0.29						
#131	R	*0.88	0.31						
#132	R	*0.48	0.20						
Mean (mSv):	**0.38**	**0.35**	**0.42**	**0.34**	**0.37**	**0.30**	**0.63**	**0.34**	
S.D (±):		0.23	0.20	0.27	0.23	0.18	0.12	0.22	0.04

R: Radiology, O: Oncology, NM: Nuclear Medicine, * high dose values than means.

All calculations were made by subtracting 34 students who did not use dosimetry. The mean whole body Hp(10) and skin doses Hp(0,07) for the 1st, 2nd, 3rd and 4th periods were calculated as 0.23±0.38mSv and 0.20±0.35mSv, 0.27±0.42mSv and 0.23±0.34mSv, 0.18±0.37mSv and 0.12±0.30mSv, 0.22±0.63mSv and 0.04±0.34mSv, respectively. Considering total number of 204 period measurements, the result of 34 measurements were above the mean values. It was seen that 26 of these high values were in radiology, 6 in oncology and 2 in nuclear medicine. The maximum accumulated equivalent doses obtained were found to be 2.07 and 2.14 mSv for body Hp(10) and skin Hp(0.07) in one student numbered as 36#.

It was observed that the average whole body and skin doses that the students were exposed to during their internship were equal to approximately 1 percent and 1 in a thousand of the stated reference reported by IAEA.

4. DISCUSSION

Monitoring of radiation exposure of personnel or student has several purposes. Work planning can be made by looking at the level of radiation and information about the external radiation exposure of the personnel is obtained. In addition, these results can be used to keep radiation exposure as low as reasonably possible (Lundberg, 2002). In our study, it was observed that suitable working environment as distance was provided in clinics according to the radiation doses that the students were exposed to. Though all of the students were aware of the importance of radiation safety, however, important errors were found in the application and information about it. The lack of standard radiation safety equipment for students was a major concern.

Although all students were given written guidelines on the use of OSL dosimeters before the internship, it was observed that 2 students in the 1st period, 33 students in the 2nd period, 14 students in the 3rd period and 2 students in the 4th period did not use the OSL dosimeter. It is thought that students are insensitive to written instructions and behave unnecessarily confident in the clinic based on their theoretical knowledge.

This study found that medical imaging techniques program's students who are legally non occupational exposed group (ICRP, 2007), are exposed to ionizing radiation without risk detection. So, It was stated that students who trained in medical imaging techniques program of vocational school of health sciences were not at risk by X-ray exposure since their university training years.

Finally, absorbed dose values obtained in this work may be compared to results from (Loya, 2016), the doses showed in this paper were found to be quite low.

5. CONCLUSION

The fact that students do not use dosimetry during their internship causes inability to follow up the dose. For this reason, it is recommended that students be briefed before the internship. The necessary information about the importance of the use of dosimeters and the method of use should form the basis of the briefing. However, students are exposed to low radiation doses and complete their internships within safe limits. It should be considered that the use of dosimetry is mandatory for a possible radiation accident.

Many hospitals still lack lead shielding materials as lead apron, thyroid sparing, is low. Future efforts should involve minimizing radiation exposure in the department of radiology, radiotherapy and nuclear medicine, and more interest in wearing and preparing protective equipment is needed.

6. REFERENCES

Baumann, M. K. 2008. Exploring the role of cancer stem cells in radioresistance, Nat. Rev. Cancer, -545 554.

Bernier, J. H. 2004. Radiation oncology: a century of achievements, Nat. Rev. Cancer, 747-737.
Botter-Jensen, L., S.W.S Mckeever, and A.G. Wintle. 2003. Optically Stimulated Luminescence Dosimetry, Published by Elsevier.

Dietze, G. 2000. Dosimetric Concepts and Calibration of Instruments.

Fellinger J., H. J. 1984. Calculation and experimental determination of the fast neutron sensitivity of OSL detectors with hydrogen containing radiators, Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment, 156-154.

Gilvin P.J., A. J. 2015. Quality Assurance in Individual Monitoring for External Radiation, Neuherberg: EURADOS.

IAEA. 1999. Occupational Radiation Protection, No: RS-G1.1-. Vienna: IAEA.

ICRP. 2007. The 2007 Recommendations of the International Commission on Radiological Protection, ICRP publication 103. Pergamon Press, Oxford, UK.

International Electrotechnical Commission. 2007. International Standard IEC 1-62378. Geneva: IEC.
Jahn, A., M. Sommer, and J. Henniger. 2 .2010D-OSL-dosimetry with beryllium oxide, Radiation measurements, 676-674.

Loya, M., L.H. Sanin, P.R. Gonzalez, O. Avila, R. Duarte, S. L. Ojeda, M.E. Montero-Cabrera. 2016. Measurements of radiation exposure of dentistry students during their radiological training using thermoluminescent dosimetry, Applied Radiation and Isotopes, 238-234.

Lundberg, T.M., P.J. Gray, M.L. Bartlett. 2002. Measuring and minimizing the radiation dose to nuclear medicine technologists. J Nucl Med Technol, 30-25.

McKeever, S. 2001. Optically stimulated luminescence dosimetry, Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms, 54-29.

Reed, A. 2011. The history of radiation use in medicine, Journal of Vascular Surgery, 5-3.

Sommer, M., J. Henniger. 2006. Investigation of a BeO-based optically stimulated luminescence dosimeter, Radiat. Prot. Dosimetry, 397-394.

Sherer, M.A.S., P.J. Visconti, E.R. Ritenour, K. Haynes. (2018). Radiation Protection in Medical Radiography, Elsevier, Missouri.

Verellen, D.D. 2007. Innovations in image-guided radiotherapy, Nat. Rev. Cancer, 960-949.
Weichselbaum, R.H. 2011. Oligometastases revisited, Nat. Rev. Clin. Oncol., 382 -378.

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JOURNAL OF HEALTH SCIENCES
A. J. Health Sci.

Volume 4, No 2 | Summer 2022, 76-88

RESEARCH ARTICLE

A DESCRIPTIVE STUDY TO DETERMINE THE RELATIONSHIP BETWEEN HEALTH LITERACY LEVEL AND CATCHING COVID-19

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RECEIVED DATE: 26.05.2022, ACCEPTED DATE: 03.06.2022

Abstract

The purpose of this study is to determine whether there is a relationship between Health Literacy level and catching Covid 19 and whether there is a relationship between catching Covid-19 and sociodemographic characteristics. The Quantitative research method was used in this study. Surveys were collected from people aged 18 and over. with a convenience sampling method. The scale's internal consistency was measured with Cronbach's alpha test, the correlation between the overall scale and its subdimensions was analyzed with Pearson's Correlation Coefficient. The relationship between health literacy level and catching Covid-19; and demographic characteristics and catching Covid-19 were measured with a chi-square test. We found a statistically significant relationship between catching Covid-19 and general health literacy level and its two subdimensions (prevention of disease, health promotion). We couldn't find a statistically significant relationship between healthcare Health Literacy level and catching Covid-19. In addition, there are statistically significant differences in four sociodemographic groups (sex, age, education, marital status) in seeing Covid-19. Public health policymakers may prevent the spread of infectious and pandemic diseases by increasing the health literacy level of citizens. Decision-makers may prioritize their studies according to sociodemographic differences, especially older and low-educated people.

Keywords: Health Literacy, Covid 19, sociodemographic characteristics

1. INTRODUCTION

Health literacy is the primary determinant of a person's health and, the health literacy studies produce new recommendations and new information for health care providers (Alias, Jaafa, and Lokman, 2022). Health literacy defines by World Health Organization (WHO) as "The cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand, and use information in ways which promote and maintain good health". It is essential to prevent infectious desease. In March 2020, WHO announced Covid-19 as a pandemic desease and emphasized the importance of the public being well informed about the causes and ways of spreading to reduce transmission. During pandemic, people mostly get information through media and web browsing programs. According to a study, searching health issues using the Baidu index web browser in China increased significantly by comparison with the pre-pandemic period (Xu, Zhang, and Wang, 2020). Distinguishing of the right and wrong information is related to the individual's health literacy (HL) level. In global pandemic conditions, the concept of HL has gained importance to prevent disease development and promote health (Norman and Skinner, 2006). HL level plays a key role in the preparation of the system and individuals, in solving the real problems that develop with the pandemic, as well as evaluating online health information(Diviani et. al., 2015), (Paakari and Okan, 2020). However, community-based researches indicate that European, North American, and Asian societies have great difficulty in interpreting health-related information (Committee on Health Literacy, 2004), (Duong et. al., 2017). Similarly, in the study with eight countries, 50% of adults were inadequate and problematic health literacy levels in terms of accessing, understanding and applying health promotion and protection information (Sorensen, 2013). Okan and others researched coronavirus related health literacy in Germany. They found 50.1% of the participants are being insufficient or problematic (Okan et. al., 2020).

Individuals with a limited HL level have worse health status and are less likely to use preventive care and are more likely to be hospitalized, and have poor outcomes (Committee on Health Literacy, 2004), (Schillinger et. al., 2002). European Centre for Disease Prevention and Control (ECDC) Report, emphasized that HL plays an important role in the consequences of infectious diseases (European Centre for Disease Prevention and Control, 2012). Failure to comply with protective behavior is associated with low HL (Castro-Sanchez et. al., 2016). In addition, people with low HL levels are less likely to adopt protective behaviors such as immunization and are less likely to be vaccinated, and lack understanding of medical labels and instructions for drugs such as antibiotics. Also, people with low HL were found to be more likely to misuse drugs than adults comparing with high HL levels (Castro-Sanchez et. al., 2016), (Bennett et. al., 2009).

2. MATERIAL AND METHODS

We obtained approval from University Clinical Ethics Committee (Ethical Number:2022/111 Date; January 20, 2022) This study was conducted according to the Declaration of Helsinki.

We collected data with convenient sampling method form people aged 18 years and above, between February 01, 2022, and February 15, 2022. We used an online self-administered survey as a data collection

tool. European Health Literacy Scale Question-16 (HLS-EU-Q16), developed by Europan Health Literacy Consortium was used in the study.

Participants rated their health literacy difficulty for each item on 4-point Likert scales (1; very difficult, 2; difficult, 3; easy, and 4; very easy). The Health Literacy index was standardized to unified metrics from 0 to 50 using the formula; Index = (Mean -1) * (50/3) "Mean is the mean of all participating items for each individual; 1 is the minimum possible value of the mean (leading to a minimum value of the index of 0); 3 is the range of the mean, and 50 is the chosen maximum value of the new metric" (Nguyen et. al., 2020).

Index score ranges from 0 to 50 and classified as; 0-25 points inadequate level; >25-33 points problematic level; >33-42 points sufficient level; >42-50 points excellent level (Sorensen, 2013).

We used the G-Power program to calculate the minimum sample size. We found 220 sample size for %95 confident level (d=0.05). We had 440 surveys back. However, we excluded 11 of them because of missing responses. Finally, we evaluated a total of n=429 surveys.

2.1. Statistical Analysis

Statistical analyses were performed using SPSS (Statistical Package of Social Science) program Version 28, (IBM SPSS Corp; NY, USA).

We used Cronbach's alpha coefficient test to determine the scale's internal consistency, bivariate method with Pearson Correlation two tails to calculate a correlation between the overall health literacy scale and its subdimensions., chi-square test to understand the relationship between health literacy level and catching Covid-19 and, difference in sociodemographic characteristics, We considered it statistically significant at $p<0,05$ level.

3. FINDINGS

3.1. Validity and Reliability of Scale

The validity of the scale in Turkey was tested by Emiral et al.[15] They found the fit index of scale as x^2/ d=2.19, RMSEA=0.08, SRMR=0.07, CFI=0.84, GFI=0.87, AGFI=0.82. Cronbach's alpha coefficient was found very high as 0,918.

3. 2. Mean Scores of Participants' HL Level

HL has three subdimensions. Healthcare, Prevention of Desease and Health Promotion. The mean scores of 429 participants' health literacy level found for;

i. Health Care HL is 33,51 (at sufficient level),
ii. Prevention of Disease HL is 31,61 (at problematic level),
iii. Health Promotion HL is 34,71 (at sufficient level), and
iv. Overall HL is 33,22 (at sufficient level).

The results of frequency analysis show us 12,6% of participants have inadequate, 36,1% of them have problematic, 38% of them have sufficient and, 13,3 %of them have excellent HL level.

3. 3. Correlations Between the Overall Health Literacy Score and the Its Subscales

According to Pearson correlation results; the correlation between the overall health literacy scale and subscales found as high positive ($r > 0.883$), correlation between health care and prevention of disease found as moderate positive($r=0.626$), the correlation between health care and health promotion also found as moderate positive ($r=0.567$), and the correlation between prevention of disease, and health promotion found as high positive ($r=0.705$) The correlation found with a very high statistical significance ($p < 0.0001$).

Correlation is interpreted as; 0,00-0,25 negligible, 0,26-0,49 low positive/negative; 0,50-0,70 moderate positive/negative; 0,70-0,90 high positive/negative; 0,90-1 very high positive/negative (Mukaka, 2012).

3. 4. Relationship Between Health Literacy Level and Catching Covid-19

Tablo 1: The Relationship Between Healthcare HL Level and Catching Covid-19 and Pearson Chi-Square-Significance.

			Healthcare HL				
			Inadequate	Problematic	Sufficient	Excellent	Total
Have you been caught in Covid-19 in the pandemic process?	Yes	Count	17	13	34	9	73
		Expected Count	11,2	18,0	30,8	12,9	73,0
		% within Have you been caught in Covid-19 in the pandemic process?	23,3%	17,8%	46,6%	12,3%	100,0%
	No	Count	49	93	147	67	356
		Expected Count	54,8	88,0	150,2	63,1	356,0
		% within Have you been caught in Covid-19 in the pandemic process?	13,8%	26,1%	41,3%	18,8%	100,0%
Chi-Square Tests			Value	df	Asymp. Sig. (2-sided)		
		Pearson Chi-Square	7,108	3	0,069		

We have seen that 214 of 356 (60,1%) of participants who have not caught Covid-19 have Sufficient and Excellent Healthcare HL level. However, we couldn't find statisticall significant difference between Healthcare HL level and catching Covid-19 (p= 0,069).

Tablo 2: The Relationship Between Prevention of Desease HL Level and Catching Covid-19 and Pearson Chi-Square-Significance.

			Prevention of Disease HL				Total
			Inadequate	Problematic	Sufficient	Excellent	
Have you been caught in Covid-19 in the pandemic process?	Yes	Count	19	13	36	5	73
		Expected Count	15,1	19,9	27,6	10,4	73,0
		% Within Have you been caught in Covid-19 in the pandemic process?	26,0%	17,8%	49,3%	6,8%	100,0%
	No	Count	70	104	126	56	356
		Expected Count	73,9	97,1	134,4	50,6	356,0
		% Within Have you been caught in Covid-19 in the pandemic process?	19,7%	29,2%	35,4%	15,7%	100,0%
Chi-Square Tests			Value	df	Asymp. Sig. (2-sided)		
		Pearson Chi-Square	10,542	3	**0,014**		

Table 2 indicates that 182 of 356 (51,1%) of particapants who have not caught Covid-19 have Sufficient and Excellent Prevention of Desease HL level. There is a statistically significant relationship between Prevention of Disease HL level and catching Covid-19 (p= 0,014).

Tablo 3: The Relationship Between Health Promotion HL Level and Catching Covid-19 and Pearson Chi-Square-Significance.

			Health Promotion HL				
			inadequate	Problematic	Sufficient	Excellent	Total
Have you been caught in Covid-19 in the pandemic process?	Yes	Count	21	2	36	14	73
		Expected Count	12,1	7,7	38,5	14,8	73,0
		% within Have you been caught in Covid-19 in the pandemic process?	28,8%	2,7%	49,3%	19,2%	100,0%
	No	Count	50	43	190	73	356
		Expected Count	58,9	37,3	187,5	72,2	356,0
		% within Have you been caught in Covid-19 in the pandemic process?	14,0%	12,1%	53,4%	20,5%	100,0%
Chi-Square Tests			Value	df	Asymp. Sig. (2-sided)		
		Pearson Chi-Square	13,212	3	**0,004**		

Table 3 indicates that 263 of 356 (73,9%) of participants who have not caught Covid-19 have Sufficient and Excellent Health Promotion HL level. There is a statistically significant relationship between Health Promotion HL level and catching Covid-19 (p= 0,004).

Tablo 4: The Relationship Between Overall HL Score and Catching Covid-19 and Pearson Chi-Square-

			Overall HL				
			Inadequate	Problematic	Sufficient	Excellent	Total
Have you been caught in Covid-19 in the pandemic process?	Yes	Count	13	23	34	3	73
		Expected Count	9,2	26,4	27,7	9,7	73,0
		% within Have you been caught in Covid-19 in the pandemic process?	17,8%	31,5%	46,6%	4,1%	100,0%
	No	Count	41	132	129	54	356
		Expected Count	44,8	128,6	135,3	47,3	356,0
		% within Have you been caught in Covid-19 in the pandemic process?	11,5%	37,1%	36,2%	15,2%	100,0%
Chi-Square Tests			Value	df	Asymp. Sig. (2-sided)		
		Pearson Chi-Square	9,706	3	**0,021**		

Table 4 indicates that 183 of 356 (51,4%) of particapants who have not caught Covid-19 have Sufficient and Excellent Overall HL level. There is a statistically significant relationship between Overall HL level and catching Covid-19. (p= 0,021).

3. 5. The Relationship Between Sociodemographic Group and Catching Covid-19

N:429	Sociodemographic Characteristic	N	Catching Covid-19	(Proportion in covid case; n=73)	Catching Covid-19 (Within Group)	P Value
Sex (Chi-Square)	Female	295	35	47,9%	11,9%	0.000
	Male	134	38	52,1%	28,4%	
Age	18-33	236	33	45,2%	14%	0.047
	34-49	146	27	37%	18,5%	
	50-65	41	10	13,7%	24,2%	
	65 and above	6	3	4,1%	50%	
Education	**Primary School**	36	15	20,8%	41,7%	0.000
	High Scholl	77	16	22,2%	20,8%	
	Graduate	262	33	45,48%	12,6%	
	Master/Phd	52	8	11%	15,3%	
Marital Status	Married	182	41	56,2%	22,5%	0.007
	Single	247	32	43,8%	13%	

Table 5 show that majority of participants were female; 18-33 age group; graduate educational level and single. Most of them working in public and private sector and earning betveen 2501-7500 TL.

We found a statistically significant difference between females and males (p=0,000). Male cathching Covid-19 more than female. 52,1% of 73 Covid-19 cases were male and 28,4% of 134 male participants caught Covid-19.

There is a statistically significant difference between the age groups (p=0,047). 50% of the "65 and above age group" and 24,2% of the "50-65 of age group" have caught Covid-19.

The Differences in the educational group are significant at the p=0,000 level. People at the primary school level more caught in Covid-19 than higher education levels.

There is a significant difference between marital status (p=0.007). The proportion of Covid-19 cases in married participants found more than single.
There are no significant differences between occupational groups (p=0,401) and monthly income (p=0,117).

4. DISCUSSION AND CONCLUSION

In this study, firstly, we measured participants' HL levels without looking at whether they were caught in Covid-19 or not. We found participants' overall HL (33,2268), Healthcare HL (33,51) Health promotion HL (34,71) are at a sufficient level from the lower limit (>33-42 point is accepted as sufficient). Prevention of disease HL (31,61) is at the problematic level (>25-33 points is accepted as problematic). Frequency analyses show that 48.7% of people have inadequate or problematic; 51,3% have sufficient and excellent HL levels. Low HL level is a problem in many countries. According to the comparative results in 8 European Countries, more than 50% of people in Austria (56.4%), Bulgaria (62.1%), and Spain (58.3%) have inadequate or problematic levels of HL. In addition, more than 40% of people in Germany (46.3%), Greece (44.8%), Ireland (40%), and Poland (44.6%) have inadequate or problematic levels of HL. Only the Netherlands has a high level of HL with a rate of 28.7% (HLS-EU, 2012).

Previous researchers indicate that HL level is related to preventing infections. People with low HL levels do not adopt the behaviors preventing the infectious disease (Castro-Sanchez et. al., 2016). These people are less likely to adopt protective behaviors such as immunization also; they have a poor understanding of medical labels and instructions such as antibiotics and are more likely to misuse medicines than people with higher HL levels (Castro-Sanchez et. al., 2016), (Bennett et. al., 2009). Also, people with low health literacy had a poorer understanding of COVID-19 symptoms, were less able to identify preventive behaviors, and experienced more difficulty finding information and understanding government messaging about COVID-19 than people with adequate health literacy (McCaffery et. al., 2020). According to Abel and McQueen, although critical health literacy argues that individuals put into context the information available and evaluate that against their fundamental values, in the case of an urgent pandemic, concerted action is also essential.[19] In line with the previous research findings, we found a statistically significant relationship between the overall HL level and being caught Covid-19.
We also researched the relationship between sociodemographic features and catching Covid-19. We found a statistically significant difference between gender (p=0,00), age (p=0,047), education (p=0,000), marital status (p=0,013) groups. However, we couldn't see a statistically significant difference in the occupational and income groups.

In gender group, men being caught in Covid-19 more than women. This can be related to the difference between the health literacy level of men and women. Some previous studies found men have fewer HL levels than women (Emiral et. al., 2018), (Cho et. al., 2008). In the research related to adopting the proper practices about the COVID-19, behaviors such as staying at home, wearing masks outside, and washing hands were researched, and found women were more adopted this behavior than men (Şirin et. al., 2020).

Looking at the age group, we found that 50-65 and 65 and above were proportionately more caught in Covid-19 than other groups. These results may be affected by older adults' health behavior and HL level

because some studies show that HL levels decrease with age (McCaffery et. al., 2020). In the study done in the US, 29% of older people reported in fair or poor health status, and 27% to 39% of them reported not utilizing three recommended preventive health care services.[13] However, in another study done Türkiye, older respondents found better at Covid-19 preventive practices.[21] In addition, some studies related to HL couldn't find a statistically significant difference between age groups (Okan et. al., 2020), (Emiral et. al., 2018).

Reviewing educational groups, we have seen that low-educated people (primary school degree) have been caught in Covid-19 more than graduates. Low educated people less adopted the correct practices (handwashing and mask-wearing) about COVID-19 than other groups (Şirin et. al., 2020). Most studies related to HL found a significant difference between primary school and graduate levels (Emiral et. al., 2018).

The present study found that married people have been caught in Covid-19 more than singles. It may not be related to the HL level. Because some studies found statistically significant differences between single and married people in terms of HL (Liu et. al., 2015), (Joveini et. al., 2019); other studies could not (Maricic, Curujiva, and Stepovic, 2020). In addition, one study found that single people have more HL levels (Joveini et. al., 2019) and another found that married people have (Liu et. al., 2015). Catching Covid-19 may be related to the infectious nature of Covid-19. Living with more people increases the risk of being Covid-19.

We couldn't find the statistically significant difference between monthly income groups and occupational groups regarding catching Covid-19. Studies researching HL levels also didn't find a significant difference between income group (Okan et. al., 2020), (Emiral et. al., 2018), (Maricic, Curujiva, and Stepovic, 2020). Some previous studies found a difference between occupational groups related to HL (Liu et. al., 2015), other studies could not (Maricic, Curujiva, and Stepovic, 2020).

Because we couldn't encounter a study researching the relationship between Covid-19 and sociodemographic characteristics, comparing the findings is limited to HL studies.
The limitation of this study is limited to the participants of the survey, and we only wanted to show relationship HL level and catch Covid-19.

According to these results, HL level is related to catching Covid-19. As mentioned above, previous studies mostly supported the current study. Therefore, Public health policymakers may give more importance to the HL to decrease the spread of infectious diseases. While making these efforts, older people and people with low educational levels may have prioritized. Thus, possible pandemic disease and its adverse effects on the public can be limited in the future.

5. REFERENCES

Abel, T., D. McQuenn. 2020. Critical health literacy and the COVID-19 crisis, health promotion international, 35:1612–1613, https://doi.org/10.1093/heapro/daaa040.

Alias, N., M.H. Jaafar, M. Lokman. 2022. Kapsam Belirleme İncelemesi: Malezya'daki Aborjinler Arasındaki Parazit Kontrol Uygulamaları Hakkında Sağlık Okuryazarlığı Açıklıkları, OTJHS, 7(1):156-164, https://doi.org/10.26453/otjhs.981964.

Bennett, I.M., J. Chen, J.S. Soroui, S. White. 2009. The contribution of health literacy to disparities in self-rated health status and preventive health behaviors in older adults. Ann Fam Med., 7(3):204-211. https://doi.org/10.1370/afm.940.

Castro-Sánchez, E., P.W.S. Chang, R. Vila-Candel, A.A. Escobedo, A.H. Holmes. 2016. Health literacy and infectious diseases: why does it matter? Int J Infect Dis. 43:103-110, https://doi.org/10.1016/j.ijid.2015.12.019.

Cho, Y.I., S.Y.D. Lee, A.M. Arozullah, K.S. Crittenden. 2008. effects of health literacy on health status and health service utilization amongst the elderly. Soc Sci Med. 2008; 66: 1809-1816, https://doi.org/10.1016/j.socscimed.2008.01.003.

Committee on Health Literacy. 2004. Board on neuroscience and behavioral health, and institute of medicine, health literacy: a prescription to end confusion. National Academies Press, Washington, D.C., p. 10883, https://doi.org/10.17226/10883.

Diviani, N., B. van den Putte, S. Giani, J.C. van Weert. 2015. Low health literacy and evaluation of online health information: a systematic review of the literature. JMIR, 17(5):1-17, https://doi.org/10.2196/jmir.4018.

Duong, T.V., A. Aringazina, G. Baisunova, T.V. Pham, K.M. Pham, T.Q. Truong, et al. 2017. Measuring health literacy in Asia: Validation of the HLS-EU-Q47 survey tool in six Asian countries. J Epidemiol. 27: 80–86, https://doi.org/10.1016/j.je.2016.09.005.

Emiral, G., H. Aygar, B. Atalay, S. Göktaş. 2018. Health literacy scale-european union-q16: a validity and reliability study in Turkey. Int. Res. J. Med. Sci., 6(1): 1-7.

European Centre for Disease Prevention and Control. 2012. A rapid evidence review of interventions for improving health literacy : insights into health communication. LU: Publications Office. Available: https://data.europa.eu/doi/10.2900/20189 (Accessed: Feb. 17, 2022).

HLS-EU Consortium. 2014. Comparative Report of Health Literacy in Eight EU Member States. The European Health Literacy Survey HLS-EU (Second Revised and Extended Version, Date July 22th 2014) p. 32.

Joveini, H., A. Rohban, P. Askarian, M. Maheri, and M. Hashemian. 2019. "Health literacy and its associated demographic factors in 18–65-year-old, literate adults in Bardaskan, Iran," J. Educ. Health Promot., 8: 244, https://dx.doi.org/10.4103%2Fjehp.jehp_26_19.

Liu, Y. et al. 2015. "The health literacy status and influencing factors of older population in Xinjiang," Iran J Public Health, 44 (7): 913-919.

Maricic, M., R.A. Curuvija, and M. Stepovic. 2020. "Health literacy in female – association with socioeconomic factors and effects on reproductive health," Serbian J. Exp. Clin. Res., 2020; 21 (2):127–132. https://doi.org/10.2478/sjecr-2018-0055.

McCaffery, K. et al. 2020. "Health literacy and disparities in COVID-19–related knowledge, attitudes, beliefs and behaviours in Australia," Public Health Res. Pract, 30 (4):1-9, https://doi.org/10.17061/phrp30342012.

Mukaka, M.M. 2012. "Statistics corner: a guide to appropriate use of correlation coefficient in medical research." Malawi medical journal: the journal of Medical Association of Malawi vol. 24,3: 69-71.

Nguyen, H., B. Do, K. Pham, G. Kim, H. Dam, T. Nguyen, et al. 2020. Fear of COVID-19 scale associations of ıts scores with health literacy and health-related behaviors among medical students. Int J Environ Res Public Health, 17(11): 1-14, https://doi.org/10.3390/ijerph17114164.

Norman, C.D., H.A. Skinner. 2006. E-health literacy: essential skills for consumer health in a networked world. JMIR, 8(2):1-10, https://doi.org/10.2196/jmir.8.2.e9.

Okan, O., T.M. Bollweg, E.M. Berens, H. Klaus, B. Ullrich, D. Schaeffer. 2020. Coronavirus-related health literacy: a cross-sectional study in adults during the COVID-19 infodemic in Germany. Int. J. Environ. Res. Public Health, 17(15):1-14, https://doi.org/10.3390/ijerph17155503.

Paakkari, L., O. Okan. 2020. COVID-19: health literacy is an underestimated problem. Lancet Public Health, 5:249-250, https://doi.org/10.1016/S2468-2667(20)30086-4.

Schillinger, D., K. Grumbach, J. Piette, F. Wang, D. Osmond, C. Daher, et al. 2002. Association of health literacy with diabetes outcomes. JAMA, 288(4):475-482, https://doi.org/10.1001/jama.288.4.475.

Sorensen, K. 2013. The European health literacy survey. in L. Hernandez, Health literacy: ımproving health, health systems, and health policy around the world: Workshop Summary USA: The National Academic Press; 2013; pp:63-64.

Şirin, H., et al. 2020. "Community approach towards COVID-19 in Turkey: one month after the first confirmed case," Turk. Bull. Hyg. Exp. Biol., 77 (4): 381–398, https://dx.doi.org/10.5505/TurkHijyen.2020.87059.

Xu, C., X. Zhang, Y. Wang. 2020. Mapping of health literacy and social panic via web search data during the COVID-19 Public Health Emergency: Infodemiological Study. JMIR, 22(7):1-8 https://doi.org/10.2196/18831.

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JOURNAL OF HEALTH SCIENCES
A. J. Health Sci.

Volume 4, No 2 | Summer 2022, 90-103

REVIEW ARTICLE

NANO FORMULATIONS AS DRUG DELIVERY SYSTEMS

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RECEIVED DATE: 10.06.2022, ACCEPTED DATE: 21.07.2022

Abstract:
Classical drug forms are used frequently and in repeated doses. Undesirable situations may occur when the dose used for the concentration of the active substance released into the system falls below the sufficient amount or rises above the toxic level. As a result of the developments achieved in nanotechnological research, nanoparticles, which have many applications in the clinic, have made a significant impact in the pharmaceutical industry. The practical use of nanoparticles in applications such as direct binding to the active substance, entrapment and targeting in the pharmaceutical industry has made nanoparticles a preferred position. When implanted systems with nanocarriers reach the target area, uptake in organs, tissues and cells increases. These structures use active and passive targeting strategies to deliver the active substance to the targeted cells. The use of nanocarriers in drug delivery systems provides many advantages. The results obtained from the studies carried out so far are that, thanks to the targeting of cancer drug-loaded nanocarriers, treatment alternatives with higher selectivity have emerged. In this study, nanoparticles as drug delivery are discussed and how to increase bioavailability with nanoparticles is discussed with their advantages.

Keywords: Nanoparticles, Drug Delivery Systems, Nanotechnology

1. INTRODUCTION

Classical drug forms are used frequently and in repeated doses. Undesirable situations may occur when the dose used for the concentration of the active substance released into the system falls below the sufficient amount or rises above the toxic level Nanoparticles have unique optical, electrical and thermal properties and are reported to have an indispensable role in many fields such as medicine, diagnostics, imaging, sensing, genetics, artificial implants and tissue engineering (Danckwerts and Fassihi, 1991). The active substance concentration in the blood is kept constant for a long time at the desired therapeutic level and the elimination of the active substance in the body is reduced. Thus,

active substance use is realized and the benefit to be obtained from the drug is increased (Zhang et. al., 2008). One of the main problems in pharmaceutical and biotechnological fields is to transport the drug to the structure where it will act. Therefore, drug delivery systems have always been the focus of attention of researchers (Wang et. al., 2008). Developments in biotechnology and research in other branches of science related to this field help the discovery and rational design of new drugs (Chien and Lin, 2007). Today, new developing technologies are used to minimize the problems that arise in the use of drugs. For this purpose, researchers working in different disciplines are brought together and the developments obtained are transformed into clinical effectiveness. Targeted drug delivery systems enable drugs to be delivered to the target more effectively and more practically than today's drugs. Due to the fact that patients generally have a geriatric disorder, it becomes difficult to follow up on the patients' relatives and caregivers following their medications. As a result, the patient refuses the drug due to the agitation caused by the disease. As a result of the developments achieved in nanotechnological researches included in this study, nanoparticles, which have many applications in the clinic, have made a significant impact in the pharmaceutical industry. The practical use of nanoparticles in applications such as direct binding to the active substance, entrapment and targeting in the pharmaceutical industry has made nanoparticles a preferred position. Nanocarriers provide the delivery of targeted drugs to the diseased structure. Thanks to the nanoparticle researches, it is possible to diagnose and treat many diseases today. In addition, due to the potential of application in drug delivery systems, it shows a rapid development in the field of health. It is taking place more and more in drug delivery system technology with each passing day (Değim, 2011). The effect of other branches of science on the field of health and the process of replacing traditional drugs with new drugs has accelerated thanks to the developing nanotechnological applications. In this process, new drugs are produced thanks to the developments in nanotechnology and biotechnology, and pharmaceutical technology applications.

2. DRUG DELIVERY SYSTEMS

One of the main problems in pharmaceutical and biotechnological fields is the transfer of the drug to the structure where it will act. Today, newly developing technologies are used to minimize the problems that arise in the use of drugs. And thanks to the studies carried out, specific drug delivery systems are developed. Targeted drug delivery systems enable drugs to be delivered to the target more effectively and more practically than today's drugs. Thanks to all these developed systems, the patient's compliance increases and the half-life of the drug is extended. As a result, health expenditures are reduced. In recent years, there has been an increasing interest in drug delivery systems (Allen & Ansel, 2013).

Drug delivery systems provide the followings (Tiwari et al., 2012):

i. They make active substances with low solubility soluble and thus increase their bioavailability.
ii. Drugs are delivered to the target tissue by crossing various anatomical and biological structures such as the blood-brain barrier, bronchioles in the respiratory system and tight junctions in the skin.

iii. Having the size of nanoparticles allows them to accumulate in areas with weak vascularity.
iv. Specific ligands can be targeted by binding.
v. They can be produced in large quantities, easily and reproducibly.
vi. They can protect the active substance in them from inactivation in the biological environment and undesirable side effects are not observed.

Drug delivery systems are divided into various classes as micelles, dendrimers, liposomes, nanoparticles and carbon nanotubes (Tanbour et. al., 2016). Nanocarriers, when the implanted systems reach the target area, uptake in organs, tissues and cells increases. These structures use active and passive targeting strategies to deliver the active substance to the targeted cells. The use of nanocarriers in drug delivery systems provides many advantages. For example, it is preferred in the release of cancer drugs because it reduces the toxic effect of drugs and prevents multi-drug resistance. The results obtained from the studies carried out so far are that treatment alternatives with higher selectivity have emerged thanks to the targeting of cancer drug-loaded nanocarriers (Zhou et. al., 2013). Thanks to this selective targeting, unwanted side effects of drugs are reduced and the most appropriate therapeutic response is obtained.

2. 1. Features Drug Required by Drug Delivery Systems

If we summarize the features that drug delivery systems should have, in items (Kolate et al.,2014); Must not interact with the active substance they carry, must be inert,

i. It should be compatible with the body, it should be degradable in the body, it should not be toxic,
ii. It should be able to carry the active substance in the required time until it reaches the targeted area,
iii. It must be durable in physiological conditions,
iv. It should be pharmaceutically stable,
v. It should be able to carry the required amounts of active substances that are dissolved in both water and oil.
vi. Since they are generally used parenterally, they should be suitable for sterilization.

2. 2. Implantable Drug Carrier Systems

Drug delivery systems, by carrying drugs or radiocontrast agents, ensure safe, controlled and effective delivery of diagnostic imaging and/or therapeutic (theranostic) materials to the target organ or tissue. The most important studies in the field of biopharmaceuticals in recent years are colloidal drug carrier systems and they exist in two forms as semi-solid and solid. When colloidal delivery systems are used, the amount of drug required for treatment is lower than the free drug (Pawar et. al., 2012). Therefore, side and toxic effects of drugs are reduced. Although the preparation technology of colloidal carrier systems is expensive, the reduction of side and toxic effects reduces the cost.

The nanoparticle system consists of the carrier portion and the drug loaded on it. The carrier portion is prepared from synthetic polymers or natural macromolecules (protein, cellulose, etc.). If the system is to be used for diagnostic purposes only, it is not expected to decompose under physiological conditions. However, disintegration is required for those used for treatment. It is expected to be broken down by lysosomal enzymes in the cell it enters by phagocytosis, to provide controlled release and to show its effect (Van Rooij et. al., 2015).

Nanoparticles, nanospheres, nanocapsules, liposomes that are the ancestors of drug delivery systems, niosomes polymeric systems, dendrimers, colloid gold, nano-sized semiconductor crystal structures (quantum dots-QDs), micelles, sphingosomes, microbubbles, microspheres and supermagnetic particles are some of the carrier systems (Wunderlich et. al., 2010). Among the different carrier systems, liposomes are the most remarkable and have the most suitable features for both diagnostic imaging and treatment (Silindir et. al., 2012).

2. 3. Vesicular systems

In cell biology, a vesicle is a relatively small intracellular sac consisting of a closed membrane that stores or transports substances. It is separated by at least one lipid bilayer that separates the vesicle from the cytosol. Drug delivery systems are divided into various classes as micelles, dendrimers, liposomes, nanoparticles and carbon nanotubes. Thanks to these systems, the active substance concentration in the blood is kept constant for a long time at the desired therapeutic level and the elimination of the active substance in the body is reduced (Kirthi et. al., 2011).

2. 3. 1. Liposomes

Liposomes are carrier systems between 30 nm – 1000 nm, containing phospholipids, resembling a cell structure, having hydrophilic and lipophilic parts, and amphiphilic (both oil and water-loving) (Nakayama et. al., 2015). It is the best model for biological membranes. Since it resembles cell structure, it can easily place active substances in the body. Thanks to these features, they are preferred in many areas as drug carriers from dermocosmetics to biotechnology. In terms of cosmetics and dermatology, liposomes have some features (Allen and Cullis, 2013);

1. They have a membranous structure like the barrier layer of the skin. Since they are modeled like artificial cells, they do not have compatibility problems with the skin and cell mem branes in the body.
2. Its membranes easily integrate into the barrier layers of the skin without changing the physical structure.
3. Since they can carry the phosphatidylcholine group to the lower layers of the epidermis, they are effective in the regeneration of the skin.

When phospholipids are added to water, their hydrophilic regions move towards the water, while their hydrophobic regions move away from the water and take the form of vesicles. Hydrophobic interactions between phospholipid and water molecules and van der Waals interactions between phospholipid molecules provide the formation of the bilayer liposome structure. The methods used to prepare liposomes generally involve 3 basic steps (Anwekar et al., 2011):

i. Drying of lipids dissolved in organic solvent
ii. Formation of liposomes in aqueous medium
iii. Analysis of the resulting liposomes

With the understanding that intravenously administered liposomes are digested by the phagocytic system, liposome-mediated drug delivery to macrophages has been achieved. In this way, liposomes have played a role in the development of treatments against parasites in phagocytic cells. Liposomes can also be used for grafting. While preparing the liposome vaccine, water-soluble substances are added to the aqueous region inside the liposome, while lipid-soluble substances are mixed into the lipid layer during vesicle formation (Değim, 2011). These liposomes are absorbed by many cells and release the substances they contain when they enter the cell. These vaccines generally target macrophages and other phagocytic cells (Coelho et. al., 2010). After the liposomes are given to the body by adding the appropriate antigen, they release the antigen in them as soon as they enter the cell. Cells that encounter the antigen produce an immune response.

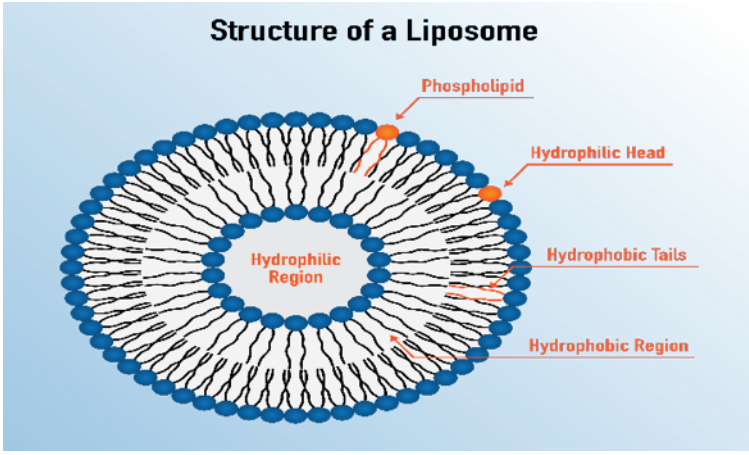

Figure 1. Structure of lipozome (Taghavi et. al., 2013).

2. 3. 2. Niosome

The first use of niosome technology in cosmetics was studied in Loreal's patented products in the 1970s and 1980s. It is expressed as proniosome when introducing the product. The missing point of

this design was that sensitive extra processing was required before using it in the cream, since some steps were skipped in the synthesis of the niosomes (Ge et al., 2019). However, in the new generation niosomes, when it is applied to the skin and interacts with the skin, its activation is provided on its own. The structure called niosome consists of spherical (vesicular) structures synthesized in small sizes. These spheres can also be called smart spheres. Because it is designed to find the damaged area by crossing the skin barriers between the thick layers of your skin.

2. 3. 3. Erythrocyte

The erythrocyte membrane is semi-permeable. It is made up of cholesterol and phospholipids. As a result of the researches, it has been found that cholesterol is effective in the form of erythrocyte. Again, in the membrane structure, there are proteins that form the skeleton of the membrane. Cell organelles such as the endoplasmic reticulum and lysosome in the erythrocyte are also present in the cell at a certain concentration to provide the erythrocyte flexibility. All these structures need to be protected from damage during targeting operations (Dong, 2018). Depending on the active ingredient loading method used, minor changes in the biochemical structure of erythrocytes, such as removal of some sialic acid residues from cell proteins from the cell surface, separation of glycoproteins, increased membrane stiffness, oxidation of sulfhydryl groups in the membrane, can greatly change the general circulation time and biological behavior of these cells in the organism (Xia et. al., 2019).

Loading of active substance into erythrocytes can be done by three methods. These (Luk et al., 2016):

i. Hypoosmotic lysis method
    a. Dilution
    b. Diluting first by swelling,
    c. Dialysis
    d. isoionic osmotic lysis
ii. Electric shock method
iii. Endocytosis method

2. 4. Solid Particulate Systems

Solid lipid nanoparticles are one of the drug delivery systems developed as an alternative to liposome, emulsion and polymeric nanoparticles. The advantage of solid fat over oil in emulsion is that it can provide controlled release. In addition, the stability of the system is high due to the solid oil. The size of solid lipid nanoparticles ranges from 10 to 1000 nm. The substances in their structures are biocompatible and biodegradable (Cancer Research, 2018). In short, solid lipid nanoparticles have great potential to be used as a drug delivery system and to be targeted to the desired region. In recent years, new generation solid lipid nanoparticles have been developed and they are called nano lipid carrier systems (NLC) and lipid-drug conjugates (LDC). These systems consist of a mixture of solid and liquid lipids. In addition to

the properties of solid lipid nanoparticles, they have higher drug loading capacity (Lang et al., 2012). They can be produced in different ways.

2. 4. 1. Microspheres

Microspheres are drug delivery systems in which the active ingredient is dispersed at the molecular level or as macroscopic particles, with a diameter distribution ranging from a few μm to mm, and providing controlled release in the form of solid, spherical particles (Prajapati et al., 2015). It can be used to target the active substance to the site of action by injection into the bloodstream. Thus, it is aimed to reduce the dose of the active substance and to reduce its side effects. Many different materials are used in the preparation of microspheres (non-magnetic).

There are several techniques in which it is used (Schirrmacher, 2019):

1) Solvent Evaporation Method
2) Protein Gelation Methods
    a. Denaturation By Heat
    b. Chemically Crosslinking
    c. Desolvation
3) Emulsion Polymerization Methods
    a. Starch Microspheres Cross-Linked With Epiclohydrin
    b. Cross-Linked Polyacryl Microspheres.

2. 5. Nanoparticles

Nanoparticles are solid colloidal particles ranging in size from 10 to 1000 nm, which release the dissolved, trapped or adsorbed active substance in a controlled manner.

Nanoparticles exist in two forms

c. nanospheres and
d. nanocapsules

Properties expected from nanoparticles (McNamara and Tofail, 2017);

e. Controlled release of the active substance
f. Collecting the active substance in the area where they are expected to affect
g. No stability problems
h. Decomposition of the carrier in the physiological environment and non-toxicity of the degradation products
i. Ability to be sterilized

2. 5. 1. Polymeric Micelles

Polymeric micelles are formed from amphiphilic polymers. Amphiphilic polymers are copolymers containing hydrophilic and hydrophobic units. Polymeric micelles are spherical particles with a size of 100 nm and less formed in the core of hydrophobic blocks and the surrounding hydrophilic corona (Nicolai et. al., 2010). The amphiphilic unimers that make up the micelles exist as polymer chains alone under a certain temperature and concentration. The self-organizing micelle formation of these unimers occurs when entropically above a certain temperature and concentration in aqueous solutions. Theoretically, the formation of micelles occurs with the reduction of free energy (Carpenter et. al., 2012)

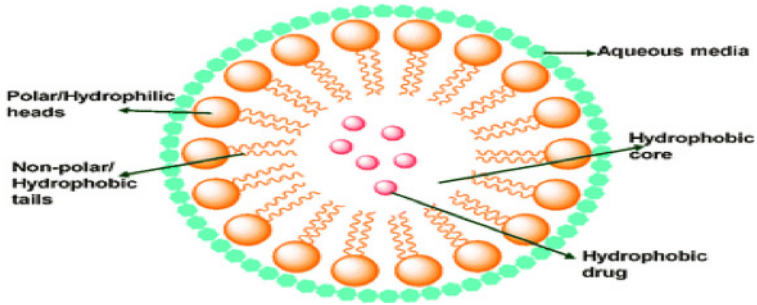

Figure 2. Structure of micelle which polar hydrophilic heads ,non polar hydrophobic talls,aqueous media,hydrophobic core. (Kurtar, 2011)

2. 5. 2. Dendrimers

Dendritic structures are one of the most common structures on earth. In the biological world, the branches and roots of trees, the vascular systems and neurons of animals and plants are the best examples of branched structures. However, it is possible to see this structure in inanimate systems (for example, snow crystals) as well as in living systems (Boas et. al., 2006). In biological systems, these dendritic structures can be in meters like trees, centimeters/millimeters like fungi, or microns like neurons. However, it is still debated whether these structures are evolutionary structures optimized to provide a large interface for energy (Thompson, 2006). Dendrimer consists of a nucleus, branching units around the nucleus, and surface groups, also called functional groups. The diversity of dendrimers is provided by functional groups. Branching units, on the other hand, ensure the repetitive growth of dendrimers (Newcome et. al., 1985). The degree of polymerization of dendrimers is indicated by the concept of generation number, which expresses the repetition cycle.

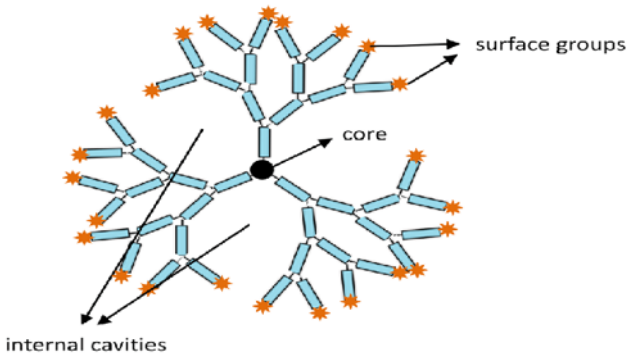

Figure 3. Dendrimer core (Taghavi et. al., 2013).

Having too many chain ends in dendrimers gives dendrimers high solubility and miscibility. The higher the chain ends, the higher the activity. The solubility of dendrimers is directly related to the groups on the surface. Dendrimers ending in hydrophilic groups dissolve well in polar solvents, while dendrimers ending in hydrophobic groups dissolve in nonpolar solvents (Tomalia et al., 1985). Dendrimers have many advantages because they have a spherical structure and have an internal cavity in the middle. The most important of these is that molecules can be trapped in this gap (Martinho et al., 2014). In this way, both the protection of the active substance is ensured and the controlled release of the active substance is achieved. Thanks to their multi-branched structure, groups that provide targeting and structures that increase solubility can be added to dendrimers at the same time. Thanks to the added groups, cytotoxicity can be reduced and biocompatible dendrimers can be obtained. However, it can be ensured that they cross the epithelial barrier. It is possible to add fluorescent substances to the dendrimer structure by conjugation with dendrimers (Gillies and Frechet, 2005).

i. Dendrimers terminate with many functional groups. Various groups can be attached to these functional groups for targeting to a particular part of the body

ii. Dendrimers may show greater permeability and retention to tumor cells than small molecules. Therefore, they can be used in tumor targeting

iii. Another advantage of dendrimers is that they can be synthesized or designed for specific applications. They are ideal drug delivery systems due to their flexible topology, features and dimensions. However, the particle size of dendrimers is quite close to some biological polymers such as DNA (Wei et. al., 2009)

2. 5. 3. Microsponges

Microsponges are patented, microscopic, polymer-based, porous, microspherical systems that can be applied mostly topically, but oral use has also been mentioned in recent studies (Stephen et al.,

2021). Particle size, pore diameter, pore volume and viscoelastic properties of microsponges may vary depending on the properties of the active substance and the desired release time. Pharmaceutical preparations such as creams, soaps, lotions, powders, tablets and capsules can be prepared after the active ingredients are confined to microsponges. Especially when applied to the skin, they cannot pass through the stratum corneum due to their large particle size. They can stay on the skin surface and release the active substance in a controlled manner. Microsponges, which are biologically inert, do not cause toxicity, allergic reaction and irritation (Pan et al., 2009). If we compare microsponges with other microencapsulation products, liposomes and microcapsules, we see that they are more advantageous systems. Since microcapsules control the exit of the active substance with the capsule wall, all of the active substance in the content can be released uncontrollably when this wall is damaged, whereas in microsponge systems, the active substance is released through the pores of the polymeric structure and the system skeleton remains intact (Sobel et al., 2014).

3. NANOPARTICLES AS DRUG DELIVERY SYSTEMS

Healthy cells in living things have the ability to divide in a controlled manner. Thanks to this feature, dead cells are replaced by new ones. With its divisibility, it is possible to repair injured tissues. These systems, which operate smoothly, can be disrupted when under the influence of any disease. As a result of the disease, the need for repair occurs in organs, tissues and cells. In this case, mostly chemical treatment methods are used. As a result of the use of chemical treatment method, healthy cells are also exposed to chemical effects (Wei et. al., 2015). To prevent this, nanocarrier systems have been developed today. Thanks to these structures, damage to healthy organs and cells is prevented and the drug concentration in the cells is increased. Nanocarriers used today make it possible to detect diseases as soon as possible, thanks to a number of diagnostic and diagnostic systems. However, there is a risk of infection to the patient during the application of nanosystems (Rao et. al., 2020). In addition, the patient may feel discomfort due to the procedure performed with the needle. In these systems, the correct symptoms cannot be obtained until the disease reaches a certain level. For this reason, developments in nanotechnology and nanomedicine, which have attracted attention in recent years, have come to the fore. Thanks to research, advances have been made in early diagnosis and treatment in many health fields, thus opening new horizons. An important part of the studies in the field of nanomedicine is to develop nanomaterials with high sensitivity and tissue targeting properties that allow early diagnosis (Nyström and Fadeel, 2012). Nanomedicine is defined as early detection of pathological processes, taking precautions and using them in targeted treatments, and making use of the physical, chemical, electrical, optical and biological properties of organic or synthesized nano-sized materials. Passive and active targeting methods have been developed to ensure that nanocarrier systems reach their target exactly (Attia et. al., 2019). The dendrimers used for this purpose have high solubility and miscibility because there are too many chain ends. The higher the chain ends, the higher the activity rate. Dendrimer solubility is directly related to surface groups. Dendrimers ending in hydrophilic groups dissolve well in polar solvents, while dendrimers ending in hydrophobic groups dissolve better in nonpolar solvents.

3. 1. Advantages of Nanocarriers in Drug Transport

There are some advantages of using a drug delivery system in nanoparticles (Mou et al., 2015). It is possible to define them as follows (Batrakova and Kim, 2015; Su et. al., 2018; Van Rooij et. al., 2015);

a. A nanocarrier can carry both the active substance and the imager at the same time.
b. It can bind to more than one active substance and targeting molecule on a nanocarrier.
c. Thanks to theronostic structures, the release and distribution of the drug can be followed, and the effectiveness of the treatment can be monitored.
d. As a result of increasing the bioavailability of the drug, an effective drug treatment is provided.
e. Targeting is easy due to their nano size.
f. Since it is in nanoparticle size, it easily passes into the veins and mixes into the circulation.
g. As a result of the preparation of nanoparticle formulations, their solubility increases. It increases the absorption of the particle and, accordingly, the bioavailability.
h. Nanoparticles can be targeted to the sick site or to the designated cell, tissue or organ.
i. Drugs, imaging agents, targeting molecules, magnetic materials, temperature and pH sensitive substances can be attached to nanocarriers.
j. Thanks to the polyethylene glycol or polyoxyethylene molecule bonding, it can remain in circulation for a long time.
k. It is suitable for making surface modifications.
l. Providing an effective drug therapy by increasing the bioavailability of the drug. Thus, they are developed to be used in the diagnosis, treatment and monitoring of diseases.
m. It provides a more reliable treatment opportunity when its side effects are reduced.

4. CONSLUSION

In this study, when the chemical structure of nanoparticles is examined, they are formed by adding various molecules, especially phospholipids such as phosphatidylcholine, phosphotidylethanolamine, phosphotidylserine and phosphotidylglycerol, and main lipids such as cholesterol, at different rates. Clinical studies on the efficacy ,these double membrane particles being tested the potential to carry hydrophobic and hydrophilic drugs separately or together and deliver them to the target cell due to their polar and nonpolar properties.The nanoparticles mentioned in this study are; nanospheres, nanocapsules, liposomes, which are the ancestors of drug delivery systems, niosomes polymeric systems, dendrimers, colloid gold, nano-sized semiconductor crystal structures (quantum dots-QDs), micelles, sphingosomes, microbubbles, microspheres and supermagnetic particles are some of the carrier systems. Thus, the accumulation of the drug in healthy tissues decreases, allowing the drug levels in the tumor tissue to increase. The aim of this is to summarize how far nanotechnology has progressed and the latest developments. how to increase bioavailability with nanoparticles is discussed with their advantages.

5. REFERENCES

Allen, L., and H.C. Ansel. 2013. Ansel's pharmaceutical dosage forms and drug delivery systems. Lippincott Williams & Wilkins.

Allen, T.M., and P.R. Cullis. 2013. Liposomal drug delivery systems: from concept to clinical applications. Advanced drug delivery reviews, 65(1), 36-48.

Anwekar, H., S. Patel, and A.K. Singhai. 2011. Liposome-as drug carriers. International journal of pharmacy & life sciences, 2(7).

Asgher, M., S.A. Qamar, and H. Iqbal. 2021. Microbial exopolysaccharide-based nano-carriers with unique multi-functionalities for biomedical sectors. Biologia, 76(2), 673-685.

Attia, M.F., N. Anton, J. Wallyn, Z. Omran, and T.F. Vandamme. 2019. An overview of active and passive targeting strategies to improve the nanocarriers efficiency to tumour sites. Journal of Pharmacy and Pharmacology, 71(8), 1185-1198.

Batrakova, E.V., and M.S. Kim. 2015. Using exosomes, naturally-equipped nanocarriers, for drug delivery. Journal of Controlled Release, 219, 396-405.

Bazak, R., M. Houri, S. El Achy, W. Hussein, and T. Refaat. 2014. Passive targeting of nanoparticles to cancer: A comprehensive review of the literature. Molecular and clinical oncology, 2(6), 904-908.

Begines, B., T. Ortiz, M. Pérez-Aranda, G. Martínez, M. Merinero, F. Argüelles-Arias, and A. Alcudia. 2020. Polymeric nanoparticles for drug delivery: Recent developments and future prospects. Nanomaterials, 10(7), 1403.

Danckwerts M, and A. Fassihi. 1991. Implantable controlled release drug delivery systems: A review. Drug. Dev. Ind. Pharm,; 17(11): 1465-1502.

De, S., R. Kundu, and A. Biswas. 2012. Synthesis of gold nanoparticles in niosomes. Journal of colloid and interface science, 386(1), 9-15.

Değim, İ. 2011. Farmasötik Nanoteknoloji. Mised.; S: 8-13; S: 198–205.

Deirram, N., C. Zhang, S.S. Kermaniyan, A.P. Johnston, and G.K. Such. 2021. pH-responsive polymer nanoparticles for drug delivery. Macromolecular rapid communications, 40(10), 1800917.

Derman, S., K. Kızılbey, Z. Akdeste. 2013. Polymerıc Nanopartıcles. Journal of Engineering and Natural Sciences Mühendislik ve Fen Bilimleri Dergisi Sigma; 31, 109- 122.

Dong, X. 2018. Current strategies for brain drug delivery. Theranostics, 8(6), 1481.

Dreaden, E.C., A.M. Alkilany, X. Huang, C.J. Murphy, and M.A. El-Sayed. 2012. The golden age: gold nanoparticles for biomedicine. Chemical Society Reviews, 41(7), 2740-2779.

Eşim, Ö. 2020. Platine dirençli over kanseri tedavisine yönelik nanopartiküler ilaç taşıyıcı sistemlerin geliştirilmesi ve değerlendirilmesi.

Fung, L.K., and W.M. Saltzman. 1997. Polymeric implants for cancer chemotherapy. Advanced drug delivery reviews, 26(2-3), 209-230.

Francia, V., C. Reker-Smit, G. Boel, and A. Salvati. 2019. Limits and challenges in using transport inhibitors to characterize how nano-sized drug carriers enter cells. Nanomedicine, 14(12), 1533-1549.

Ge, X., M. Wei, S. He, and W.E. Yuan. 2019. Advances of non-ionic surfactant vesicles (niosomes) and their application in drug delivery. Pharmaceutics, 11(2), 55.

Gillies, E.R., and J.M. Frechet. 2005. Dendrimers and dendritic polymers in drug delivery. Drug discovery today, 10(1), 35-43.

Gunaseelan, S., K. Gunaseelan, M. Deshmukh, X. Zhang, and P.J. Sinko. 2010. Surface modifications of nanocarriers for effective intracellular delivery of anti-HIV drugs. Advanced drug delivery reviews, 62(4-5), 518-531.

Gupta, V., and S.K. Nayak. 2015. Dendrimers: a review on synthetic approaches. J. Appl. Pharm. Sci, 5(03).

Hawthorne, M.F. 1993. The role of chemistry in the development of boron neutron capture therapy of cancer. Angewandte Chemie International Edition in English, 32(7), 950-984.

Juneja, R., and I. Roy. 2018. Iron oxide-doped niosomes as drug carriers for magnetically targeted drug delivery. International journal of nanomedicine, 13(T-NANO 2014 Abstracts), 7.

Jun, H.K., M.A. Careem, and A.K. Arof. 2016. Plasmonic effects of quantum size gold nanoparticles on dye-sensitized solar cell. Materials Today: Proceedings, 3, S73-S79.

Kannan, R.M., E. Nance, S. Kannan, and D.A. Tomalia. 2014. Emerging concepts in dendrimer-based nanomedicine: from design principles to clinical applications. Journal of internal medicine, 276(6), 579-617.

Karabulut, B., O. Kerimoğlu, and T. Uğurlu. 2015. Dendrimerler-ilaç taşıyıcı sistemler. Clinical and Experimental Health Sciences, 5(1), 31-40.

Klajnert, B., and M. Bryszewska. 2001. Dendrimers: properties and applications. Acta biochimica polonica, 48(1), 199-208.

Kohli, K., S. Chopra, D. Dhar, S. Arora, and R.K. Khar 2010. Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability. Drug discovery today, 15(21-22), 958-965.

Kolate, A., D. Baradia, S. Patil, I. Vhora, G. Kore, and A. Misra. 2014. PEG—a versatile conjugating ligand for drugs and drug delivery systems. Journal of controlled release, 192, 67-81.

Kontermann, R. 2012. Dual targeting strategies with bispecific antibodies. In MAbs (Vol. 4, No. 2, pp. 197-182). Taylor & Francis.

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JOURNAL OF HEALTH SCIENCES
A. J. Health Sci.

Volume 4, No 2 | Summer 2022, 104-116

REVIEW ARTICLE

DIAGNOSIS AND TREATMENT METHODS OF AUTOIMMUNE MYASTHENIA GRAVIS: A SYSTEMATIC REVIEW

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RECEIVED DATE: 17.06.2022, ACCEPTED DATE: 20.07.2022

Abstract

Myasthenia Gravis (MG), which is an autoimmune disorder, causes abnormalities in the neuromuscular junction and has a prevalence of 15-20 per 100,000 people. Although skeletal and extraocular muscles are commonly affected by the disease, approximately 10% of patients have severe involvement in the muscles necessary for respiration. A myasthenic crisis may cause life-threatening consequences. The prevalence and incidence of autoimmune MG increase with age. Women's disease incidence peaks between the ages of 30 and 40, while men's incidence peaks between the ages of 60 and 80. The existence of autoantibodies against postsynaptic membrane proteins is the most crucial indicator of MG. Anti-AChR (acetylcholine receptor antibody) positive is a distinct feature of MG (% 80). While anti-MuSK (muscle-specific kinase antibody) positivity is detected in 1-10% of all patients, LRP4 (low density lipoprotein receptor related protein 4) antibody positivity is seen in 3-25% of MG patients without AChR and MuSK antibodies (anti-LRP4). Despite many methods used in the diagnosis of MG, it is not possible to make the diagnosis in some patients because of conditions that may vary from patient to patient, such as fluctuation in symptoms and clinical findings. Rapid diagnosis is crucial in patients with MG, because effective treatment must begin as early as possible to prevent potentially fatal complications. Moreover, rapid diagnosis of patients and determination of the patient's subtype is an important step in the treatment process. Therefore, the aim of this study is to summarize the techniques used in the diagnosis and treatment of MG which is one of the rare diseases.

Keywords: Myasthenia Gravis; Diagnosis Methods; Treatment Methods; Rare Diseases; Neuromuscular Disorders; Autoimmune Disorders

1. INTRODUCTION

MG is an autoimmune disease that causes a postsynaptic neuromuscular conduction abnormality that can be caused by a variety of factors including toxicity, immunology, or genetics (Sieb, 2014). The immune system can distinguish between the body's cells and tissues and does not produce antibodies against its antigens. However, autoimmune diseases, such as MG, are caused by the body's inability to tolerate its cells and tissues. The body's immune response is compromised and it begins to produce autoantibodies against its antigens. As a result, the body's cells and tissues, which are the target of the immune response, are damaged (Lleo et al., 2010; Ngo et al., 2014). MG develops in individuals who are genetically predisposed and subjected to trigger conditions, just like autoimmune diseases. Infections, surgery, drugs and immunization can all be triggering factors. Muscle weakness is a symptom of this condition. The production of autoantibodies against postsynaptic membrane proteins results in a reduction in the transmission of electrical impulses at the neuromuscular junction, resulting in muscle weakness (Beloor Suresh and Asuncion, 2022).

MG can lead to a whole slew of complications. The most serious of these is respiratory muscle involvement, which is known as myasthenic crisis and necessitates immediate medical attention. It commonly affects ocular, bulbar, oculobulbar, limbs and respiration muscles. Long-term medication therapy can cause adverse events such as opportunistic infections and lymphoproliferative cancers (Beloor Suresh and Asuncion, 2022). The commencement of MG is marked by ocular muscle weakness, which is apparent in the majority of patients. Diplopia and ptosis develop as the condition worsens. Oropharyngeal weakness causes difficulties in chewing, articulation and swallowing. MG is categorized based on symptoms, onset age and treatment requirements (Sieb, 2014).

2. DIAGNOSIS OF MG

Clinical symptoms of patients are an important indicator in the diagnosis of MG. The clinical symptoms are double vision, drooping eyelids and weakness/fatigue in the bulbar, extremity and cervical muscles (Yavuz, 2019). Moreover, other symptoms may be a coexistence of droopy eyelids, facial paralysis greater effort to make a sound, exhaustion and weakness in neck muscles. Additionally, unexplained muscle weakness and symptoms that worsen with exercise may be seen. Furthermore, there are variable symptoms such as increased nighttime fatigue or symptoms that exacerbate the menstrual period and a cyclical increase in symptoms that occurs every few months or weeks.

Several tests are performed on patients who present with the suspicion of MG with these symptoms, both to diagnose and to determine the MG subgroup, which has a substantial impact on the treatment method.

The initial step to be applied to the patient is a serological test. First, anti-AChR and anti-MuSK are examined. If the test results are positive, additional testing may not be required (Gilhus and Verschuuren, 2015; Gilhus et al., 2019). Thymus and thyroid tests, on the other hand, may be performed to rule out other disorders. Nevertheless, many competent sources show a high false-positive rate for MG (Shelly et al., 2020; Pasnoor et al., 2018).

Electrophysiological examinations are the next step for seronegative patients who do not have anti-AChR or anti-MuSK. Because it is more accessible, repetitive nerve stimulation (RNS) is utilized first. It is quite specific, though less sensitive. When RNS yields a negative result, single fiber electromyography (SFEMG) is conducted. It would be wise to include as many muscles as possible in the tests (Meriggioli and Sanders, 2004). Instead of electrophysiological tests, the edrophonium test might be utilized as a secondary diagnostic step. However, it is difficult to access. The ice pack test is also advised, particularly for ocular-MG (Rousseff, 2021). Despite numerous diagnostic procedures, it is difficult to detect and distinguish the disease at its onset from other disorders.

2. 1. Serological Test

A specific diagnostic approach for MG is determining the anti-AChR levels in serum and additional testing may not be required. It can also be used to identify disease subgroups (Rousseff, 2021; Vincent et al., 2018). However, it does not provide information about the severity or course of the disease. This approach is 85 percent sensitive in individuals with generalized MG and 50 percent sensitive in people with ocular MG (Lennon, 1997; Vincent and Newsom-Davis, 1985). The probability of false positives is less than five percent in patients with Lambert-Eaton myasthenic syndrome (LEMS), three or five percent in patients with motor neurons and less than one percent in patients with polymyositis (Dincer, 2015). The radioimmunoprecipitation (RIP) is the most commonly used anti-AChR test (Lazaridis and Tzartos, 2020). Normal reference values vary per laboratory but are usually between 0.03 and 0.5 nmol/L (Yavuz, 2019) Anti-MuSK testing should be performed on suspected patients who test negative for anti-AChR. These tests are known as radioimmunoprecipitation (RIP) or enzyme-linked immunosorbent assays (ELISA). Anti-MuSK antibodies are detected in 6-8% of cases (Rousseff, 2021).

Anti-LRP4 testing should be performed on MG patients who are anti-AChR and anti-MuSK negative. The prevalence of anti-LRP4 in patients ranges from 2 to 50%. Anti-LRP4 positivity has also been observed in patients with amyotrophic lateral sclerosis (ALS), various neuroimmune disorders, including MuSK-MG. As a result, anti-LRP4 is not a particular MG diagnostic technique (Frykman et al., 2020; Zhang et al., 2012).

The presence of antibodies against actin, titin, -actinin, myosin and ryanodine receptors in the serum of MG patients may raise the possibility of thymoma. The presence of these antibodies in EO-MG patients raises the risk of developing thymoma. They are not, however, specific for MG because these antibodies

are also present in individuals who do not have thymoma or in people who have thymoma but do not have MG. Furthermore, titin and ryanodine antibodies are a predictor of the severity of the disease in LO-MG individuals who develop MG after the age of 40 (Dincer, 2015; Yavuz, 2019).

2. 2. Electrophysiological Tests

Diagnosis with this method can be effective in seronegative MG patients or in situations where rapid results are required. It not only determines the neuromuscular disorder but also can make a differential diagnosis from other neuromuscular disorders. It has two different methods: (1) repetitive nerve stimulation (RNS) and (2) single fiber electromyography (SFEMG) (Meriggioli and Sanders, 2004)

2. 2. 1. Repetitive Nerve Stimulation (RNS):

The goal of this test method is to determine the factor of safety and a muscle is successively stimulated with frequencies of 2Hz or 5Hz. If the first and fifth impulse muscle action potentials decline by 10% (decremental response), this is indicative of MG. When patients who were unable to be diagnosed the first time get weary after 1 minute of activity, the test is repeated and a secondary decrement is sought. Significant results are found in 75% of generalized MG patients and 50% of ocular MG patients (Dincer, 2015; Oh et al., 1992).

2. 2. 2. Single Fiber Electromyography (SFEMG):

It is the most sensitive approach to diagnosing MG, which determines a single muscle fiber's action potential. The action potentials of two muscle fibers stimulated by the same axon are monitored and the temporal fluctuation between them is referred to as "jitter." The jitter response increases as the NMJ safety response decreases in MG. The test is diagnostic in 90 to 95 percent of MG patients when conducted appropriately. Abnormal jitter is present in 50% of ocular-MG patients and 85% of generalized MG patients. For differential diagnosis from other NMJ patients, routine needle electromyography EMG should be conducted (Dincer, 2015; Gwathmey and Burns, 2015; Yavuz, 2019).

2. 3. Edrophonium Test

Edrophonium chloride, which is an acetylcholinesterase inhibitor, is only effective for a short period and is reversible. The patient is given 10 mg of edrophonium intravenously. By inhibiting the acetylcholinesterase enzyme, it amplifies the action of acetylcholine in NMJ. As a result, it improves extraocular muscle signs such as ptosis. The sensitivity for MG ranges from 71% to 95%. The test is not advised since it may yield negative results in anti-MuSK-MG patients. As an alternative to edrophonium, neostigmine can be used by injecting intramuscularly. It may take five to ten minutes for the healing effect and be recommended for diagnosis in young children (Evoli and Padua, 2013; Pasnoor et al., 2018).

2. 4. Ice Pack Test

For 2-5 minutes, an ice pack is administered to the eye with drooping eyelids. The acetylcholinesterase

enzyme is suppressed by cold action. This slows acetylcholine breakdown, resulting in a transient improvement in NMJ signal transduction. A positive test is indicated by an improvement of more than 2 mm in the eyelid. It is specific for 80-90 percent MG (Rousseff, 2021).

2. 5. Imaging

Radiological investigations for thymus pathology should be conducted in MG patients. These tests may include computed tomography (CT) and magnetic resonance imaging (MRI). CT scans have a sensitivity of more than 90% for thymoma and 30-60% for thymic hyperplasia. Patients with anti-AChR MG who were not thymectomized should have their thymus examined every five years (Berrih-Aknin et al., 2014; Sieb, 2013).

3. TREATMENT OF MG

The therapeutic strategy used for MG is patient-specific. It is calculated by taking into account the patient's age, the severity and the symptoms of the condition. As a result, it necessitates continual monitoring and attentive follow-up. There are four fundamental therapeutic methods (Dincer, 2015). These are: (1) Symptomatic therapy (acetylcholinesterase inhibitors), (2) Immunosuppressive therapy, (3) Immunomodulatory therapy (IVIg and Plasmapheresis), (4) Surgical intervention (thymectomy)

3. 1. Acetylcholinesterase Inhibitor

These medications are used to treat symptoms without impacting the disease's immunological system. It stops AChE from destroying acetylcholine in the NMJ, allowing it to persist in the synaptic cleft for a longer period. This ensures that neuromuscular conduction is accurate. Mestinon (pyridostigmine bromide) is the most often used acetylcholinesterase inhibitor. Other inhibitors that can be employed include pyridostigmine (neostigmine bromide) and mytelase (ambenonium chloride). These acetylcholinesterase inhibitors are given when symptoms develop and expecting to fade or lessen within 1-2 hours (Pascuzzi, 2003).

Acetylcholinesterase inhibitor medicines are not recommended in anti-MuSK positive patients since they can have negative side effects. On the other hand, while some patients show significant improvement, which may be adequate treatment, some patients have little or no effect (Gwathmey and Burns, 2015).

In patients without thymoma, patients with regional improvement following thymectomy and individuals with only ocular-MG, acetylcholinesterase inhibitors are the only therapy options (Dincer, 2015).

3. 2. Immunosuppressive Therapies

Several drugs are used in immunosuppressive therapies, which have different effective mechanisms. These drugs and their mechanisms are detailed in Table 1.

Table 1. Immunosuppressive medications used to treat MG and their mechanisms of action [Jayam Trouth et al., 2012; Melzer et al., 2016; Yavuz, 2019]

Drug	Effect mechanism
Corticosteroids	It causes T cell death, lowers cytokine gene transcription, and impairs dendritic cell maturation.
Azathioprine	It reduces serum anti-AChR levels. It functions as a purine analog. It inhibits nucleic acid synthesis. It inhibits the proliferation of T and B cells.
Mycophenolate mofetil	It limits T and B cell proliferation and briefly inhibits purine synthesis. It inhibits the production of antibodies that are involved in complement-dependent degradation. It suppresses cytotoxicity.
Methotrexate	It is an antimetabolite, an analog of folic acid. It inhibits the enzyme dihydrofolate reductase as well as lymphocyte proliferation.
Cyclophosphamide	It is nitrogen mustard that acts as an alkylating agent. It creates DNA crosslinks by introducing an alkyl group into the DNA. It affects DNA replication.
Cyclosporine	It inhibits the synthesis of proteins required for the function of IL-2 cytokine receptors and CD4+ T cells.
Tacrolimus	It functions as a calcineurin inhibitor. It suppresses the activation and development of antigen-specific lymphocytes. It also prevents lymphocytes from performing efficient activities.
Rituximab	It is a monoclonal IgG1 antibody that targets the CD20 antigen. CD20 B cell surface activation promotes differentiation and growth.
Eculizumab	It is an IgG 2/4k human monoclonal antibody. It interacts with the C5 complement protein, blocking the activation of endpoint complement.

3. 2. Immunomodulatory Therapy

Plasma exchange (plasmapheresis) or intravenous immunoglobulin (IVIg) therapy may be considered in patients who have an aggravation of symptoms. It is utilized as a therapeutic approach in patients with severe MG who have not responded to previous immunosuppressive or symptomatic treatments. The therapy approach used is determined by the patient's characteristics. Plasmapheresis is not an option for patients with sepsis and IVIg is not an option for individuals with renal failure. Because the treatment effect is only temporary, it should be used in conjunction with immunosuppressive therapy. It can be repeated as the treatment's effectiveness fades.

3. 2. Intravenous immunoglobulin (IVIg):
Immunoglobulins are separated from human plasma collected from hundreds of donors using ethanol cryoprecipitation and given to patients at a dose of 0.4 g/kg/day for 5 days. Within a week, healing begins and the impact lasts for several months. IVIg has several therapeutic effects. It prevents cytokines from competing with autoantibodies, T cells from recognizing antigens, the synthesis of anti-AChR and complement-dependent degradation. It also affects the expression and activity of Fc receptors on macrophages. Moreover, it inhibits the binding of Ig receptors on the surface of B cells (Jayam Trouth et al., 2012; Samuelsson et al., 2001).

Plasmapheresis is frequently advised as IVIg therapy is less successful in anti-MuSK positive individuals. However, IVIg therapy is a more acceptable treatment because it has fewer adverse effects. Recovery is seen in 50-100 percent of patients (Yavuz, 2019).

3. 3. 2. Plasma Exchange (Plasmapheresis):
It entails exchanging two or three liters of plasma three times per week. Healing usually begins after the second and third iteration and treatment continues for about 5-6 replacements until it stabilizes. Plasmapheresis can be applied intermittently to patients with severe exacerbation of symptoms, before surgical interventions such as thymectomy, patients who are resistant to all treatments and generally to patients with respiratory involvement (Conti-Fine et al., 2006; Yavuz, 2019).

3. 4. Surgical Intervention
The thymus plays a significant part in the pathogenesis of MG by inducing anti-AChR production (Marx et al., 2013). Thymic pathology occurs in 80-90% of MG patients and is most subtle in seronegative MG. Thymic hyperplasia occurs 60-70% of anti-AChR-positive MG patients while thymoma occurs10-15% patients. Because of these cases, thymectomy is a surgical procedure performed in patients with MG. Patients with MG who develop thymoma benefit from thymectomy, which removes the thymus. However, it has been suggested that in EO-MG patients, total thymectomy would be advantageous without waiting for the development of thymoma. In numerous studies, patients who applied thymectomy showed greater improvement than patients who received other treatments (Gronseth and Barohn, 2000). In MG patients, thymectomy results in 54-94% improvement and 13-46% remission (Murai et al., 2006). The remission rate is roughly 35% if the operation is performed within the first two years of the disease, but it lowers if the operation is delayed. The effect of thymectomy is long-lasting and begins within a few months. Antibody levels drop or eliminate in people who recover. Thymectomy is not recommended in patients who have anti-MuSK and anti-LRP4 antibodies or negative for all MG-specific antibodies (Yavuz, 2019).

Remes Troch et al. (2002) recommends thymectomy to be performed in Generalized MG patients between the ages of 15-60, in patients with stable moderate or severe MG despite medical treatment, in patients with resistant Ocular-MG, in patients with suspected thymoma and patients over 60 years

of age who do not respond to medical treatment or react to therapeutic drugs such as corticosteroids (Remes Troch et al., 2002).

Using IVIg or Plasmapheresis before surgery minimizes the risk of problems and allows for a speedier recovery. Even in critically patients, the mortality rate with thymectomy is less than 1% (Gronseth and Barohn, 2000). Myasthenic crisis (6%), infection (11%) and phrenic nerve injury (2%) are all possible complications the following thymectomy (Yavuz, 2019).
Finally, MG patients should avoid taking certain drugs that may affect the NMJ. These drugs are showed in Table 2.

Table 2. Drugs that are contraindicated for use in MG [Dincer, 2015]

Antibiotics	Antiarrhythmic agents	Others
Aminoglycoside antibiotics, especially gentamicin, kanamycin, neomycin, and streptomycin	Beta-blockers (pindolol, propranolol, timolol)	Some antiepileptics (Diphenylhydantoin)
		Lithium
macrolides	Calcium channel blockers (verapamil, diltiazem, nifedipine)	Morphine and other narcotic analgesics
		Tranchylazanes and barbiturates
fluoroquinolones	Quinidine	Some antidepressants (tricyclics)
		Muscle relaxants
Tetracyclines	Lidocaine	Levothyroxine
Sulfonamides	Procainamide	Adrenocorticotropic hormone (ACTH)
Penicillin (high dose)	Trimethaphan	Magnesium salts
		Iodized contrast agents
		Succinylcholine, D-tubocurarine or other neuromuscular blocking agents
		D-Penicillamine (never use)
		Estrogen-containing preparations
		Calcium channel blockers

4. CONCLUSION

The biomarkers employed in the subgrouping of MG and the patient-specific clinical character of the disease are assessed when deciding on the therapeutic approach to be used. The existence of autoantibodies against proteins in the post-synaptic membrane is the most crucial marker in the diagnosis of MG and patients are classified based on the presence of these antibodies. Serological confirmation or exclusion of the diagnosis is required in MG, especially when clinical and electrophysiological investigations fail to indicate neuromuscular junction dysfunction (Vincent et al., 2003). When anti-AChR or anti-MuSK cannot be confirmed serologically, treatment may be delayed. Clarifying the pathogenesis of MG is critical for accurate and early diagnosis, as well as the development of innovative diagnostic and treatment techniques (Skeie et al., 2010)

Despite many methods used in the diagnosis of MG, the diagnosis is not possible for some patients. Conditions that may vary from patient to patient, such as fluctuation in symptoms and clinical findings, delay diagnosis in 13 percent of patients for more than 5 years and causes non-deterministic diagnoses in 26 percent (Gilhus et al., 2016). Chewing difficulty, droopy eyes, speech difficulties and muscle exhaustion in elderly persons, on the other hand, can be misinterpreted as age-related, hindering the diagnosis. Moreover, there are cases in which elderly patients with MG symptoms are diagnosed with Parkinson's disease, stroke and motor neuron disease (Montero-Odasso, 2006). Meanwhile, normal electrophysiology in seronegative patients is another circumstance that complicates diagnosis (Vincent et al., 2003).

Rapid and early diagnosis is critical in MG patients. Because proper therapy must be initiated as soon as possible to avoid life-threatening consequences. At the same time, because it is an autoimmune disease, patients may require long-term immunosuppressive therapy. This circumstance may expose the person to unneeded treatments, as well as being a burden in terms of time and money in the case of an incorrect diagnosis.

As a result, new techniques for the most accurate and rapid diagnosis of MG are necessary. Furthermore, research into the molecular mechanism of MG is continuing (Guo et al., 2019; Ingelfinger et al., 2021; Lushchekina et al., 2015). These investigations will contribute to the development of new therapeutic medications, thus, successful treatment approaches.

Acknowledgement

We would like to thank Scientific and Technical Research Council of Turkey, TUBITAK-1003 SBAG-Project number:218S986 and Altinbas University, AYP2021-3 project.

Conflict of Interest

Authors declare no conflict of interest.

5. REFERENCES

Beloor Suresh, A. and RMD. Asuncion. 2021. Myasthenia Gravis, StatPearls [Internet], Available from: https://www.ncbi.nlm.nih.gov/books/NBK559331/?report=classichttps://www.ncbi.nlm.nih.gov/books/NBK559331/

Berrih-Aknin, S., M. Frenkian-Cuvelier, and B. Eymard. 2014. Diagnostic and clinical classification of autoimmune myasthenia gravis. J Autoimmun, 48-49:143-8.

Conti-Fine, BM., M. Milani, and HJ. Kaminski. 2006. Myasthenia gravis: past, present, and future. J Clin Invest, 116(11):2843-54.

Dincer, A. (2015) Expression of TRAIL/TRAIL Receptors in T-Cell Subtypes in the Clinical Presentations of Myasthenia Gravis (Dissertation for specialty in medicine). Retrived from Ulusal Tez Merkezi – Turkey & Adana. (426698)

Evoli, A. and L. Padua. 2013. Diagnosis and therapy of myasthenia gravis with antibodies to muscle-specific kinase. Autoimmun. Rev, 12, 931–935.

Frykman, H., P. Kumar, and J. Oger. 2020. Immunopathology of Autoimmune Myasthenia Gravis: Implications for Improved Testing Algorithms and Treatment Strategies. Frontiers in neurology, 11, 596621.

Gilhus, N.E. and J.J. Verschuuren. 2015. Myasthenia gravis: Subgroup classification and therapeutic strategies. Lancet Neurol, 14, 1023–1036.

N.E. Gilhus, S. Tzartos, A. Evoli, J. Palace, T.M. Burns, and J.J.G.M. Verschuuren. 2019. Myasthenia gravis. Nat. Rev. Dis. Prim., 5, 30.

Gilhus, NE., Skeie, GO., Romi, F., Lazaridis, K., Zisimopoulou, P. & Tzartos, S. 2016. Myasthenia gravis autoantibody characteristics and their implicationsfor therapy. Nat Rev Neurol, 12:259- 268.

Gronseth, G.S. and Barohn, R.J. 2000. Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology, 55:7-15.

Guo, F., C. Y. Wang, S. Wang, J. Zhang, Y. J. Yan, Z. Y. Guan, and F. J. Meng. 2019. Alteration in gene expression profile of thymomas with or without myasthenia gravis linked with the nuclear factor-kappaB/autoimmune regulator pathway to myasthenia gravis pathogenesis. Thoracic cancer, 10(3), 564–570.

Gwathmey, K.G. and T.M. Burns. 2015. Myasthenia Gravis Semin Neurol, 35 (4):327-39.

Ingelfinger, F., S. Krishnarajah, M. Kramer, S. G. Utz, E. Galli, M. Lutz, P. Zwicky, A. U. Akarca, N. P. Jurado, C. Ulutekin, D. Bamert, C. C. Widmer, L. Piccoli, F. Sallusto, N. G. Núñez, T. Marafioti, D. Schneiter, I. Opitz, A. Lanzavecchia, H. H. Jung, and B. Becher. 2021. Single-cell profiling of myasthenia gravis identifies a pathogenic T cell signature. Acta neuropathologica, 141(6), 901–915.

Jayam Trouth, A., A. Dabi, N. Solieman, M. Kurukumbi, and J. Kalyanam, 2012. Myasthenia gravis: a review. Autoimmune diseases, 2012, 874680.

Lazaridis, K. and S.J. Tzartos. 2020. Autoantibody Specificities in Myasthenia Gravis; Implications for Improved Diagnostics and Therapeutics. Front. Immunol, 11, 212.

Lennon, V.A. 1997. Serologic profile of myasthenia gravis and distinction from the Lambert- Eaton myasthenic syndrome. Neurology, 48:S23–S27.

Lleo, A., P. Invernizzi, B. Gao, M. Podda, M.E. Gershwin. 2010. Definition of human autoimmunity--autoantibodies versus autoimmune disease. Autoimmun Rev, 9(5):A259-66.

Lushchekina, S., Kots, E., Kharlamova, A., Petrov, K., Masson, P. 2015. Molecular modeling of mechanism of action of anti-myasthenia gravis slow-binding inhibitor of acetylcholinesterase. Int J Risk Saf Med.;27 Suppl 1:S74-5

Marx, A., F. Pfister, B. Schalke, G. Saruhan-Direskeneli, A. Melms, and P. Ströbel. 2013. The different roles of the thymus in the pathogenesis of the various myasthenia gravis subtypes. Autoimmun Rev, 12: 875–84.

Melzer, N., T. Ruck, P. Fuhr, R. Gold, R. Hohlfeld, A. Marx, A. Melms, B. Tackenberg, B. Schalke, C. Schneider-Gold, F. Zimprich, S. G. Meuth, and H. Wiendl. 2016. Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the Guidelines of the German Neurological Society. Journal of neurology, 263(8), 1473–1494.

Meriggioli, M.N. and D.B. Sanders 2004. Myasthenia Gravis: Diagnosis. Semin. Neurol, 24, 31–39.

Montero-Odasso, M. 2006. Dysphonia as first symptom of late-onset myasthenia gravis. J Gen Intern Med, 21(6):C4-6.

Murai, H., T. Noda, E. Himeno, Y. Kawano, Y. Ohyagi, H. Shiraishi, M. Motomura, and J. Kira. 2006. Infantile onset myasthenia gravis with MuSK antibodies. Neurology, 67(1):174

Ngo, S.T., F.J. Steyn and P.A. McCombe. 2014. Gender differences in autoimmune disease. Front Neuroendocrinol, 35(3):347-69.

Oh, S.J., Kim, D.E., Kuruoglu, R., Bradley, R.J. and Dwyer, D. (1992). Diagnostic sensitivity of the laboratory tests in myasthenia gravis. Muscle and Nerve, 15:720–724.

Pascuzzi, RM. 2003. The edrophonium test. Semin Neurol, 23:83-8.

Pasnoor, M., M.M. Dimachkie, C. Farmakidis, and R.J. Barohn. 2018. Diagnosis of Myasthenia Gravis. Neurol. Clin, 36, 261–274.

Remes-Troche, J.M., J.F. Téllez-Zenteno, B. Estañol, J. Garduño-Espinoza, and G. García-Ramos. 2002. Thymectomy in Myasthenia Gravis: Response, Complications, and Associated Conditions. Arch Med Res 33: 545-51.

Rousseff, R.T. 2021. Diagnosis of Myasthenia Gravis. J Clin Med, 16; 10(8):1736.

Samuelsson, A., T.L. Towers, and J.V. Ravetch. 2001. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. Science, 19;291(5503):484-6.

Shelly, S., P. Paul, H. Bi, D. Dubey, M. Milone, E.J. Sorenson , B.A. Crum, R.S. Laughlin, T. Liewluck, J. Mandrekar, S.J. Pittock, A. Zekeridou, A. McKeon, M.C. Harper, J.R. Mills, and C.J Klein. 2020. Improving accuracy of myasthenia gravis autoantibody testing by reflex algorithm. Neurology, 95, e3002–e3011.

Sieb, J. P. 2014. Myasthenia gravis: an update for the clinician. Clinical and experimental immunology, 175(3), 408–418.

Skeie, G. O., S. Apostolski, A. Evoli, N. E. Gilhus, I. Illa, L. Harms and H. W. Horge. 2010. Guidelines for treatment of autoimmune neuromuscular transmission disorders. European Journal of Neurology, 17(7), 893–902.

Vincent, A. and J. Newsom-Davis. 1985. Acetylcholine receptor antibody as a diagnostic test for myasthenia gravis: results in 153 validated cases and 2967 diagnostic assays. Journal of Neurology Neurosurgery and Psychiatry, 48:1246–52.

Vincent, A., J. Bowen, J. Newsom-Davis, and J. McConville. 2003. Seronegative generalised myasthenia gravis: clinical features, antibodies, and their targets. The Lancet Neurology. 2(2), 99–106.

Vincent, A., S. Huda, M. Cao, H. Cetin, I. Koneczny, P.M.R. Cruz, L. Jacobson, S. Viegas, S. Jacob, M. Woodhall, A. Nagaishi, A. Maniaol, V. Damato, M.I. Leite, J. Cossins, R. Webster, J. Palace, and D. Beeson, 2018. Serological and experimental studies in different forms of myasthenia gravis. Ann. N. Y. Acad. Sci, 1413, 143–153.

Yavuz, Z. 2019. Myastenia Gravis Klinik ve Demografik Özellikleri (Dissertation for specialty in medicine). Retrived from Ulusal Tez Merkezi – Turkey & Ankara. (602539)

Zhang, B., J.S. Tzartos, M. Belimezi, S. Ragheb, B. Bealmear, R.A. Lewis, W.C. Xiong, R.P. Lisak, S.J. Tzartos, and L. Mei 2012. Autoantibodies to lipoprotein-related protein 4 in patients with double-seronegative myasthenia gravis. Arch Neurol, 69(4):445-51.