Volume 6 Issue 1, January 2024

Turkish Journal of Internal Medicine

ISSN: 2687-4245

Review

Original Articles

Case Report

Turkish Journal of Internal Medicine

http://www.tjim.org

e-ISSN: 2687-4245

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Publisher

Turkish Journal of Internal Medicine

Nizameddin KOCA

SBU Bursa Şehir SUAM

Nilüfer/BURSA-TURKEY

https://dergipark.org.tr/en/pub/tjim

Turkish Journal of Internal Medicine

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TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Internal Medicine

Turkish Nephrology on the Centenary of the Republic

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A B S T R A C T

After the establishment of the Turkish Republic on October 29, 1923, the main targets in the field of health were determined as combating contagious diseases, increasing the number of physicians and healthcare personnel, improving the interregional distribution of physicians, giving women the right to receive medical education, and granting only Turkish citizens the right to practice medicine (except formerly working foreign physicians and those working in hospitals established by foreign states). Modern medical education was introduced in the Ottoman Empire with the "Tıphane ve Cerrahhane-i Amire (Mekteb-i Tıbbiye-i Şahane)" school opened on March 14, 1827. After the implementation of the University reform in Turkey in 1933, Istanbul University Faculty of Medicine became one of the most important centres in Europe with the contributions of well-known foreign scholars and Turkish faculty members. After World War II, the first medical school of the republican era was opened in Ankara in 1945. This article provides a chronological review of the developments in Turkish nephrology during the Republican period.

Turk J Int Med 2024;6(1):1-6
DOI: 10.46310/tjim.1408413
Review

Keywords: *Turkey, world, nephrology, history, kidney biopsy, dialysis, transplantation*

Received: *December 22, 2023;* ***Accepted:*** *January 10, 2024;* ***Published Online:*** *January 29, 2024*

How to cite this article: *Ersoy A. Turkish Nephrology on the 100th Anniversary of the Republic. Turk J Int Med 2024;6(1):1-6. DOI: 10.46310/tjim.1408413*

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Nephrology specialisation, obtained by completing a three-year subspecialty training after internal medicine specialisation in Turkey, focuses mainly on diagnosing and treating kidney diseases. For thousands of years before the advent of the nephrology speciality, doctors struggled to diagnose kidney disorders. Nephrology is a term of Greek origin, nephros, meaning "kidney," combined with the suffix -logy, meaning "the study of." The word "kidney" appears for the first time in Turkish in the Orkhon inscriptions as "bögür," which indicates the name of the space between the rib bone and the hip. In the historical periods of Turkish, it is in the form of words meaning "kidney, bögür, böğür, bügür, bögr, yan." Later, in the Ottoman Period, the word "böğrek" was probably used in the sense of kidney by adding the suffix "-ek" to the word "böğür." Although the term "böğür" is still widely used among the public to associate it with where the organ is located, it is now referred to as "kidney = böbrek".[1,2]

Kidney biopsy, dialysis, and kidney transplant treatments have been milestones in the advancement of nephrology science.[3] By the mid-1960s, kidney biopsies increased the experience in kidney histopathology. Kidney biopsy has transformed the diagnostic approach to kidney disease from a clinical methodology to an approach based on morphological analysis. In the 1980s, with the understanding of the immunopathological mechanisms of glomerular diseases, immunological agents began to be used in treatment. With the advances in molecular biology tests and molecular genetics in the 1990s, it became possible to distinguish between hereditary and acquired diseases.[1]

In addition to hereditary or acquired primary kidney diseases and many systemic diseases that affect the kidneys secondarily, the frequency of health problems such as diabetes, hypertension, obesity, atherosclerotic heart disease, rheumatological diseases, and cancer, which negatively affect our kidneys, is increasing as a result of today's modern lifestyle. To raise awareness about kidney disease, "World Kidney Day" was celebrated for the first time on March 9, 2006, with the joint initiative of the International Society of Nephrology (ISN) and the International Federation of Kidney Foundations (IFKF). Since then, it has been celebrated every year on the 2nd Thursday of March. Chronic kidney disease (CKD) is an increasingly important public health problem worldwide and in Turkey and is a significant cause of morbidity and mortality. World Kidney Day, celebrated on March 9, 2023, focused on the theme "Healthy Kidneys for All". The fact that awareness of the disease in society is below 10% makes it difficult to detect the condition in the early stages and leads to the progression to end-stage kidney disease. The CREDIT study conducted in our country estimated the prevalence of CKD in adults as 15.7% (~7.5 million people) and the awareness of kidney diseases as 1.6%.[4] In recent years, end-stage kidney disease (ESKD) incidence rates have remained relatively stable in many high-income countries but have increased significantly, predominantly in East and Southeast Asia. This global increase is likely due to increased survival rates in patients with ESKD, population demographic shifts, higher prevalence of ESKD risk factors, and increased access to renal replacement therapy (RRT) due to economic growth.[5] The total and per capita treatment expenditure amounts for central hemodialysis, home hemodialysis and peritoneal dialysis patients across Turkey 2020 USD (TRY) were calculated as 311,539,594/6,337$ (2,190,813,676/44,563 TL), 4,378,976/6,328$ (30,798,372/44,506 TL) and 42,496,272/11,844$ (298,855,007/83,29 TL), , respectively.6 Today, it is estimated that approximately 10% of the world's population (850 million people) suffers from CKD.[7] The annual cost of dialysis usually exceeds $25,000.[8] In our country, the General Directorate of Public Health of the Ministry of Health has initiated the Turkey Kidney Diseases Prevention and Control Program action plan with the contributions of public institutions and organisations, universities and non-governmental organisations to increase awareness and early diagnosis rates of kidney diseases and to reduce the adverse effects of diseases on the society.[9]

Development of nephrology in Turkey

Erich Frank was invited to our country in 1934 and served at Istanbul University Internal Medicine Clinic for 23 years.[10] He trained hundreds of students and scientists, some of whom were first-generation Turkish nephrologists, and pioneered the establishment of the discipline of nephrology.[11] Kurt Steinitz, a prominent internist in chemistry and Erich Frank's assistant opened new testing laboratories in Turkey with Erich Frank and Erica Bruck. He used the measurement of endogenous creatinine clearance and glomerular filtration rate, showing that progressive loss of kidney function caused a hyperbolic increase in creatinine level. He contributed to Turkish medicine by establishing the infrastructure for transferring conserved blood. He immigrated to Israel in 1943, where he performed the first artificial kidney and dialysis on patients.[12,13] Elisabeth Wolff, one of the founders of modern dietetics and brought with her by

Erich Frank as a dietitian, trained many nurses as dietitians and wrote a Turkish diet treatment book, including kidney diseases. Erich Frank has researched orthostatic proteinuria, albuminuria, essential hypertension, hypertension due to renal parenchymal diseases, renal glycosuria and pregnancy glycosuria. Frank gifted two books to Turkish medicine: "Medical Kidney Diseases Clinics (1941)", which contained wholly original and modern information and was considered the first Turkish nephrology textbook, and "Carbohydrate Metabolism Pathology", published in our country the same year it was published abroad.[13] Then, Dr Cavit Sökmen, who worked at Ankara University Faculty of Medicine, wrote the book "Internal Kidney Diseases" in 1950.[14]

Studies in the field of nephrology in our country began in the 1950s. Peritoneal dialysis was applied to two patients with septic abortion and acute renal failure at Istanbul Haseki Hospital. The first kidney biopsy was performed by Dr Selahattin Koloğlu (Ankara University) in 1954. Dr Necdet Koçak laid the foundations of the branch of nephrology by establishing a department in 1958 to research "Kidney diseases, water and electrolyte metabolism", and in 1960, he studied "Kidney functions in diabetes insipidus, mechanism of action of mercury diuretics in diabetes insipidus, phosphorus excretion of renal tubules, renal tubular asthenia and juxtaglomerular filtration.".[15] In 1958, Dr Nihat Sipahi applied acute peritoneal dialysis in the style of peritoneal lavage to a young patient (Ankara University). In June 1962, Dr Ergün Ertuğ and his team performed the first acute hemodialysis treatment with Kolff's artificial kidney device. Subsequently, acute peritoneal dialysis was performed in 1963, and percutaneous kidney biopsy was performed in 1964.[15,16]

The Istanbul University Faculty of Medicine Treatment Clinic is Turkey's first legal nephrology institution. In 1967, the Turkish Ministry of Health and Social Assistance accepted Nephrology as one of the postgraduate branches. In 1968, Dr Kemal Önen established the first official nephrology unit at the Internal Medicine Clinic of Cerrahpaşa Faculty of Medicine. Between 1970 and 1982, Dr Saim Yeğinboy (Ege University), Dr Cemil Kobal (Çukurova University), Dr Şali Çağlar (Hacettepe University), Dr Aydoğan Öbek (Bursa Uludağ University), Dr Ergün Ertuğ (Ankara University) and Dr Ayla San (Atatürk University) were other founders of the science of nephrology in our country.

In 1973, Dr Şerafettin Tuna and Dr Ergin Ark introduced intermittent peritoneal dialysis into routine practice in patients with chronic renal failure. In 1981, a patient-administered chronic intermittent peritoneal dialysis application using the Tenckhoff catheter was initiated at the Istanbul Faculty of Medicine under the responsibility of Dr Ahmet Kadıoğlu. Dr Nejdet Koçak et al.[17] published the results of 18 patients who performed bottle dialysis by keeping the dialysate in the abdomen for 6-8 hours with a Tenckhoff catheter, as described by Popovich and Moncrief. In 1985, Dr Bülent Erbay and Dr Oktay Karatan from Ankara University initiated continuous outpatient peritoneal dialysis treatment in its current sense.[18] In 1965, Istanbul University Cerrahpaşa Medical Faculty Dr Kemal Önen initiated the first hemodialysis application. Dr Şali Çağlar at Hacettepe University started Turkey's first continuous hemodialysis program in 1973. Shunts were used as vascular access in hemodialysis treatment until October 30, 1972, and then, arteriovenous fistulas were used. Dr Selahattin Çetin and his team performed the first arteriovenous fistula operation in 1975.[19,20] Dialysis science boards were officially established under the Ministry of Health in 1993, and the Dialysis Science Board Dialysis Centers Regulation was published in the Official Gazette.[15]

The first living donor transplant in Turkey was performed in 1968 by Istanbul Medical Faculty 1st Internal Medicine and Surgery Clinic. After successful operations, the first patient died 5 hours later due to ventricular fibrillation, and the second patient died 27 days after the transplant due to gastrointestinal bleeding and infection.[21] Dr Mehmet Haberal and his team performed the first successful kidney transplant from a living donor (from mother to son) on November 3, 1975, at Hacettepe University. In the following years, the same team performed the first kidney transplant from a deceased donor.

After the department of nephrology was officially established in 1982 by the decision of the Council of Higher Education, Turkish nephrology managed to reach world standards in the 1990s.

Nephrology associations around the world began to be established in the 1960s. On March 3, 1970, the " Turkish Society of Nephrology (TSN)" was founded in the pharmacology and treatment clinic of Haseki Hospital affiliated with Istanbul University (Founding members; Dr Ekrem Şerif Egeli, Dr Sedat Tavat, Dr Reşat Garan, Dr Kemal Önen, Dr Osman Barlas, Dr Ferhan Berker, Dr Gıyas Korkut, and Dr Necdet Koçak).[22] In 1976, Dr Mustafa Yurtkuran founded the "Kidney Diseases Diagnosis and Treatment Foundation", and then in 1980, Dr Ayla San founded the "Chronic Kidney Diseases Treatment Foundation". The first international Nephrology meeting was held on 6-11 January 1964 under the

name "Paris and Ankara Medical Faculties Cardiology and Nephrology Week". The first physician in Turkey to receive Nephrology subspecialty training abroad was Dr Kemal Önen, and the first person to take the nephrology specialisation exam was Dr Şali Çağlar. The first international meeting (EDTA and EDTNA Meeting) was held by Dr Kemal Önen at the Atatürk Cultural Center on 4-7 June 1978. On 4-6 June 1980, "1. National Dialysis and Transplantation Congress" was held in Bursa under the chairmanship of Dr Aydoğan Öbek.[15]

The close relations established by the Turkish Nephrology community with international associations such as the International Society of Nephrology (ISN) and the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) have enabled our young scientists to advance nephrology education or conduct research in Europe and the USA. Association members have taken active roles in international associations, boards, congresses and journals. Together with ISN and EDTA–ERA, the TSN organised a Nephrology Course in Istanbul in 1997, an International Summer School in Izmir in 1998, and a congress at the Aegean Faculty of Medicine jointly with the Balkan Cities Congress (BANTAO) in 1999. On June 5, 2000, the TSN celebrated its 30th and ISN's 40th anniversary and a joint congress was held with ISN. After 27 years, the TSN had its 42nd ERA-EDTA Congress, the largest Nephrology Congress in Europe, for the second time in Istanbul on 4-8 June 2005. On June 21-25, 2008, TSN hosted the 12th International Society for Peritoneal Dialysis (ISPD) Congress in Istanbul.[22] Turkey is among the countries that submitted the most abstracts at ERA-EDTA Congresses.[23]

The TSN supported the establishment of the Nephrology–Dialysis and Transplantation Nursing Association, and nurse congresses are still held together. Association branches continue to update physicians' knowledge in the nephrology field in their region through educational activities. In addition, many important books in the field of nephrology continue to be translated into Turkish and many national books and guidelines continue to be published as TSN publications.[22] Turkish Journal of Nephrology (formerly Turkish Journal of Nephrology, Dialysis and Transplantation), the official publication of TSN, started its publication life in 1992 under the editorship of Ekrem Erek. Turkish Journal of Nephrology is indexed in the "Web of Science-Emerging Sources Citation Index".

Another association, the Turkish Society of Hypertension and Renal Diseases, was founded in Ankara in 1995 to combat hypertension, kidney diseases and their negative consequences. It was accepted as a member of the "World Hypertension League" in 2006 and the "World Initiative on Salt and Health" in 2007. It has been regularly organising "World Hypertension Day" events since 2006. This association has carried out critical scientific studies on hypertension in our country ("Turkish Hypertension Prevalence Study [PatenT], Turkish Hypertension Incidence Study [HinT], Salt Consumption and Hypertension in Turkey [SALTurk] and Turkey Home Blood Pressure Measurement Devices studies).[24]

In 1990, Dr Ekrem Erek laid the foundation of the TSN National Registration and Statistics Board, which has been operating successfully for more than 30 years. In addition, Turkey's RRT data has been included in the ERA annual registration reports since 2001 and in the 'International Comparisons' section of USRDS yearly reports since 2003. Thus, our country's RRT results can be compared with world data.[25]

During the 17 August 1999 Marmara earthquake, nephrologists, under the coordination of the TSN, made an intense effort for the treatment of patients with acute kidney injury due to Crush syndrome and achieved a relatively low mortality rate of 15%. Dr Mehmet Şükrü Sever pioneered many scientific studies that contributed significantly to the medical literature in this field after the 1999 Marmara Earthquake. He was appointed as a field doctor and disaster relief coordinator by the Turkish and World Nephrology Societies and contributed to the preparation of the largest disaster database in the world. He was the co-chairman of the group that prepared the world's first and only guide on the prevention and treatment of crush syndrome, and this guide, published in 2012, began to be used as the "Disaster Field Guide" by Medecins Sans Frontieres (MSF) Rescue Teams. Turkish nephrologists actively participated in many domestic and international disasters in the following years.

Pediatric nephrology became a subspecialty of paediatrics in Turkey in 1983. The Pediatric Nephrology Association was established in 1990. Today, there are 107 pediatric nephrology centres, 265 well-trained specialists, 28 pediatric hemodialysis units, 39 pediatric peritoneal dialysis units, and 26 pediatric transplant centres in Turkey.[11]

Hemodialysis is available in 98% of countries, peritoneal dialysis is available in 79%, and kidney transplantation is available in 70%. 63% of countries provide public financing for hemodialysis, 55% for peritoneal dialysis, and 59% for kidney transplantation. Nephrologists are primarily responsible for kidney failure care in 87% of

countries worldwide, and primary care physicians are responsible for 7%. While 5.8% of nephrologists treat children, the proportion of female nephrologists (treating adults and children) is 35%. The density of nephrologists increased worldwide from 9.5 pmp (rate per million population ≥18 years) to 12.4 pmp (30.4% increase) between 2019 and 2023. The median prevalence of nephrologists worldwide is 11.75 pmp. It is highest in North and East Asia (28.7 pmp) and lowest in Africa (1.1 pmp). The prevalence of nephrologists varies significantly across regions and income groups. The density of nephrologists in high-income countries is 80 times higher than in low-income countries. The prevalence of nephrology trainees is 1.15 pmp despite a 0.74% increase and varies widely between countries.8 In our country, as of the end of 2022, there are 921 hemodialysis (18,736 machines), 81 home hemodialysis, 134 peritoneal dialysis and 78 transplantation centers (Ministry of Health, University and Private) where RRT is applied.[25] The prevalence of nephrologists in Turkey is between 1.8-11.7 pmp.[8] Currently, some science branches provide nephrology speciality training in many centres in Turkey. However, considering the increase in CKD results and ESRD patients, it is clear that the number of nephrologists[26] and their regional distribution are not at the desired level. In more than half of the world's countries, there is a need for more key health professionals required to provide optimal care, including nephrologists (who treat adults and children) and transplant surgeons, dietitians, transplant coordinators and dialysis nurses.

CONCLUSIONS

In the 100th year of our Republic, our country's nephrology has come a long way and has reached a level that competes with the world in every field. Today, the decrease in interest in nephrology, depending on various reasons, may become a severe problem in the coming years. Ways should be sought to overcome the lack of interest in this speciality among young physicians worldwide. Focusing on genetics, molecular studies, and applications of new technologies, especially computer software and artificial intelligence, is critical in nephrology.

Funding Sources

No specific funding from the public, private, or non-profit sectors was received to carry out the work mentioned in this article.

Authors' Contribution

Study Conception: AE, İI; Study Design: AE; Literature Review: AE; Critical Review: AE; Data Collection and/or Processing: AE,; Analysis and/or Data Interpretation: AE; Manuscript preparing: AE.

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TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Internal Medicine

Evaluation of the relationship between papillary thyroid cancer and radiation exposure

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ABSTRACT

Background It has been identified that ionising radiation is the definitive cause of human cancer. One-third of the tumours that develop after radiation exposure are malignant, with papillary thyroid cancer (PTC) being the most common cancer type. This study investigated the relationship between total radiation dose (TRD) received during imaging tests and thyroid cancer occurrence in patients diagnosed with PTC.

Methods The study was designed to retrospectively review the data of adult patients aged ≥18 years diagnosed with PTC between 2005 and 2022. Patients diagnosed with a condition other than PTC were excluded from the study.

Results Three hundred seven patients with papillary thyroid cancer were 256 (83.4%) women, with a mean age of 44.7±13.5 years. A statistically significant relationship was observed between TRD and multifocality (p=0.02). Tumour size (r=0.200, p=0.07) weakly correlated with TRD, and TRD (OR: 0.9, 95% CI: 1.0-1.1, p=0.006) was found to be significant according to multifocality.

Conclusion This study found an association between TRD taken during imaging tests and multifocality. As a result, the authors aimed to remind clinicians that the disease may progress more aggressively and that thyroid cancer may develop in patients exposed to radiation due to excessive imaging tests.

Turk J Int Med 2023;5(4):7-11
DOI: 10.46310/tjim.1255695
Original Article

Keywords: *.Thyroid cancer, papillary thyroid cancer, radiation, multifocality*

Received: *February 24, 2023;* ***Accepted:*** *July 11, 2023;* ***Published Online:*** *29 October 2024*

How to cite this article: *Geze D, Ecin SM.Evaluation of the relationship between papillary thyroid cancer and radiation exposure. Turk J Int Med 2024;6(1):7-11. DOI: 10.46310/tjim.1255695*

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INTRODUCTION

The incidence of thyroid cancer is increasing worldwide,[1] with over diagnosis being one of the most common causes.[2] However, over diagnosis cannot be ruled out as the sole reason. Furthermore, occupational exposure and several environmental factors are thought to be important risk factors.[3] The International Cancer Organization has identified ionising radiation as the definitive cause of human cancer.[4] One-third of the tumors that develop after radiation exposure are malignant, with papillary thyroid cancer (PTC) being the most common cancer type. Cancer develops at least 5-10 years after radiation exposure.[5] Meta-analysis and studies show a relationship between radiation and thyroid cancer.[6,7]

The present study aimed to investigate the relationship between the total radiation dose (TRD) received during imaging tests and the occurrence of thyroid cancer in patients diagnosed with PTC by retrospectively reviewing direct X-ray and computed tomography (CT) examinations performed for diagnostic purposes between 2005 and the time of diagnosis.

MATERIAL AND METHODS

The study was designed to retrospectively review the data of adult patients aged ≥18 years who were diagnosed with PTC at Mersin City Training and Research Hospital between 2005 and 2022. Data related to age, gender, year of diagnosis, tumour size, multifocality, presence of invasion, hemogram (haemoglobin and hematocrit) results, and the availability and number of X-rays and CT scans performed before the diagnosis was recorded. Patients diagnosed with a condition other than PTC were excluded from the study. Radiation is exposed during imaging methods such as X-ray and CT scans taken for imaging purposes. The Turkish Society of Radiation Oncology has declared a radiation exposure of 0.02 mSv from an X-ray and 8 mSv from a CT scan.8 The TRD was calculated using the following formula: TRD = (number of X-rays × 0.02) + (number of CT scans × 8).

Statistical Analysis

The data was processed using the SPSS 21.0 statistical software package (IBM Corp., Armonk, NY, USA). The conformity of the variables in the study to the normal distribution was examined using the Kolmogorov–Smirnov test. Numerical variables were expressed as median±standard deviation, and categorical variables were expressed as numbers and percentages. The t-test and Mann–Whitney U test were used for intergroup comparisons of numerical variables, and categorical variables were compared using the chi-square test or Fisher's exact chi-square test. When showing the relationship between total radiation dose, univariable and multivariable logistic regression, and other independent variables, the direction and degree of the relationship between the variables can be obtained by using a proportional or interval scale.

Pearson correlation analysis was used if variables showed normal distribution. If it did not show a normal distribution, Spearman correlation analysis was used.

RESULTS

Between 2005 and 2022, 307 patients with papillary thyroid cancer were 256 (83.4%) women, with a mean age of 44.7±13.5 years. Invasion was detected in 16.3% of the patients, and multifocality was detected in 31.9%; the number of direct X-rays taken before diagnosis was 1.0 (0-24), and the number of CT scans was 0.0 (0-12). Demographic and laboratory data of the patients with papillary thyroid cancer was given in Table 1.

Table 1. Demographic and laboratory data of the patients with papillary thyroid cancer (n: 307)

Variables	Values
Gender (Female/Male)	256 (83.4%)/51 (16.6%)
Age (years)	44.7±13.5
Diagnosis (years)	3.2±1.8
Tumor size (cm)	1.2±1.2
Tumor invasion	50 (16.3%)
Multifocality	98 (31.9%)
Haemoglobin (g/dL)	13.2±1.6
Hematocrit (%)	40.1±4.9
X-ray numbers	1.0 (0:24)
CT numbers	0.0 (0:12)
X-ray radiation dose (mSv)	0.02 (0:0.48)
CT radiation dose (mSv)	0.0 (0:96.0)

CT: computed tomography.
The values were expressed as n (%), mean ± standard deviation or median (minimum:maximum).

A statistically significant relationship was observed between TRD and multifocality (p=0.02). TRD was found to be 5.6±11.3 in those with low haemoglobin levels and 12.0±19.9 in those with normal

haemoglobin levels, which was significant (p=0.010). TRD was found to be 6.6±13.9 in patients with low hematocrit levels and 11.8±18.9 in patients with normal hematocrit levels, which was found to be significant (p=0.030). The association between total radiation dose and clinicopathological characteristics in papillary thyroid cancers was given in Table 2.

Table 2. Association between total radiation dose and clinicopathological characteristics in papillary thyroid cancers

Features	Total radiation dose (mSv)	*P*-value
Gender		0.258
Female	8.05±15.1	
Male	10.9±20.4	
Tumour size		0.251
<1 cm	7.5±14.9	
≥1 cm	9.9±17.6	
Invasion		0.289
Yes	9.2±16.1	
No	8.4±16.2	
Multifocality		0.022
Yes	11.5±19.5	
No	7.2±14.1	

The values were expressed as mean ± standard deviation.

In papillary thyroid cancer, tumour size (r=0.200, p=0.070) and haemoglobin (r=0.200, p=0.090) weakly correlated with total radiation dose. There was no significant correlation between age (r=0.08, p=0.100) and total radiation dose. The correlation between total radiation dose and age, tumour size and haemoglobin was given in Figure 1.

In the adjusted multivariable logistic regression analysis, total radiation dose (OR: 0.9, 95% CI: 1.0-1.1, p=0.006) according to multifocality was significant. The adjusted multivariable logistic regression analysis according to tumor size and multifocalty in papillary thyroid cancers was given in Table 3.

DISCUSSION

In our study, invasion was detected in 16.3% of the patients and multifocality was detected in 31.9%. A statistically significant relationship was observed between TRD and multifocality. Tumour size had a weak correlation with TRD, and TRD was significant based on multifocality.

In our study, the frequency was five times higher in females than in males. Thyroid cancer is 4-5 times more common in women.[9] It was found that it is 2-3 times more common in cancers caused by external radiation exposure.[10] However, gender influence could not be found in people who were exposed to radiation after the Chernobyl disaster or in a pooled analysis of 12 studies.[10,11] Consistent with the literature data, the present study found no significant relationship between gender and TRD.

The present study found no significant relationship between TRD and age when it examined the relationship between radiation exposure associated with imaging tests and the occurrence of PTC in adult patients aged ≥18 years who presented to the internal medicine outpatient clinic. It has been determined that the risks associated with radiation exposure are the highest if the exposure has occurred in the first years of life. Furthermore, the related risk decreases with age and is the lowest if the exposure occurred in adulthood.[5,6]

The tumors measuring 1 cm or less were classified as papillary microcarcinoma by the World Health Organization, and a better understanding of the biological and etiological factors responsible for its development has emphasized the importance of revealing the reasons behind the overall increase in the incidence of thyroid cancer.[12] In our study, a weak correlation was found between TRD and tumor size, and no statistically significant correlation was found between papillary microcancer and TRD. Similar to our study, the

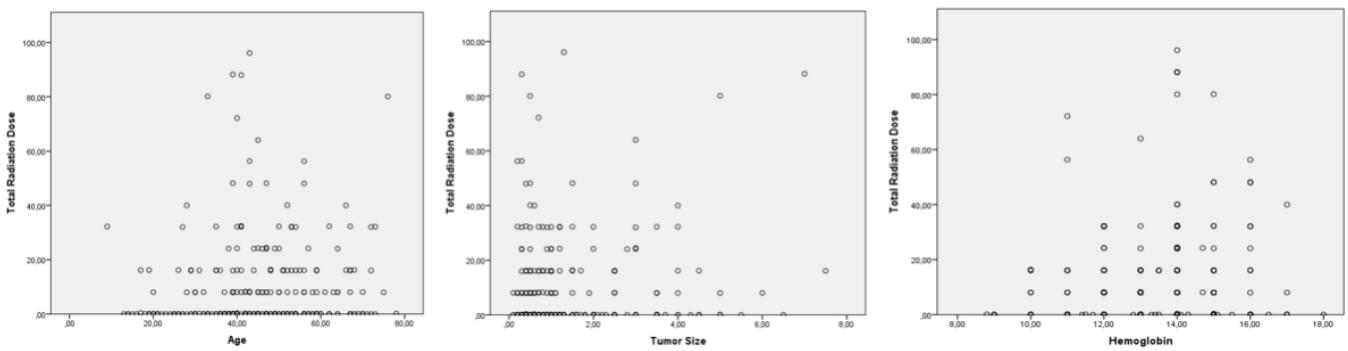

Figure 1. Correlation between total radiation dose and age, tumour size and haemoglobin

Table 3. The adjusted multivariable logistic regression analysis according to tumour size and multifocalty in papillary thyroid cancers

Features	Tumour size		Multifocality	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	0.9 (0.9-1.0)	0.100	1.0 (0.9-1.0)	0.113
Gender	0.6 (0.3-1.2)	0.200	0.0 (0.0-)	0.997
Total radiation dose	1.0 (1.0-1.1)	0.100	0.9 (1.0-1.1)	0.006
Haemoglobin	0.8 (0.5-1.3)	0.400	1.1 (0.6-1.8)	0.835

study carried out after the atomic bombing of Japan in 1945 determined that radiation exposure might be associated with the development of papillary microcarcinoma.[13]

The present study included 340 patients with PTC and TRD was evaluated in addition to the radiation history. TRD was significantly higher among those with multifocal tumors, indicating a more severe disease progression. A study conducted in Toronto with 125 patients diagnosed with thyroid cancer found that the incidence of multifocality increased with a positive history of radiation exposure in the last three years, indicating a more aggressive disease course in these patients.[14]

In a pooled analysis of seven studies examining the relationship between external radiation and thyroid cancer, post- atomic bombing survivors, thymus, thyroid hypertrophy treatment, or children who received external radiotherapy for the treatment of tinea capitis were examined.[5] Another study found no increased risk of developing thyroid cancer associated with radiation exposure caused by diagnostic X-rays or occupational exposure.[15] To the best of our knowledge, there are not many studies examining the relationship between radiation exposure from imaging tests and PTC. The present study is one of those examining the relationship between TRD associated with imaging tests and PTC.

The limitations of our study; that it is a retrospective study. Therefore, environmental and occupational exposure to radiation in childhood and later periods could not be evaluated. The strength of the present study is that it examines the relationship between pathological markers and the radiation exposure associated with imaging tests.

CONCLUSIONS

PTC is a cancer with an increasing incidence and one of the most important causes is radiation exposure. Previous studies have examined the relationship PTC and radiation exposure after atomic bombing or high-dose irradiation for therapeutic purposes. There has been a significant increase in the number of imaging tests performed for diagnostic purposes, and the impact of this exposure cannot be ignored. The present study found a relationship between TRD received during imaging tests and multifocality. As a result, the authors intended to remind clinicians that the disease may progress more aggressively and that patients exposed to radiation due to excessive imaging tests may develop thyroid cancer.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Mersin University, Mersin, Turkey. (Decision number: 20227453, date: 06.07.2022).

Authors' Contribution

Study Conception: DG, SME,; İI; Study Design: DG, SME,; Literature Review: DG, SME,; Critical Review: DG, SME,; Data Collection and/or Processing: DG, SME,; Analysis and/or Data Interpretation: DG, SME,; Manuscript preparing: DG, SME.

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TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Internal Medicine

The relationship of sexual dysfunction and quality of life patient with type 2 diabetes

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ABSTRACT

Background Diabetes, along with being able to play a role in forming many health problems such as psychological, psychosocial, and sexual dysfunction, also indirectly affects the duration and quality of life. This research was conducted as a descriptive, cross-sectional research model to determine the relationship between sexual dysfunction and the quality of life of patients diagnosed with type 2 diabetes.

Methods The research sample consisted of 485 individuals diagnosed with type 2 diabetes. The data were collected through the General Information Form, the Female Sexual Function Index, the Erection Function International Assessment Form and the Quality of Life Scale (SF-36).

Results It was found that 91% of women had sexual dysfunction and were experiencing sexual desire (92.2%), orgasmic function, arousal (92.9%) and pain, satisfaction, and lubrication (92.5%), respectively. This rate was found to be 91.3% in men, and the degree of erectile dysfunction was found to be moderate (55%), mild (21.6%) and severe (14.7%), respectively. It was found that the problems experienced in sexual dysfunction were in the sub-dimensions of general satisfaction 20.6%, orgasmic function 49.5%, sexual desire 50.9%, and relationship satisfaction 72.5%. The study found that sexual dysfunction affects the quality of life in both sexes, and the scale sub-dimensions have a statistically significant difference ($p<0.05$). It was found that the physical role difficulty, physical function, emotional role, mental health, and social function sub-dimension score had a statistically significant difference in men and women with sexual dysfunction, and the pain and vitality sub-dimension scores in men were significantly lower compared to those without sexual dysfunction ($p<0.05$).

Conclusion As a result, we showed that sexual dysfunctions were common in men and women with type 2 diabetes, and, in parallel, their quality of life was low.

Turk J Int Med 2023;5(4):12-22
DOI: 10.46310/tjim.1258050
Original Article

Keywords: *Type 2 diabetes, sexual dysfunction, erectile dysfunction, sexuality, quality of life*

Received: *February 28, 2023;* ***Accepted:*** *August 15, 2023;* ***Published Online:*** *29 October 2024*

How to cite this article: *Atacana G, Çelik S. The relationship of sexual dysfunction and quality of life patient with type 2 diabetes. Turk J Int Med 2024;6(1):12-22. DOI: 10.46310/tjim.1258050*

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INTRODUCTION

Since diabetes is a health problem that is increasing in frequency all over the world and in Turkey, it is considered the epidemic of the 21. century.[1] According to the data of 2017, there are 451 million people with diabetes between the ages of 18-99 worldwide, and it is estimated that this number will increase to 693 million in 2045. It is also estimated that about half of all people living with diabetes (49.7%) are undiagnosed.[2]

Diabetes can play a role in the formation of many health problems such as psychological, psychosocial and sexual dysfunction, and indirectly affects the duration and quality of life. Since sexual dysfunction (SD) is a condition associated with disorders in the cycle of sexual desire and sexual response, it is seen as physiological and psychological changes that occur in both men and women.[3] Although sexual dysfunction is one of the important causes in both men and women, it is reported in studies that it is twice as common in people with diabetes as in those without diabetes and that starts 10-20 years earlier.[4-7]

Although sexuality is not a vital necessity for a person to maintain his existence, it is important in affecting the quality of an individual's life. Considering sexuality as a multidimensional concept, considering quality of life as a concept that expresses the satisfaction of an individual's sexual life in addition to sexual function contributes to ensuring the awareness of individuals with diabetes about sexuality and quality of life.[7,8] It is expected that SD, which is included in the complications that develop due to diabetes, will be recognized at an early stage, counselling with the necessary trainings, reducing the symptoms associated with the disease and treatment. As a result, positive contributions to the sexual functions of individuals with diabetes will be made.[6] But it seems that sexual dysfunction is not addressed in the clinical practices of people with diabetes, it is often never questioned, the health professional avoids talking about the topic, people with diabetes; are approached more metabolically, but their counselling is insufficient. This information aimed to evaluate the relationship between sexual secondary function and quality of life in patients diagnosed with type 2 diabetes mellitus (DM) in this study.

MATERIAL AND METHODS

Purpose and type of research

The research was conducted as a descriptive, cross-sectional research model in order to determine the relationship between SD and quality of life in patients diagnosed with type 2 DM.

Sample and study design

The universe of the research was composed of 1,600 diabetic patients admitted to the outpatient clinics of Internal Medicine and Adult Endocrinology and Metabolism at an Education and Research Hospital located in Istanbul. The sample size was calculated using the formula determined by Salant and Dillman.[9] Using the sampling formula, the required sample size (n) with a ±5% sampling error at a 95% confidence interval for this universe, which was not in a homogeneous structure, was calculated as follows: n = [1,600 (1.96)2 (0.2) (0.8)] / [(0.5)2 (450-1) + (1.96)2 (0.2) (0.8)] = 213. December-August 2020, a total of 485 patients, including 287 women and 218 men, who met the research criteria, were included in the sampling in this context. Individuals aged 18 years and older who have been diagnosed with type 2 DM for at least six months, who have been sexually active for the last four weeks, who have no problems with verbal communication, who are married or have a regular sexual partner and who have agreed to participate in the study were included in the study.

Data collection

The study was approved by the Clinical Research Ethics Committee of Okan University (dated 31.01.2020). After obtaining the institution's permission, verbal consent was obtained from the patients registered in the centre to participate in the study. The data were collected by Patient Diagnosis Form, Female Sexual Function Index (FSFI), International Erectile Function Form (IIEF) and SF36 Quality of Life Questionnaire.

Patient diagnosis form

The form prepared according to the literature consists of two parts. The first part of the form consisted of sociodemographic characteristics; the second part consisted of questions about diabetes complications, metabolic parameters and other factors that may affect sexuality, as well as attitudes of cases

to sexuality and information about diabetes (duration of diagnosis, medical treatment).

International index of erectile function (IIEF)

The validity and reliability of the scale developed by Rosen et al.[8,10] was performed in 32 languages. The Erection Function International Assessment Form, approved by the Turkish Andrology Association, evaluated aspects of male sexual function. In this form, orgasmic function, erectile function, sexual desire, satisfaction from sexual intercourse and general satisfaction were assessed. The scores of the five sub-dimensions related to sexual function in the Erection Function International Assessment Form, which consisted of 15 questions, differed. In forms 11, 12 and 15. the questions were calculated with 6 points (between 0-5 points), and the other questions were calculated with 5 points (between 1-5 points). Decal scores were calculated with Decal scores. The scale, which can be applied to those who have had sexual intercourse in the last month, was scored negatively, and as the score increased, sexual dysfunction was interpreted as no or little. The highest score obtained from the scale was 75, and the lowest score was 5.8,10,11 In the current study, the Cronbach alpha value of the scale was found to be 0.90.

Female sexual function index (FSFI)

Rosen et al.[12] developed this instrument to evaluate female sexual function. The index included a total of 19 items questioning sexual function or problems within the last week in 6 subdimensions: desire, arousal, lubrication, orgasm, satisfaction, and pain. The first two items questioned the frequency and level of sexual desire (1–5 points); items 3 to 6 questioned arousal level, confidence, and satisfaction (0–5 points); items 7 to 10 questioned the frequency or difficulty of lubrication and maintaining lubrication (0–5 points), items 11 to 13 question orgasm frequency, difficulty, and satisfaction (0–5 points), items 14 to 16 question satisfaction with amount of closeness with partner, sexual relationship, and overall sex life (1–5 points), and items 17 to 19 question the frequency and level of pain during and after penetration (0–5 points). Total FSFI score ranges from a minimum of 2 to a maximum of 36, with scores below 26.55 indicating SD. Aygin and Aslan13 conducted the reliability and validation study of the FSFI for Turkey in 2005. In the current study, Cronbach's alpha value of the scale was found to be 0.90.

Quality of life scale (SF-36)

Developed by Ware1[4] in 1987, the form was designed for use in clinical practice and research to evaluate health policies and general population studies. The scale had Likert-type scoring. 35 of the 36 statements in the scale were assessed by considering the last four weeks. The evaluation did not consider the expression in the scale containing the perception of changes in health in the previous 12 months. The scale did not have a single total score, but each dimension's score was calculated separately. The score of each sub-dimension and the two main dimensions varied between 0 and 100. SF-36 was scored so that the higher the score of each health area, the higher the quality of life associated with health decency.[15] In the current study, the Cronbach alpha value was 0.90.

Collecting data

The researchers obtained the data by face-to-face interviews with the patients in the interview room. The researcher gave verbal information about the research to the patients and, after receiving the verbal and written consent of the patients, applied the survey forms to those who accepted the study. The surveys took an average of 20 minutes to complete. In addition, the glycaemic control parameters, including routine controls of diabetes patients, were obtained from the laboratory result paper and patient files after the measurement requested by the physician during admission to the outpatient clinic.

Analysis of the data

The distribution of the data was examined by the Shapiro-Wilk test. An independent sample t-test was used to compare groups with normal distribution decently. Fisher-Freeman-Halton Exact test, Fisher Exact test and Pearson Chi-square tests were used to evaluate the difference of categorical variables. Descriptive statistics of the data are explained as mean, standard deviation and frequency (percentage). All statistical analyses were analysed and reported at the significance level of 0.05 in the IBM SPSS Statistics 22.0 program.

Etchical aspect of the research

Before starting the research, written permission was obtained from the Okan University Research Ethics Committee-Ethics Committee (31/01/2020-32) and the institution where the research was conducted. The purpose of the study was explained to the individuals

Table 1. Distribution of sociodemographic disease characteristics

Variables		Male (n: 218)	Female (n: 267)	*P*-values*
Age (year)	36-45 age	67 (30.7)	137 (51.3)	<0.001
	46-55 age	84 (38.5)	91 (34.1)	
	56-65 age	58 (26.6)	38 (14.2)	
	65 age and over	9 (4.1)	1 (0.4)	
Education level	Primary school	51 (23.4)	87 (32.6)	0.069
	High school	138 (63.3)	153 (57.3)	
	College	29 (13.3)	27 (10.1)	
Working Status	Housewife	-	133 (49.8)	<0.001
	Worker	135 (61.9)	117 (43.8)	
	Officer	17 (7.8)	13 (4.9)	
	Self-employment	12 (5.5)	-	
	Retired	49 (22.5)	4 (1.5)	
	Not working	5 (2.3)	-	
Economic level	Bad	21 (9.6)	35 (13.1)	<0.001
	Medium	193 (88.5)	153 (57.3)	
	Good	4 (1.8)	79 (29.6)	
Marriage time	10 years and less	38 (17.4)	129 (48.3)	<0.001
	11-20 year	74 (33.9)	50 (18.7)	
	21-30 year	45 (20.6)	54 (20.2)	
	30 year and over	61 (28)	34 (12.7)	
Smoking status	Yes	75 (34.4)	21 (7.9)	<0.001
	Quit	74 (33.9)	23 (8.6)	
	Not using	69 (31.7)	223 (83.5)	
Drinking alcohol status	Yes	2 (0.9)	8 (3)	<0.001
	Quit	12 (5.5)	-	
	Not using	204 (93.6)	259 (97)	
Diabetes times	1-5 year	121 (55.5)	207 (77.5)	<0.001
	6 year and over	97 (44.5)	60 (22.5)	
Form of treatment	Just diet treatment	-	4 (1.5)	0.361
	Insulin	37 (17)	49 (18.4)	
	OAD[1]	75 (34.4)	87 (32.6)	
	OAD and insulin	106 (48.6)	127 (47.6)	
Additional diseases	Yes	119 (54.6)	107 (40.1)	0.001
	No	99 (45.4)	160 (59.9)	
HbA1c (%)		9.09±1.10	8.87±1.24	0.045
BMI (kg/m^2)		26.33±2.49	25.50±2.19	<0.001

OAD: oral antidiabetic; BMI: body mass index.
* t-test. The values were expressed as n (%) or mean ± standard deviation.

who will participate in the research and their written consent was obtained for their participation in the research. It's stated that the data will be used only within the scope of research, confidentiality will be strictly ensured.

RESULTS

Of the 485 patients included in the study, 55.1% were women and 44.9% were men. The rate of those in the 36-45 age group for women was 51.3%, and those in the 46-55 age group for men was 38.5%. It was stated that the majority of high school graduates in women and men, 133 (49.8%) of were housewives,

Table 2. Evaluation of sub- and total scores of the frequency of sexual dysfunction by gender

Variables		Scores	Sexual dysfunction (%)	
			Yes	No
Female (n: 267)	Sexual desire	3.65±0.89 (1.20:4.80)	92.2%	7.08%
	Arousal	2.88±0.90 (0:3.60)	92.9%	7.1%
	Lubrication	3.29±1.02 (0:4.80)	92.5%	7.5%
	Orgasmic function	3.19±0.97 (0:4)	92.9%	7.1%
	Satisfaction	3.41±1.02 (0:4.80)	92.5%	7.5%
	Pain	3.24±0.97 (0:4.40)	92.5%	7.5%
	FSFI total	19.70±5.41 (1.20:23.80)	91%	9%
Male (n: 218)	Erectile function	13.57±7.25 (1:27)	91.3%	8.7%
	Orgasmic function	4.41±2.40 (0:8)	49.5%	50.5%
	Sexual desire	5.37±1.87 (2:9)	50.9%	49.1%
	Relationship satisfaction	5.83±3.08 (0:10)	72.5%	27.5%
	General satisfaction	5.60±1.81 (2:8)	20.6%	79.4%
	IIEF total	34.79±15.97 (5:62)	91.3%	8.7%
Erectile dysfunction grade				
Mild		47 (21.6%)		
Moderate		120 (55%)		
Severe		32 (14.7%)		

The values were expressed as n (%) or mean ± standard deviation (minimum:maximum).

and 61.9% of men were workers. It was found that 55.5% of men and 77.5% of women with diabetes duration between 1-5 years, the majority of both groups received oral antidiabetic therapy (OAD) and insulin therapy, 54.6% of men and 40.1% of women had other diseases. While the mean glycated haemoglobin (HbA1c) in women is 8.87±1.24% and the mean body mass index is 25.50±2.19 kg/m^2, the mean HbA1c in men was 9.09±1.10%, and the mean body mass index was 26.33±2.49 kg/m^2 (Table 1).

91% of the 267 women included in the study had SD. SD was experienced in the areas of sexual desire (92.2%), orgasm function, arousal (92.9%) and pain, satisfaction, and lubrication (92.5%), respectively. Erectile dysfunction (ED) in men was 91.3%. While the degree of erectile dysfunction was moderate (55%), mild (21.6%) and severe (14.7%), respectively. The problems experienced were overall satisfaction at 79.4%, orgasm function at 50.5% and sexual desire at 49.1% in the lower dimensions. (Table 2).

The physical functionality, physical role, general health, vitality, social functionality and emotional role scores of the sub-dimension scores of the SF-36 scale concerning gender showed a statistically significant difference according to gender ($p<0.05$). Accordingly, in other significant sub-dimensions except for the

Table 3. Comparison of the sub-dimensions of the quality of life scale by gender

Sub-dimensions	Male (n: 218)	Female (n: 267)	*P*-value*
Physical functioning	62.31±20.56	39.66±15.26	<0.001
Physical role function	65.13±27.76	19.85±9.96	<0.001
Bodily pain	55.95±9.86	57.62±11.13	0.928
General health	40.71±9.85	40.67±5.08	0.019
Vitality	28.48±12.26	37.39±7.57	<0.001
Social functioning	41.45±22.40	52.43±14.66	<0.001
Emotional role functioning	49.23±22.89	43.07±15.72	0.010
Mental health	41.54±22.40	52.43±14.66	0.270

The values were expressed as mean ± standard deviation.
* t-test.

Table 4. Comparison of the effect of sexual dysfunction on quality of life by gender

Quality of life	Male (n: 218)			Female (n: 267)		
	SD (–)	SD (+)	*P*-value*	SD (–)	SD (+)	*P*-value*
Physical function	83.68±10.90	60.27±2.11	<0.001	46.66±18.97	38.97±14.72	0.018
Social function	75±00	38.25±5.78	<0.001	59.37±15.30	51.74±14.44	0.015
Physical role	100±0	61.80±4.70	0.001	50.36±10.27	38.24±2.45	0.005
Emotional role	78.94±6.51	46.39±1.37	<0.001	50±17.02	42.38±15.46	0.023
Mental health	51.78±0.91	40.56±7.64	<0.001	42.66±7.42	39.70±5.60	0.017
Vitality	44.73±1.14	26.93±11.70	<0.001	39.58±7.92	37.18±7.52	0.139
Pain	66.84±2.86	54.91±9.67	<0.001	61.04±13.57	57.28±10.84	0.115
General health	54.73±2.02	39.37±9.23	<0.001	42.50±6.07	40.49±4.95	0.065

SD: sexual dysfunction.
The values were expressed as mean ± standard deviation.
* t-test.

vitality and social functionality sub-dimension, the mean score of men was found to be significantly higher compared to women. In contrast, the quality of life of men in terms of physical functionality, physical role, general health and emotional role was higher compared to women, while the quality of life in terms of vitality and social functionality was higher in women than men (Table 3).

The quality of life scale sub-dimensions had a statistically significant difference according to whether men had SD or not ($p<0.05$). The scores of physical role, physical function, emotional role, pain, vitality, mental health, and social function sub-dimension were significantly lower in men with SD disorder than those without SD disorder. In women, physical function, social function, physical role, emotional role and mental health sub-dimension score had a statistically significant difference ($p<0.05$). Accordingly, physical function, social function, physical role, emotional role and mental health sub-dimension scores were significantly lower in women with SD disorder than women without SD disorder (Table 4).

DISCUSSION

In this study, the relationship between SD and quality of life in men and women with type 2 DM was evaluated.

In studies conducted with men diagnosed with type 2 DM, it is reported that ED was detected at a rate of 35-90%.[16-19] The prevalence of ED in 541 diabetic cases was found to be about 35%.[20] In a study conducted with 422 individuals diagnosed with diabetes, the majority of ED was found to be 85.5%.[21] In a study from the Netherlands, the frequency of ED in patients diagnosed with type 2 DM was about 41.3%.[22] Corona et al.[23] reported a prevalence of mild, mild-moderate, moderate and severe ED in men with DM of 19.4%, 15.4%, 10.4% and 21.6%, respectively. In a study by the Turkish Andrology Association, mild ED was detected in 22% of men diagnosed with diabetes, moderate ED in 49% and severe ED in 19% and 90% in total.[24] In the study of Yalcin et al.[25], mild ED was detected in 18% of men diagnosed with type 2 DM, moderate ED in 24% and severe ED in 22% for a total of 64%. Another study found that 33.1% of male cases experienced ED, 42.6% had mild ED, 42.6% had moderate ED, and 14.8% had severe ED.[26] ED was observed in 91.3% of the men included in the current study, the degree of erectile function was moderate by 55%, mild by 21.6% and severe by 14.7%, respectively. Problems with SD areas, on the other hand, were found to be experienced in the sub-dimensions of general satisfaction 20.6%, orgasmic function 49.5%, sexual desire 50.9% and relationship satisfaction 72.5%. While the current study results showed similarities with some of the results in the literature, they differed with some. This may be due to the sample size in the studies, the duration of diabetes, the presence of complications, and cultural differences. Also, as it is known, sexual dysfunctions have vascular, neurological, local, hormonal, drug-related and psychogenic causes. This suggests that the high level of dysfunction in our study may have

resulted from the joint evaluation of diabetic patients in the group without comorbidity in the analysis of the study. In this sense, conducting studies on only diabetes and groups with diabetes and comorbidities will contribute to the literature.

Studies investigating the effect of diabetes on SD observed that most studies focus on sexual problems in men, while studies on sexual issues of women diagnosed with diabetes were in the minority. However, studies show that diabetes also negatively affects female sexuality, and the incidence of SD among women diagnosed with diabetes is 80%.[18,26]

Various studies comparing women without a diabetes diagnosis with those diagnosed with diabetes have found that the incidence of SD is high in diabetic women. Still, despite this, the sexual problems of women diagnosed with diabetes and the risk factors associated with this condition have not been identified or explicitly stated.[27-30] Studies by Doruk et al.[18] and Erol et al.[27] conducted with women diagnosed with type 2 DM showed that the incidence of sexual dysfunction varied between 42% and 51.3%. When looking at the subgroups of sexual dysfunction, some studies have shown that sexual desire is associated with type 2 DM in diabetic women; a decrease in sexual desire and insufficient lubrication are commonly observed.[28-32] In another study, 84.4% of women diagnosed with type 2 DM had sexual dysfunction according to the FSFI sub-dimensions. While ¾ of women had sexual desire, ½ had lubrication, arousal and pain disorders.[33] Similarly, Yıldız and Pınar's study[34] found that 67.3% of women diagnosed with type 2 DM had sexual desire, 45.6% arousal, 27.9% lubrication, 34% orgasm, 38.1% satisfaction, and 38.8% pain disorder. Another study indicated that women with diabetes had low sexual desire, lack of sexual satisfaction, low vaginal lubricity and orgasmic dysfunction.[35] The present study showed that 91% of the 267 women included in the study had SD, and SD in women, respectively, 92.2% of them experienced sexual desire and orgasmic function, 92.9% of them experienced arousal and 92.5% experienced pain, satisfaction, lubrication. We think that the reason for the variability in the incidence of sexual dysfunction in women in our country and various countries may be a cultural and demographic feature factor affecting sexuality and related to different tests applied.

SD, one of the common complications of diabetes, negatively affects the patient's quality of life.[36,37] In a study by Lau et al.[38], in male patients with at least one sexual problem, SD negatively affected the quality of life. Another study stated that all quality of life scores except social function were statistically significant in patients diagnosed with type 2 DM with SD compared to those who did not have SD.[26] Okur et al.[39] found that the quality of life in individuals diagnosed with diabetes was poor compared to those without a diabetes diagnosis. In a study comparing male patients diagnosed with diabetes with ED and men without diabetes in terms of ED severity and quality of life, it was found that the ED rate was high in people with diabetes.[40]

Similarly, Auld et al.[37] stated that ED affects the quality of life in 36% of men. Litwin et al.[41] said that ED affects the quality of life; there was a relationship between ED and the general health perception, physical and emotional role dimensions of the SF-36 quality of life sub-dimensions.[41] Similarly, ED negatively affects the health-related quality of life in patients diagnosed with type 2 DM. It has been stated that SF-36 sub-dimension scores are less for individuals with ED than for individuals without ED.[41] In a study conducted on cases with diabetes, Penson et al.[40] found that the quality of life in individuals with ED was less compared to those without ED. The current study found that the quality of life scale sub-dimensions had a significant and positive relationship with physical function, physical role difficulty, emotional role difficulty, vitality, mental health, social functionality, pain and general health perception scores, erectile function, orgasmic function, sexual desire, sexual satisfaction, general satisfaction and total scores, which were each sub-dimensions of the IIEF scale. As the quality of life increases in men with ED disorders, the IIEF scale sub-dimension scores also increase significantly, and ED affects the quality of life. Our study findings were in line with the literature. In research, SD is often observed in women who do not have an active lifestyle and have a low quality of life, and it is reported that the quality of life is affected by the FSFI sub-dimensions.[41-43] Another study reported that women with a low quality of life experienced 6.6 times more SD than women with a high quality of life.[44] In a study conducted with 13,882 women aged 40 to 80 in twenty-nine countries, Lauman et al.[46] observed that 27% of women had a decrease in

desire for sexuality, 21% had orgasm disorders, 17% had lubrication problems, and 10% had dyspareunia. The quality of life of women with a high rate of deceleration in desire was most affected.[46]

Similarly, in a study conducted by Enzlin et al.[47], SD in women often showed impaired desire (17%), lubrication (14%), orgasm (14%), and pain (12%), and quality of life was affected. All sub-dimensions of quality of life and quality of life were affected in the female cases detected by SD in the current study; the area most affected by SD was emotional role function, and satisfaction and pain with physical function from the FSFI subgroups; lubrication and orgasmic function with social function; arousal with physical role function; mental health and sexual desire, orgasmic function decency and FSFI total score; fitness and orgasmic function and satisfaction; pain and orgasmic function, satisfaction, pain and FSFI total score; general health perception and pain; physical dimension and orgasmic function and satisfaction; mental dimension and satisfaction; global quality of life and orgasmic function and satisfaction were found to have significant relationships. It was seen that our study findings were compatible with the literature.

Study limitations

The fact that sexuality is considered a private subject by many patients due to their cultural values and that the research was conducted at a single centre limits the generalisation of the research results to all patients with diabetes. During the study, when patients felt that there was a medical staff with whom they could make comfortable statements about sexuality, they tended to search for the answer to their problems related to the subject, which caused the planned time decoupled to patients during the interview to be exceeded.

CONCLUSIONS

It has been concluded that sexual dysfunction is observed at a high rate in both men and women in patients diagnosed with type 2 DM, and in parallel, the quality of life is low. In this context, it is recommended to routinely evaluate patients with type 2 diabetes in terms of SD to improve the quality of life of diabetics by making the necessary plans according to the evaluation result.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of İstanbul Okan University, İstanbul, Turkey. (Decision number: 32, date: 31.01.2020).

Authors' Contribution

Study Conception: GA, SC; Study Design: GA, SC; Literature Review: GA, SC; Critical Review: GA, SC; Data Collection and/or Processing: GA, SC; Analysis and/or Data Interpretation: GA, SC; Manuscript preparing: GA, SC.

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TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Artificial Intelligence and Clinical Sciences

Do the platforms where professional health organizations inform the public answer all the needed questions?

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A B S T R A C T

Background We aimed to assess the comprehensiveness of patient information websites from academic organisations regarding the most searched statements on "nocturia". Additionally, we aimed to analyse the frequency of these statements based on their classification as definition, aetiology, diagnosis, or treatment.

Methods The website www.answerthepublic.com was used to retrieve outputs related to nocturia. After applying exclusion criteria, the outputs were searched within the American Urological Association (AUA) and European Association of Urology (EAU) patient information websites, and the comprehensiveness scores were evaluated.

Results The search engine retrieved 615 results, of which 67 queries were eligible for analysis. The most searched query was "nocturia definition", with 6,600 average monthly clicks. The distribution of analysed queries was 16.4% for definition, 46.3% for aetiology, 11.9% for diagnosis, and 25.4% for treatment. The AUA and EAU websites had median comprehensiveness scores of 2.0 (IQR: 3.5) and 3.0 (IQR: 4.0), respectively, with no significant relation found (p=0.438). The selected websites did not cover a substantial proportion of searched items related to nocturia.

Conclusions Although the patient information websites provided by prominent academic organisations offer valuable information, there needs to be more clarity between the information they provide and the public's concerns regarding nocturia. Tools like www.answerthepublic.com may provide valuable insights into public concerns but have limitations.

Turk J Int Med 2023;5(4):23-28
DOI: 10.46310/tjim.1329810
Original Article

Keywords: *Nocturia, health literacy, search engine.*

Received: *July 19, 2023;* ***Accepted:*** *August 18, 2023;* ***Published Online:*** *29 October 2024*

How to cite this article: *Coskun B, Koca N. Do the platforms where professional health organizations inform the public answer all the needed questions?. Turk J Int Med 2024;6(1):23-28. DOI: 10.46310/tjim.1329810*

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INTRODUCTION

Waking up at night to urinate is defined as nocturia, which tremendously affects the quality of life. It can cause sleep deprivation.[1] Complications such as bone fractures due to falls or cardiovascular events are also significant.[2] Nocturia is age-dependent, and almost one in two men experiences it after age 70.[3] Various factors are responsible for nocturia and can also be multifactorial. While lower urinary tract disorders are a common source of nocturia in the elderly, cardiovascular or neurological diseases, obesity, hypertension, obstructive sleep apnea syndrome, and certain medications like diuretics can also be responsible.[4] Patients may consider nocturia as an expected consequence of normal ageing. These patients may not seek any treatment options. However, even conservative treatment options may make a difference in addition to medical therapy.[5]

Proper patient information is essential, especially for multidimensional problems such as nocturia. Today, information technology has reinforced easy access to patient information from various sources.[6] Google and online video streams are popular sources patients use to find medical information. However, when evaluated in an academic context, the accuracy and quality of the information they provide may be limited due to the uncontrolled upload of context from various sources.[7]

Patient information materials from academic organisations are reliable, updated, and unbiased. They are written in lay language, making them easy to understand.[8] Although comprehensive, they may only cover some areas and concerns from the patient's perspective.[9] To assess patients' perspectives, www.answerthepublic.com can be a valuable free online tool. It captures the most searched queries on Google, the leading global search engine, and is the primary gateway for patients seeking health information.[10,11] In this study, we aimed to evaluate the comprehensiveness of patient information websites from academic organisations for the search term "nocturia" using the outputs retrieved from the www.answerthepublic.com website. Additionally, we aimed to classify these outputs based on their type (definition, aetiology, diagnosis, or treatment) and analyse how frequently they were searched for.

MATERIAL AND METHODS

On June 2, 2023, the search term "nocturia" was entered into the website www.answerthepublic.com, with English selected as the language option and the USA chosen as the location. The search results were exported as a CSV file and sorted by their search volume. Absolute duplicates, results without search volume data, non-English outputs, and irrelevant queries were removed. Only the most searched one was kept for outputs with similar meanings. The remaining outputs were classified as definition, aetiology, diagnosis, and treatment.

After applying the exclusion criteria, the remaining outputs were searched to determine whether they had been included in the patient information materials on the American Urological Association (AUA) and the European Association of Urology (EAU) websites.

We have newly developed a 5-item scoring system for assessing the comprehensiveness of the information provided by AUA and EAU patient information websites. The scoring criteria were as follows:

1. Not presented: The website's content must mention the statement or question.
2. Only mentioned: The statement or question is mentioned, but no further details are provided.
3. Incomplete: The statement or question is partially answered.
4. Substantial: The statement or question is answered with enough detail and explanation, but there may be minor gaps or room for improvement.
5. Comprehensive: The statement or question is answered with detailed information and explanations to fully answer or clarify the topic.

Statistical analysis

Descriptive statistics, including frequencies and percentages, were used to summarise the distribution of queries across the categories. Median comprehensiveness scores and interquartile ranges (IQR) were calculated for each type and the selected websites. The Mann-Whitney U test was used to compare the comprehensiveness scores between the AUA and EAU websites. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 26.0.

RESULTS

The www.answerthepublic.com search engine retrieved 615 results for nocturia, including 90 questions, 81 prepositions, 49 comparisons, 380

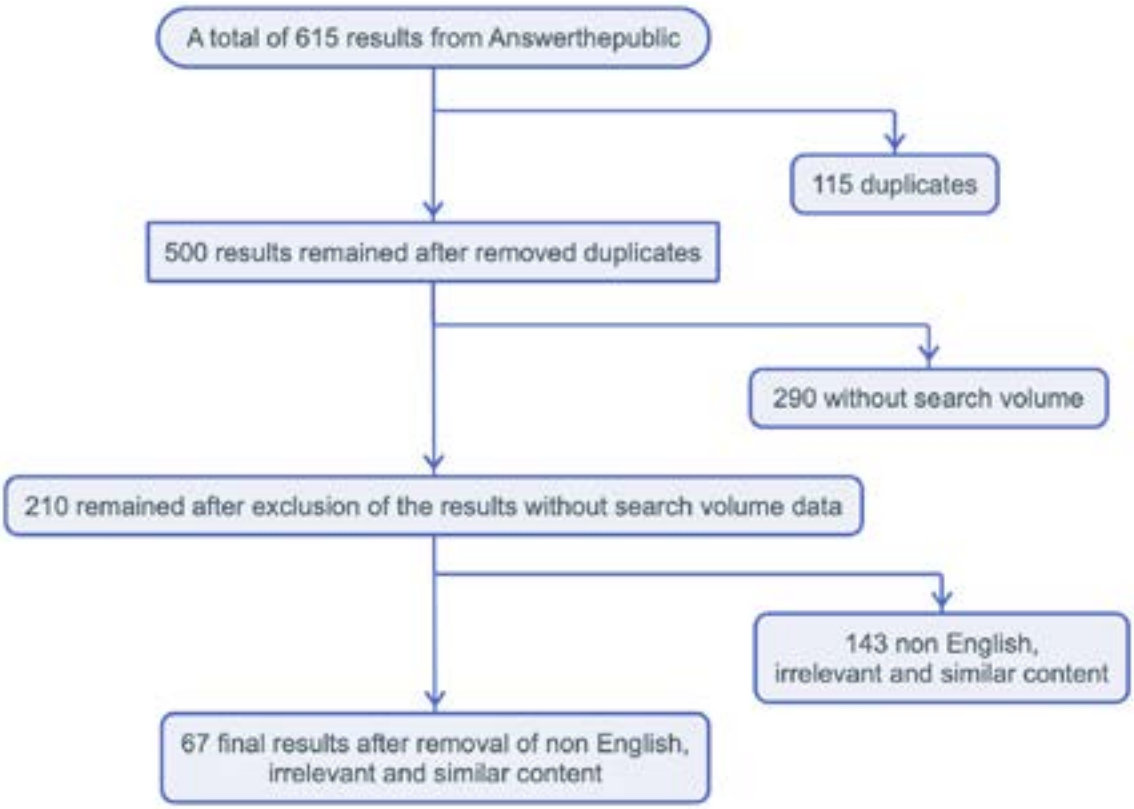

Figure 1. Applying exclusion criteria to the results retrieved from www.answerthepublic.com

alphabetical, and 15 related searches. After applying the exclusion criteria, the number of outputs was reduced to 67 for further analysis *(Figure 1).*

The distribution of the analysed outputs was as follows: 11 (16.4%) were related to the definition of nocturia, 31 (46.3%) focused on aetiology, 8 (11.9%) were about diagnosis, and 17 (25.4%) were concerned with treatment options.

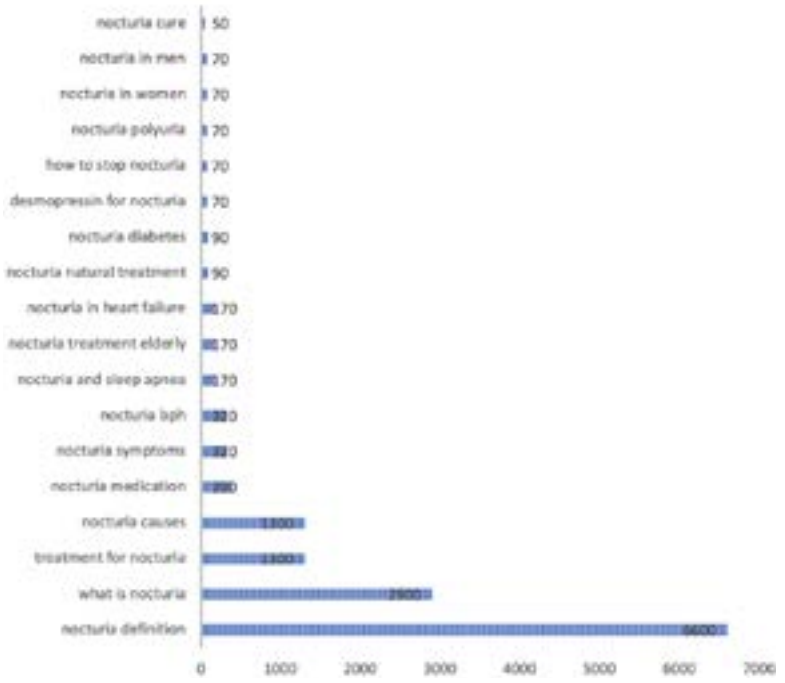

Figure 2. Results with 50 or more clicks per month (search volume/month).

Table 1. Comprehensiveness of information on AUA and EAU patient information websites by classification

Classification	Median comprehensiveness score (IQR)		*P*-value
	AUA	EAU	
Definition	4 (2)	4 (2)	1
Aetiology	1 (1)	1 (2)	0.56
Diagnosis	3 (1)	3 (1)	1
Treatment	5 (4)	5 (3)	0.85
Total	2 (3.5)	3 (4)	0.438

IQR: interquartile range, AUA: American Urology Association, EAU: European Association of Urology.

The most frequently searched query was "nocturia definition," with an average of 6,600 clicks per month. Results with 50 or more clicks per month were presented in Figure 2.

In terms of the comprehensiveness of the information provided on patient information websites, AUA had a median comprehensiveness score of 2.0 (IQR: 3.5). In contrast, the EAU had a slightly higher median score of 3.0 (IQR: 4.0). With a p-value of 0.438, no significant relation was found between the comprehensiveness scores of the AUA and EAU websites.

The analysis revealed that AUA patient information websites received a score of "1" (not mentioned) for 27 (40.30%) of the queries, with 70.37% of these relating to aetiology, 18.52% to treatment, 7.41% to diagnosis, and 3.7% to definition. Similarly, EAU patient information websites scored "1" for 26 (38.81%) queries, with 73.08% focusing on aetiology, 15.38% on treatment, 7.69% on diagnosis, and 3.85% on the definition.

The comprehensiveness of the information provided by AUA and EAU patient information websites, according to each classification, was summarised in Table 1. No statistically significant relationship was found between the comprehensiveness score and classification categories.

DISCUSSION

Nocturia is a prevalent symptom, especially in older people. It is not a disease but a consequence of illness or ageing.[1,12] Since it can be difficult for patients to determine the underlying cause independently, they may find it convenient to search the web.[13] In this study, we found nocturia is a point of interest in online patient information searching with substantial monthly clicks. We classified the most searched items related to nocturia and found that the etiological factors were the leading class, with a rate of 46.3%.

Assessment of patients' perspectives and concerns is vital for developing high-quality patient information materials. We used www.answerthepublic.com to retrieve the most searched items regarding nocturia on the web. This tool was used in a study by Dey *et al*.[14] to search for public perception and priorities in rheumatology. They found the tool effective and inexpensive compared to traditional methods for designing research priorities.[14] To the best of our knowledge, this is the first study to use www.answerthepublic.com to search for patients' perspectives on the concept of patient information. The results of the study may increase the awareness of health professionals regarding patients' concerns related to etiological factors.

According to the results from this tool, the most searched item on Google needs to match the academic websites assessed in the present study comprehensively. Although etiological factors are commonly explored, these websites focus on diagnosis, definition, and treatment. This discrepancy may be due to complex causalities related to nocturia, including lower urinary tract disorders, sleep problems, systemic disease, and medications. In this broad spectrum of conditions, any given source of information may fail to cover all aspects. An inherent bias may also be possible since these organisations are prone to providing interventions instead of preventive medicine. From a patient-centred view, preventive medicine and searching for causality may be more critical.[15]

No statistically significant difference was observed regarding scores between AUA and EAU. This reflects a consensus between the two associations regarding nocturia patient information. This consensus is most likely due to their tendency to share information on intervention rather than preventive measures, as mentioned previously.

The main strength of our study is the use of www.answerthepublic.com as a powerful tool. However, some things could be improved related to our research. Firstly, since Google is not limited to patients, other stakeholders such as researchers or content producers may also contribute to the data, contaminating the results. The lack of validation for our comprehensive score may be another limitation and could lead to subjective results. The contribution of only two websites may be another limitation, and adding more websites may change the results.

Future studies should include assessing special patient groups, such as older age or patients using diuretics. These patients may require unique information that these websites have not covered exclusively. Furthermore, utilising validated tools can enhance the precision of feedback necessary for organisations to generate patient information.

CONCLUSIONS

In conclusion, this study underscores the importance of aligning online health information with the public interest. We identified a discrepancy between the public's interest in nocturia's etiological factors and the primary focus of academic resources on diagnosis and treatment. Tools like www.answerthepublic.com provide valuable insights into public concerns but have limitations, such as influence from non-patient stakeholders. Lastly, future research should consider the unique informational needs of specific patient groups, aiming for a more comprehensive and patient-centred health information landscape.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Bursa Uludag University, Bursa, Turkey. (Decision number: 2023-11/6, date: 16.05.2023).

Authors' Contribution

Study Conception: BC; Study Design: BC; Literature Review: BC, NK; Critical Review: BC, NK; Data Collection and/or Processing: BC, NK,; Analysis and/or Data Interpretation: BC, NK; Manuscript preparing: BC, NK.

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TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Clinical Sciences

Use of Nicotine Products and Awareness among The Young Generation

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ABSTRACT

Background With the increasing prevalence of the use of nicotine products in educational institutions by the young generation, this research investigates the prevalence and awareness of nicotine products at Shifa Tameer-e-Millat University in Islamabad, Pakistan. It explores demographics, consumption patterns, and perceptions related to nicotine products.

Methods This study was conducted at Shifa Tameer-e-Millat University, Islamabad, from March 2022 to August 2023. Individuals aged 18 or older of both genders, including students from the university and Shifa Medical College, as well as healthcare employees and teachers who had consented to participate and had a history of nicotine product usage, were included.

Results The sample size was 320, with most being students (83.0%) with a mean age of 22.31 years, predominantly using cigarettes (57.5%), followed by e-cigarettes (23.4%). Participants reported exposure mainly to university (41%) and college (37%). Usage frequency varied, with 34.7% using nicotine products once daily, 32.5% 2-3 times daily, 20.6% 4-6 times daily, and 12.2% more than seven times daily. Peer pressure had a moderate influence (mean rating of 5.96), and a significant association was found between gender and nicotine product usage ($p=0.003$). Preferences favoured modern nicotine products (n: 233) over conventional ones (n: 87), but no linear trend was observed. Health impact perception was linked to willingness to quit; 167 believed their health was affected and were willing to quit, while 48 hesitated, and 79 were indecisive ($p=0.009$), with a linear trend ($p<0.05$).

Conclusion This study illuminated nicotine usage patterns, thus informing public health efforts to reduce consumption.

Turk J Int Med 2024;6(1):29-37
DOI: 10.46310/tjim.1368098
Original Article

Keywords: *Nicotine, young generation, e-cigarette, prevalence, awareness*

Received: *September 30, 2023;* ***Accepted:*** *December 13, 2023;* ***Published Online:*** *29 January 2024*

How to cite this article: *Hayat A, Farooq T, Niazi SWK, Hussein S, Munir H. Use of Nicotine Products and Awareness among The Young Generation. Turk J Int Med 2024;6(1):29-37. DOI: 10.46310/tjim.1368098*

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INTRODUCTION

Since the mid-2000s, due to the availability of various nicotine products, conventional tobacco purchases and usage have shifted to alternate products, raising concerns due to the increase in public interest.[1] Among the alternative products, e-cigarettes, nicotine patches, and nicotine gums are found to be the most widely used. Electronic cigarettes are novel battery-operated handheld devices designed to deliver smokeless doses of nicotine. In contrast, a nicotine patch is a patch impregnated with nicotine that is worn on the skin. These are designed to stimulate the same sensory experience of smoking without the factor of smoke.[2]

Nowadays, a wide variety of nicotine brands are easily accessible in retail and online shops. Nicotine products are highly advertised in markets, while safety and long-term health are still vague based on the present scientific evidence. Due to large-scale marketing, these nicotine products gained widespread pervasiveness among teenagers and young adults.[3] Indeed, according to recent reports from the USA, between 2012 and 2019, there was a marked decline in conventional tobacco smoking and a surge in the usage of e-cigarettes among the young age groups. 4.3% of middle school students repeatedly use modern nicotine products, and 11.3% of high school students reportedly used nicotine products in 2016. Furthermore, data from 24,658 individuals in the 2012 Youth Tobacco Survey reported that almost 1/3rd of adolescents in the United States consider e-cigarettes as less harmful than conventional tobacco.[4,5]

Most e-cigarettes consist of four different components: a cartridge, reservoir, or pod that holds a liquid solution (e-liquid or e-juice) containing varying amounts of nicotine, flavourings, and other chemicals; a heating element (atomiser); a power source (usually a battery) and a mouthpiece that the person uses to inhale.[6]

Pakistan has witnessed a steady increase in the use of Tobacco Harm Reduction (THR) products such as e-cigarettes and nicotine pouches over the last five years. Variously called Electronic Nicotine Delivery Systems (ENDS) or Safer Nicotine Delivery Systems (SNDS), these harm reduction products (HRPs) are used in a regulatory vacuum. However, e-cigarettes and other HRPs are legally imported as consumer goods, with tax duties imposed on them. Currently, the data on tobacco use in Pakistan is old, if not outdated.[7]

Diverse characteristics influence the vulnerability of young age groups to nicotine products. These can be intrapersonal, e.g., an adolescent's age, interpersonal, e.g., conflict with family and peers, and depend on community structure and laws. An analysis of modern nicotine products retail websites, marketing, and promotional campaigns demonstrates frequent appeals to young age groups as they feature social media influencers, famous cartoonists, and celebrities. This is shown as a symbol of fashion trends, maturity, style, and sexual appeal. It is symbolised as a way of enhancing social activity.[8]

E-cigarette vapor contains many of the known harmful toxins of traditional cigarettes such as formaldehyde, cadmium, and lead, even though usually at a reduced percentage.[9] However, short and long-term health implications on e-cigarette users remain foggy. E-cigarettes and other nicotine product marketing are of particular concern because they create the illusion that e-cigarettes are safer and healthier. Their safety and their potential role in smoking cessation is still a matter of ongoing debate.[10]

This research is imperative to illustrate the association between the use of nicotine products and gender, along with different factors that influence the use of nicotine products in the young generation. The study will further explore the health awareness among the young generation related to nicotine products. The research will also explore the willingness factor among the young generation to stop using nicotine products in terms of their health and safety. This study will provide insight into the trending use of nicotine products, and their awareness of such products will help resolve complications related to them in the future.

MATERIAL AND METHODS

The research was conducted in Shifa Tameer-e-Millat University Islamabad between March 2022 and August 2023.

Participants

The inclusion criteria were age 18 years and above for both genders. Participants are students of Shifa Tameer-e-Millat University and Shifa Medical Faculty and healthcare workers or teachers. Participants gave consent and used nicotine products.

Recruitment and randomization

The eligible participants for the study were approached with proper informed consent. Patients were recruited through a snowball sampling technique with online surveys and written questionnaires. A

target population was defined to uphold randomisation, and each eligible participant was given a unique ID.

Sample size calculation

Yamane's formula, n=N/(1+N(e)2), was used to calculate the sample size. The total population included students from different faculties and healthcare workers. The total population was estimated to be 1500. Using the above formula, a confidence interval (CI) of 95% and a margin of error of 5% were kept. It was calculated to be 317, rounding off to 320.

Statistical analysis

Data were entered into SPSS (Version 26, IBM© SPSS© Statistics) by the principal investigator. Descriptive and frequency studies were done to assess different variables. The chi-square test was used for categorical datasets.

Ethical aspects

Participants who wished to withdraw were able to do so without any requirement to give a reason.

RESULTS

A total of 320 participants were enrolled in the study. The mean age of the participants is 22.31±2.028 years *(Figure 1).* The median age was 22 years. The age of participants ranged from a minimum of 18 years to a maximum of 27 years. The 25th percentile (Q1) was found to be 21. The 50th percentile (Q2) was 22 while the 75th percentile (Q3) was 23.75. The gender distribution of the valid 320 participants revealed that 74.4% of the participants identify as male while the remaining 25.6% identify as females.

Out of the 320 participants, the majority of the individuals were students, accounting for approximately 83.0% of the participants. Forty-six of the individuals were healthcare workers (about 14.2%). Three individuals were teachers (0.9%), while another 3 participants (0.9%) falled into the others category. The majority of the participants in the research study were pursuing undergraduate education, about 254 (79.4%), and graduate-level participants account for 58 (18.1%) of the valid participants. Post-graduate participants represented a small fraction of 8 (2.5%) of the sample *(Figure 2).*

The analysis of the used nicotine products among the participants provided captivating insight into the widely used nicotine products. The most commonly used product by the participants was reported to be cigarettes, accounting for 184 individuals (57.5% of the valid participants). E-cigarettes were the second most common choice, with 75 individuals (23.4% of participants using them). 53 participants (approximately 16.6%) reported using the nicotine patches/gums. A smaller group of 8 participants (approximately 2.5%) reported using cigars *(Table 1).*

The data analysis indicated that the majority of the participants were exposed to nicotine products in university, about 130 participants (approximately). Another substantial group of 118 participants (about 36.9%) had exposure to nicotinic products in college, followed by 57 participants (17.8%) who reported the place as school. In comparison, a smaller group of 15

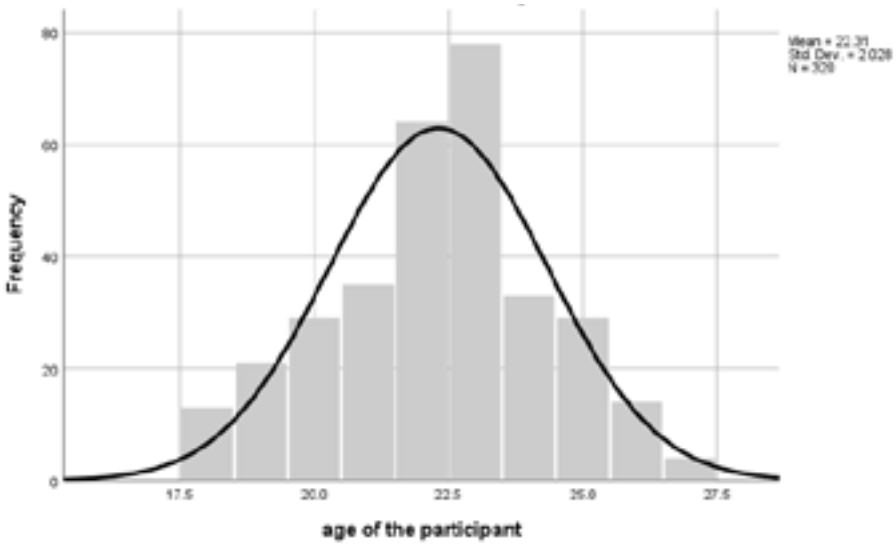

Figure 1. Histogram of the age of the participants

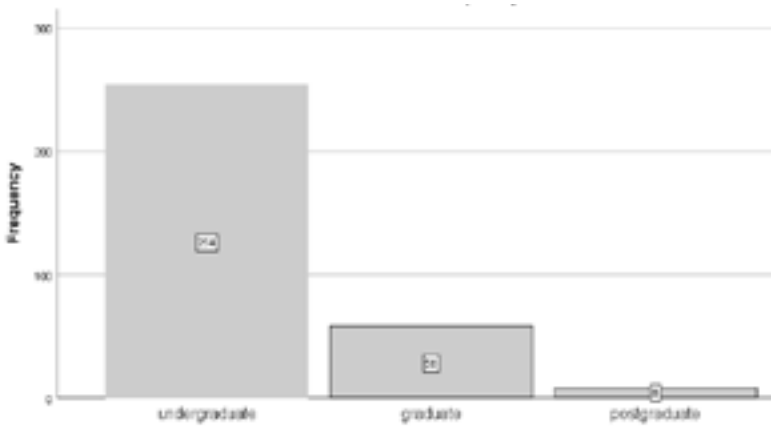

Figure 2. Education level of the participants

participants (4.7%) said an "other" place *(Figure 3).*

Participants' daily nicotine use frequency was evaluated. One hundred eleven participants (34.7%) reported using one time a day. The second most common frequency was 2-3 times per day registered by 104 participants (32.5%); 66 participants (20.6%) reported using 4-6 times a day while a small group of 39 participants (12.2%) reported using seven or more than seven times a day.

The analysis of the influence of peer pressure on the participants to use nicotine products on a scale of 1-10 provided us with the following results. The mean value for this variable was 5.96. The median value was 6.00 *(Figure 4),* while the mode was 5, indicating many participants rated the influence as moderate. The skewness value was –0.261, suggesting more individuals rated the influence lower than the mean. The kurtosis value was -0.629, suggesting that the responses were relatively spread out and not heavily clustered around the mean. The data analysis provided insight into the frequency of nicotine usage.

The data analysis using Pearson Chi-Square suggested a significant association between gender and usage of nicotine products (χ^2=14.320, df=3, p=0.003). The analysis provided strong evidence that there was a meaningful connection between gender and the reported usage of nicotine products by the participants in the present times *(Table 2).*

The chi-square test was used to assess the association between "at what place you were exposed to the nicotine product" and "how frequently the participant used the nicotine product". The Pearson Chi-Square result exhibited the following values (χ^2=18.208, df=9, p value=0.033) while the Likelihood ratio showed the values (χ^2=17.276, df=9, p value=0.045). The Pearson Chi-Square and Likelihood Ratio suggested a significant association between the two variables, as the p-value was less than 0.05. The linear-by-linear association (χ^2=2.116, df=1, p=0.146) test did not show a statistically significant linear trend *(Table 3).*

On data analysis between the variables "At what place you were exposed the first time" and "Will you prefer modern nicotine products over conventional". In total, 233 individuals preferred modern products over cigarettes. Eighty-seven individuals did not prefer modern products over conventional nicotine products. It appeared that a higher number of participants from all places preferred modern nicotine products over conventional nicotine products *(Figure 5).*

The Chi-Square test showed values as (χ^2=12.852, df=3, p=0.005), showing a statistically significant association between the two variables (*Table 3*). Linear by linear association (χ^2=2.356, df=1, p=0.125 not significant) showed no linear trend between the two variables.

The research findings based on the responses of

Table 1. Distribution of nicotine products currently used by the participant

		Frequency	Percent	Valid percent	Cumulative percent
Valid	Cigarette	184	57.5	57.5	57.5
	Cigar	8	2.5	2.5	60.0
	Nicotinic pouches/gums	53	16.6	16.6	76.6
	E-cigarette	75	23.4	23.4	100.0
	Total	320	100.0	100.0	

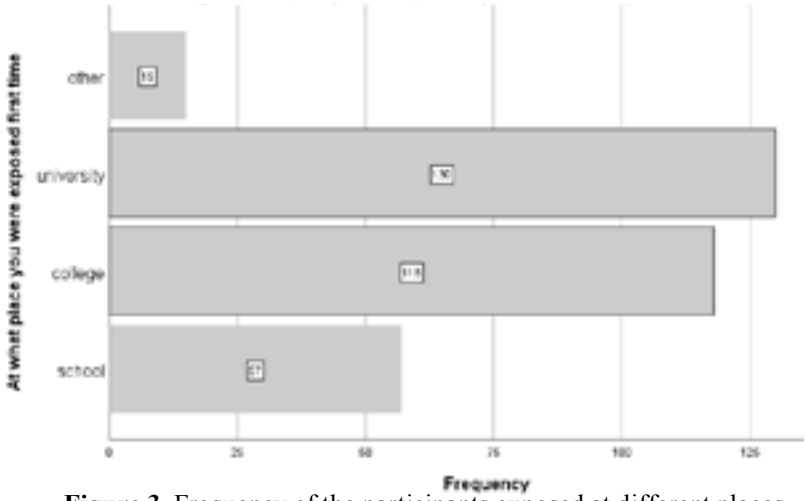

Figure 3. Frequency of the participants exposed at different places

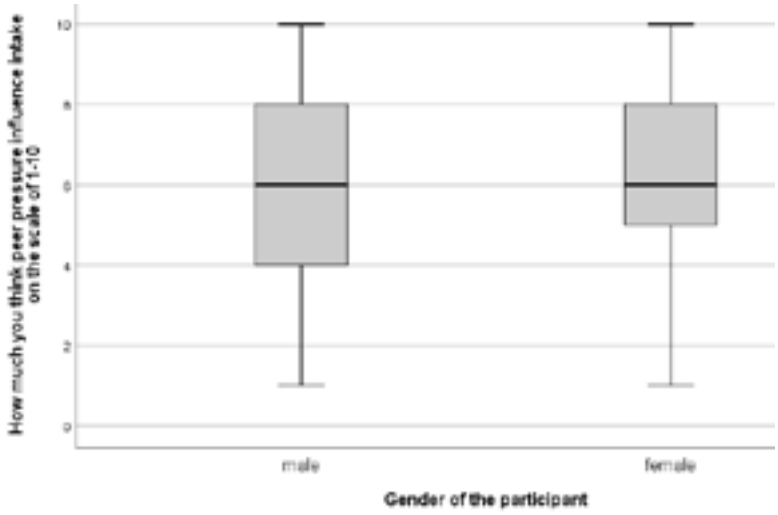

Figure 4. Participant perception of the peer pressure influence

Table 2. Nicotine products currently used by the participant according to gender*

	n	Male	Female	Total
Nicotine product used	Cigarette	150	34	184
	Cigar	7	1	8
	Nicotinic pouches/gums	32	21	53
	E-cigarette	49	26	75
	Total	238	82	320

*p=0.003

Table 3. Chi-Square tests

	Value	df	Asymptomatic significance (2-sided)
Pearson Chi-Square	12.852[a]	3	0.005
Likelihood ratio	12.496	3	0.006
Linear-by-linear association	2.356	1	0.125
N of valid cases	320		

[a]1 cell (12.5%) had expected count less than 5. The minimum expected count was 4.08.

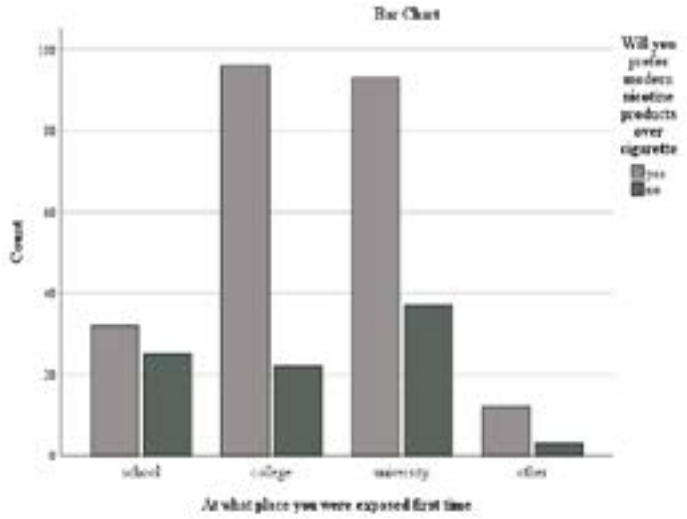

Figure 5. A bar showing participants' preferences for modern nicotine products at different places

320 participants regarding the place of their exposure to nicotine products and which place was more prone to exposure to nicotine products varied significantly. The majority of participants perceived college to be the most common place of exposure to nicotine products, followed by university and school. The "other" category had the lowest number of responses and perceptions of being prone to the use of nicotine products. The Chi-Square test (χ^2=19.576, df=9, p=0.021) suggested a significant association between the two variables.

The relationship between individuals' perception of whether their health was currently being affected by the use of nicotine products and their willingness to stop using the nicotine products showed that 26 individuals did not believe their health was being affected by the use of nicotine products and were willing to stop using nicotine products. Forty-eight individuals hesitated to stop, regardless of their health status. 79 were still deciding. One hundred sixty-seven individuals were willing to stop using nicotine products, irrespective of their health status. There were individuals in both groups (those who believed their health was affected and those who didn't) willing to quit. Still, there were also individuals in both groups who were hesitant or indecisive *(Table 4).*

The Chi-Square values (χ^2=11.618, df=3, p=0.009) showed a significant association between individuals' perception of the impact of nicotine products on health and their willingness to quit them. Linear-by-linear association held the p value=0.041 (less than 0.05), suggesting a linear trend between the two variables *(Table 5).* It was important to note that all cells in the cross-tabulation table had expected counts

Table 4. Cross-tabulation of perception of the health of participants and willingness to quit nicotine products

Count		Due to your health, what is your willingness to stop using nicotine product				Total
		Does not affect	Hesitant	Indecisive	Willing	
Do you think your health is currently being affected by the use	Yes	14	24	33	107	178
	No	12	24	46	60	142
Total		26	48	79	167	320

Table 5. Chi-Square tests

	Value	df	Asymptomatic significance (2-sided)
Pearson Chi-Square	11.618[a]	3	0.009
Likelihood ratio	11.652	3	0.009
Linear-by-linear association	4.163	1	0.041
N of valid cases	320		

[a]0 cell (0%) had expected count less than 5. The minimum expected count was 11.54.

greater than 5, and the minimum expected count was 11.54. This indicated that chi-square analysis was not affected by the low count, which enhanced the reliability of the result.

DISCUSSION

The findings from our study of 320 participants provided valuable insight into the demographics, frequency, and perception regarding the usage of nicotine products in the young population at the University of Islamabad, Pakistan. In this study, we examined the key findings, their implications, and areas of further exploration.

In examining the demographics of our study, we found the mean age to be 22.31 years, with a median age of 22 years, indicating a relatively young population. The National Survey on Drug Use and Health of America, 2014, had similar findings.11 Most participants identify as male, comprising 74.4% of the population. This gender distribution aligns with the previous research demonstrating a high prevalence of use of nicotine products among males.[12] Most participants were students, signifying the experimentation and use within the educational institutions.

Cigarettes emerged as the most commonly used nicotine product, with 57.5% reporting the use, followed by e-cigarettes, with 23.4% of the participants reporting its usage *(Figure 6).* These findings indicate that although conventional nicotine products remain highly prevalent, newer alternatives are gaining rapid popularity among the young generation.[13]

In terms of exposure, notable participants reported being exposed to nicotine products during university years, with college being the second most registered place. These findings implicate that educational institutions play a pivotal role in shaping attitudes and behaviour related to the use of nicotine products.[14]

The frequency of usage of nicotine products among the participants varied. One-third of the population reported using it once daily, and another one-third reported using it 2 to 3 times daily. A smaller group of people reported more frequent usage, with 12.2% of them saying the usage to be seven times a day. These findings demonstrate the diversity of consumption habits among the participants.

The analysis of peer pressure on the study population revealed that the mean influence rating was 5.96, signifying a moderate level of peer pressure influence on the young participants. This result underscores the impact of social factors among the participants.

Our research found significant associations between different variables. Gender was found to be significantly associated with nicotine product usage, with men more likely to use nicotine products.[12] Additionally, the place of exposure was significantly associated with the frequency of usage of nicotine products, indicating that the context in which individuals are exposed may influence their consumption pattern. Furthermore, the place of exposure was significantly associated with the preference for using modern nicotine products over conventional ones, highlighting the role of environmental factors in shaping preference.

Finally, participant's perceptions of the impact of using nicotine products on their health and their willingness to quit were assessed. This asserts that

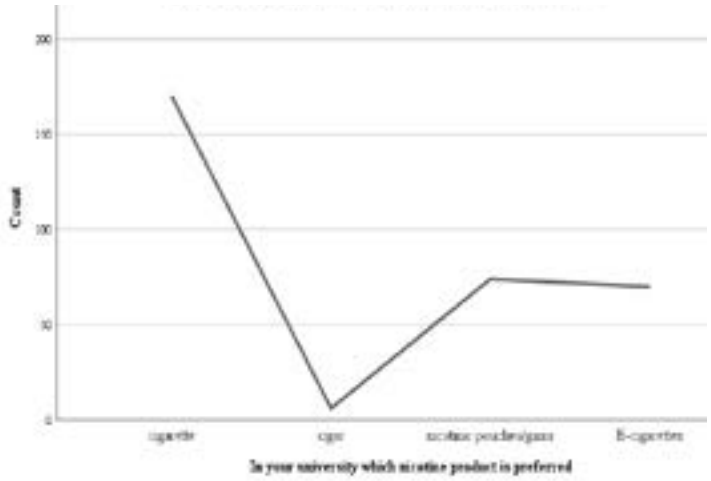

Figure 6. Line graph showing preference of nicotine product at their institution

individuals who believe that the usage of nicotine products is impacting their health are more inclined to quit, indicating the potential health-focused interventions.

This research had limitations, including cross-sectional design, potential self-reporting bias, and specific demographic characteristics of our population. Future research should explore these factors in more diverse populations and employ a longitudinal design to understand better the dynamics behind the usage of the nicotinic product.

The study provides valuable insight into the complex relationship between demographics, usage patterns, and perceptions of the young generation regarding nicotine products. Given the high prevalence among the young generation, healthcare programs and agencies should prioritise targeted prevention and educational programs in educational institutions.[11] Tailored intervention may be more beneficial regarding the needs of male and female users.[12] Educational institutions may consider adopting and enforcing nicotine-free campus policies and offering resources for nicotine cessation.[14] In primary settings, healthcare providers can integrate brief assessments of nicotine usage, peer influence, and health perceptions into routine patient care. This proactive approach can identify high-risk individuals and provide timely support.

CONCLUSIONS

In conclusion, our study sheds light on various aspects of the usage of nicotine products, from demographics to consumption patterns and perceptions. These findings can inform public health interventions and educational programs aimed at reducing nicotine products and promoting healthier choices, especially among the young population in Pakistan. Further research is needed to understand the underlying factors and effectiveness of intervention strategies.

Acknowledgment

No funding was required for the research project.

Conflict of Interest

All authors declare that there is no conflict of interest in this study.

Ethical Approval

Approved by IRB review board & ethics committee (Shifa Tameer-e-Millat University) Ref: IRB #027-22.

Authors' Contribution

Study Conception: AH, TF, SWKN, SH, HM, SN; Study Design: AH, SN; Literature Review: AH, TF, SWKN; Critical Review: AH, TF, SWKN, SH, HM, SN; Data Collection and/or Processing: SH, SWKN, HM, TF; Analysis and/or Data Interpretation: AH, SN; Manuscript preparing: AH.

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TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Internal Medicine

The Coronavirus Anxiety Level of Elderly Individuals with Diabetes Mellitus and Associated Factors during the COVID-19 Pandemic

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ABSTRACT

Background Individuals with chronic diseases are less often presented to hospitals due to the restrictions enforced during the pandemic period and the fear of contracting the disease. The purpose of the present study was to investigate the effects of the anxiety level associated with novel coronavirus on daily life, treatment compliance, and metabolic conditions in elderly diabetes mellitus (DM) patients.

Methods This study included 263 patients diagnosed with type 2 DM aged >65 years. The researchers collected the study data through the face-to-face interview method. The Patient Information Form, Coronavirus Anxiety Scale (CAS), Morisky Medication Adherence Scale, Insomnia Severity Index, and the Depression Anxiety Stress Scales (DASS-21) were used for data collection.

Results The mean CAS score was 4.25±3.76. Mean CAS scores were higher in the participants who reported a decrease in the frequency of shopping, grocery/market visits, public transport use, hospital visits, and attending routine checks, during the pandemic ($p<0.05$). Furthermore, a significant positive correlation was found between the mean CAS score and the DASS-21 score ($p<0.05$). There was a significant negative correlation between the mean CAS score and the treatment compliance score ($p<0.05$).

Conclusion The pandemic and coronavirus anxiety have had an adverse effect on daily life, treatment compliance, and metabolic conditions in elderly DM patients.

Turk J Int Med 2024;6(1):38-50
DOI: 10.46310/tjim.1290771
Original Article

Keywords: *Coronavirus, diabetes, elderly, metabolic control, treatment compliance.*

Received: *May 6, 2023;* ***Accepted:*** *October 11, 2023;* ***Published Online:*** *29 January 2024*

How to cite this article: *Ersoy S, Pehlivan S, Doğan DA, Ateş M, Ersoy İH. The Coronavirus Anxiety Level of Elderly Individuals with Diabetes Mellitus and Associated Factors during the COVID-19 Pandemic Turk J Int Med 2024;6(1):38-50. DOI: 10.46310/tjim.1290771*

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INTRODUCTION

First appeared in Wuhan, China, in December 2020, a new disease associated with the SARS-CoV-2 causative factor was defined as coronavirus disease 2019 (COVID-19).[1] The World Health Organization (WHO) defined "COVID-19: Vulnerable and High Risk Groups" in March 2020. Accordingly, older adults and individuals with health conditions, including diabetes mellitus (DM), pulmonary or cardiovascular diseases, and diseases affecting the immune system, were included in that classification.[2]

The Turkish Statistical Institute (TURKSTAT) reported that the Turkish population aged ≥65 years increased by 22.6% in the last five years, reaching 8,451,669 people in 2022.[3] advanced age was also associated with increased mortality.[4,5] Pneumonia, influenza, and healthcare-associated infections (HAIs) are among the top 10 causes of mortality in people aged ≥65 years.[6] Infections are the primary cause of mortality in 1/3 of individuals aged ≥65 years and contribute to mortality in many older adults.[7] Chinese Centre for Disease Control and Prevention reported that the overall mortality rate associated with COVID-19 was 2.3%, compared to 8% and 15% in the 70-79 years and ≥80 years age groups, respectively.5 However, it had a significant contribution to morbidity. COVID-19 is associated with exacerbation in diseases of older adults, causing an increase in the likelihood of secondary risk and functional decline. The restrictions in place to take further measures to protect older adults and the reactions of the older adults in the face of such restrictions also affected the prognoses of chronic diseases.[8]

DM, another global epidemic, is a chronic disease that affects approximately 10.5% of the world's population (536.6 million) in the 20-79 year age group based on the 2021 data. The prevalence of DM is expected to increase to 642.7 million (11.3%) in 2030 and 783.2 million (12.2%) in 2045. The Turkish data is indicative of the fact that the prevalence of DM in adults has reached an alarming level of 15.9% in 2021.[9] The coexistence of two pandemics (dual pandemic) results in a large number of patients affected by both pandemics and is associated with poor prognosis in such patients.[10] Furthermore, studies have reported that based on the preliminary data, the prevalence of COVID-19 infection and severe pneumonia was higher in DM patients than in individuals without DM; therefore, the associated mortality rates were also higher.[11,12]

It was suggested that DM patients should be followed up at home during the COVID-19 pandemic, and results of blood glucose measurements should be communicated to healthcare professionals to allow drug and insulin dose adjustments. Nevertheless, it was also suggested that DM management was not only limited to blood glucose monitoring but also included an ongoing monitoring of comorbidities and complications.[13] Notwithstanding above, it is evident that there have been particular problems for patients and healthcare professionals, who have to deal with this contingent situation. It was suggested that one of the most critical problems was the decreased metabolic control of the DM patients, who were not willing to leave their homes and present to the hospital out of fear of infection. Older adults and DM patients are at serious risk of mortality and morbidity during the COVID-19 pandemic. The extensive COVID-19 coverage both in the press and visual media, as well as the prolonged curfews, can lead DM patients to experience problems both in terms of the pandemic and the prognosis of DM. The present study was planned to investigate the effect of the anxiety level associated with the new coronavirus on daily life, treatment compliance, and metabolic conditions of elderly DM patients.

MATERIAL AND METHODS

The population of the present study comprised patients diagnosed with type 2 DM and followed up at the Endocrine and Metabolic Diseases Outpatient Clinics of Isparta City Hospital. The sample consisted of patients aged >65 years (n: 263) diagnosed with type 2 DM who attended the control visits during the study term and volunteered to participate. According to the study's inclusion criteria, patients aged >65 years with type 2 DM who agreed to participate in the research and could communicate in Turkish were included in the study. Patients who did not meet these criteria and could not complete the entire questionnaire were excluded from the study.

Ethical aspect

The required permission for the study's conduct was obtained from the Isparta Clinical Research Ethics Committee. Informed voluntary consent of the patients who participated in the study was obtained before the onset of the study.

Data collection

The study data was collected by the researchers

using the face-to-face interview method. The questionnaire form developed by the researchers based on a literature review was used for data collection. The questionnaire consisted of 5 sections, including patient sociodemographic data, COVID-19 information and interventions, Coronavirus Anxiety Scale (CAS), Morisky Medication Adherence Scale (MMAS), Insomnia Severity Index (ISI), and Depression Anxiety Stress Scale.

Sociodemographic data included inquiries regarding age, sex, educational status, marital status, duration of disease, and treatments. In addition, the patient's preprandial blood glucose (PPBG) and haemoglobin A1c (HbA1c) before the pandemic and during the data collection phase were retrieved from their electronic files and recorded in the sociodemographic data section.

COVID-19 information and interventions

This section included inquiries about information on COVID-19 history, whether COVID-19-related news was followed, vaccination considerations, behavioural patterns during the pandemic period (going out, paying visits, having guests, eating out, and going on a holiday) and habits (hand washing, shopping at grocery store and malls, and use of public transport), presentation to hospital, and attending regular control visits.

The Coronavirus Anxiety Scale (CAS), developed by Lee[14], was defined as "a short mental health screener of dysfunctional anxiety cases associated with the COVID-19 crisis." The five-point Likert-type scale consists of 5 items and one domain. Biçer *et al*.[15] conducted a language validity and reliability study for Turkey. The Cronbach's alpha coefficient of the scale was 0.832 in the above research. In the present study, Cronbach's alpha was 0.863.

Morisky Medication Adherence Scale (MMAS) was developed by Morisky and validated by Morisky, Green, and Levine in 1986.[16] It was a self-report and easy-to-use scale that measured the patient's treatment compliance. The scale comprises six closed-ended items with two options (yes/no). There were several validity and reliability studies of the scale for use in Turkey[17,18], and Cronbach's alpha coefficient was 0.782 in DM patients.[19] In the present study, the Cronbach's alpha coefficient was 0.551.

Insomnia Severity Index (ISI), developed by Morin[20], was a measurement tool for assessing insomnia severity with high validity and reliability. The scale consisted of seven items scored between 0–4 points. The overall score on the scale ranged from 0 to 28. Higher scores suggested a higher severity of insomnia. The validity and reliability study of the scale for Turkey was conducted by Boysan *et al*.[21], with a Cronbach's alpha coefficient of 0.79. In the present study, Cronbach's alpha coefficient was 0.833.

Depression Anxiety and Stress Scales (DASS-21), developed by Lovibond and Lovibond[22,23], the unabridged DASS scale consists of 42 items. Subsequent studies demonstrated that a 21-item shorter form of DASS-21 was also valid to perform the same measurement.[24,25] DASS-21 consisted of 7 items each to measure the depression, stress, and anxiety subdomains. The overall score varied between 0–63, while the subdomain scores ranged from 0 to 21. An individual with a subdomain score of ≥5 points from the depression subdomain, ≥4 points from anxiety, and ≥8 points from stress was considered to have the pertinent problem. Sarıçam[26] reported in the validity and reliability study of the scale for Turkey that the Cronbach's alpha coefficients for the subdomains were 0.85, 0.80, and 0.77 in the depression, anxiety, and 0.77 stress subdomains, respectively. In the present study, the Cronbach's alpha coefficients for the subdomain were 0.552, 0.652, and 0.890 in the anxiety, depression, and stress subdomains, respectively, with a Cronbach's alpha coefficient of 0.819 for the overall scale.

Statistical analysis

The study data were electronically analysed using the IBM Statistical Package for the Social Sciences v22 (SPSS Inc., Chicago, IL, USA) software. The normal distribution hypothesis was investigated by the Shapiro–Wilk test. The percentage, one-way ANOVA or chi-squared, Mann–Whitney U or Student t-test, and Pearson correlation analysis were used to assess data on SPSS.

RESULTS

The effect of coronavirus anxiety on daily life

Most older DM patients reported not going out more than once a week, visiting relatives, receiving guests, eating out/drinking out, and going on vacation since the start of COVID-19. In addition, there was an increase in the frequency of hand washing and a decrease in the frequency of shopping at grocery

Table 1. Distribution of mean MMAS, CAS, ISI, and DASS-21 scores by sociodemographic data of diabetes mellitus patients

Sociodemographic data		n (%)	MMAS	CAS	ISI	DASS-21	DASS-21 Anxiety	DASS-21 Depression	DASS-21 Stress
Gender	Female	150 (57.03)	2.34±1.54	4.25±3.87	8.99±3.66	40.07±14.21	14.13±4.70	13.05±7.82	12.89±4.79
	Male	113 (42.97)	2.55±1.23	4.24±3.64	8.96±4.21	37.92±14.05	13.96±5.44	11.80±7.20	12.16±4.56
	t		1.680	0.012	0.045	1.226	0.267	1.340	1.264
	P value		0.94	0.991	0.964	0.221	0.790	0.181	0.208
Marital status	Married	225 (85.6)	2.44±1.15	4.26±3.73	9.08±3.82	39.11±13.83	14.12±5.11	12.41±7.17	12.57±4.68
	Single	38 (14.4)	2.39±1.02	4.15±4.01	8.34±4.03	39.39±15.97	13.66±4.45	13.13±9.71	12.61±4.85
	Mann-Whitney U		4223.000	4107.000	3965.500	4153.000	4194.500	4256.500	4168.500
	P value		0.900	0.694	0.466	0.777	0.851	0.965	0.803
People living together	Alone	24 (9.10)	2.58±1.10	3.96±3.85	8.58±3.79	38.88±11.91	13.54±4.23	12.33±5.12	13.00±4.46
	Spouse	126 (47.90)	2.48±1.15	4.75±4.12	8.98±3.92	40.21±14.19	14.77±5.73	12.71±7.01	12.73±4.91
	Spouse and children	56 (21.30)	2.23±1.04	3.64±3.26	9.23±3.94	37.01±15.12	13.21±4.66	12.14±8.77	11.66±4.20
	Children	57 (21.70)	2.43±1.19	3.88±3.30	8.89±3.94	39.02±13.97	13.51±3.69	12.54±8.49	12.96±4.78
	χ^2		3.654	3.221	0.564	3.121	3.168	2.203	2.186
	P value		0.301	0.359	0.905	0.373	0.366	0.531	0.535
Education status	Literate	15 (5.70)	1.93±0.79	5.33±3.52	9.07±4.86	40.53±11.04	15.53±5.45	12.13±3.91	12.87±4.61
	Primary school	143 (54.04)	2.48±1.12	4.31±3.88	8.94±3.55	40.77±14.58	14.14±4.60	13.31±8.15	13.31±4.94
	High school	84 (31.90)	2.54±1.14	4.24±3.78	9.18±4.15	37.36±13.98	13.82±5.26	11.78±7.55	11.75±4.29
	University	21 (8.00)	2.05±1.13	3.09±2.95	8.38±4.58	34.28±12.29	13.33±6.47	10.28±4.42	10.66±3.69
	χ^2		8.476	3.904	0.703	5.894	3.200	5.164	8.115
	P value		0.037	0.272	0.872	0.117	0.362	0.160	0.044
Occupation	Working	47 (17.90)	2.57±1.07	3.77±3.87	8.72±4.09	36.45±13.62	13.68±5.79	11.34±5.27	11.43±4.67
	Housewife	89 (33.80)	2.38±1.15	4.16±3.77	9.54±3.52	41.76±14.18	14.67±4.92	13.59±7.77	13.49±4.8
	Retired	107 (40.70)	2.42±1.10	4.64±3.55	8.74±3.98	37.34±12.47	13.49±4.36	11.71±6.74	12.14±4.21
	Other	20 (7.60)	2.35±1.38	3.70±4.67	8.35±4.51	43.50±20.47	15.15±6.56	14.80±13.15	13.55±6.02
	χ^2		1.368	5.072	5.358	7.260	3.580	5.483	7.556
	P value		0.713	0.167	0.147	0.064	0.310	0.140	0.056
DM in their family	Yes	124 (47.10)	2.47±1.17	4.33±3.68	8.66±3.82	37.87±14.46	13.61±4.66	12.19±8.16	12.07±4.64
	No	139 (52.90)	2.40±1.10	4.17±3.85	9.26±3.96	40.28±13.79	14.44±5.31	12.81±7.03	13.03±4.72
	t		0.520	-0.357	1.245	1.383	1.355	0.64	1.653
	P value		0.604	0.721	0.214	0.168	0.177	0.507	0.100
Drugs used	OAD	111 (42.20)	2.43±1.05	4.50±3.87	8.75±3.86	38.06±13.22	13.84±4.86	12.10±6.90	12.13±4.55
	Insulin	87 (33.10)	2.37±1.13	4.45±3.56	8.84±3.81	38.12±11.27	14.03±4.71	11.62±4.67	12.52±4.54
	Switching from OAD to insulin	14 (5.30)	2.79±1.67	4.43±3.27	10.78±3.77	43.71±14.59	15.64±5.85	14.21±6.89	13.86±4.47
	OAD and insulin	51 (19.40)	2.43±1.17	3.31±3.96	9.22±4.12	41.92±19.25	14.12±5.68	14.49±11.80	13.31±5.31
	χ^2		0.649	6.176	6.228	1.836	1.952	2.111	3.542
	P value		0.885	0.103	0.101	0.607	0.582	0.550	0.315
Trained in DM	Yes	239 (90.90)	2.44±1.16	4.23±3.76	8.88±3.99	39.11±13.82	14.04±4.92	12.45±7.10	12.62±4.77
	No	24 (9.10)	2.33±0.81	4.46±3.95	9.96±2.69	39.54±17.32	14.21±6.09	13.21±11.47	12.13±4.07
	Mann-Whitney U		2804.500	2752.000	2624.500	2854.500	2791.000	2860.000	2742.500
	P value		0.852	0.740	0.484	0.970	0.827	0.982	0.720

CAS: Coronavirus Anxiety Scale, DASS: Depression Anxiety Stress Scale, DM: Diabetes Mellitus, ISI: Insomnia Severity Index, MMAS: Morisky Medication Adherence Scale, OAD: Oral Antidiabetic Drug.

Table 2. Distribution of mean MMAS, CAS, ISI, and DASS-21 scores by COVID-19 data of diabetes mellitus patients

COVID-19 data		n (%)	MMAS	CAS	ISI	DASS-21	DASS-21 Anxiety	DASS-21 Depression	DASS-21 Stress
Source of information about COVID-19	TV	78 (29.70)	2.86±1.09	5.36±4.85	9.04±4.36	35.99±11.52	13.51±4.91	10.37±3.65	12.10±5.94
	Internet	22 (8.40)	2.73±1.35	4.23±3.22	11.91±3.38	36.50±12.00	14.36±9.30	9.00±4.26	13.14±2.85
	Health workers	10 (3.80)	3.50±1.35	4.10±4.20	8.10±4.33	38.70±14.76	13.00±4.11	12.80±5.94	12.90±6.03
	Social media	21 (8.00)	2.67±0.96	4.47±3.03	6.66±2.37	25.57±7.34	9.19±2.96	7.62±1.69	8.76±3.86
	All	132 (50.20)	2.01±0.96	3.58±3.02	8.89±3.58	43.65±14.77	15.17±3.82	15.13±9.25	13.35±3.77
	$\chi 2$		3.548	0.591	16.467	22.956	17.154	20.087	14.270
	P value		0.315	0.899	0.001	<0.001	0.001	<0.001	0.003
Frequency of following news about COVID-19	More than once a day	142 (54.00)	2.48±1.10	5.09±3.25	8.91±4.16	38.08±11.80	14.23±5.31	11.97±4.65	11.87±4.33
	Once a day	121 (46.00)	2.37±1.17	3.26±4.09	9.06±3.58	40.41±16.42	13.84±4.67	13.16±9.96	13.41±4.99
	t		–0.521	4.030	–0.313	–1.299	0.632	–1.266	–2.664
	P value		0.602	<0.001	0.755	0.195	0.528	0.277	0.008
Considering COVID-19 vaccination	Yes	159 (60.50)	2.50±1.21	3.59±4.13	8.94±4.19	38.87±15.64	13.42±5.42	12.22±9.04	13.22±5.31
	No	104 (39.50)	2.32±1.00	5.25±2.88	9.02±3.41	39.56±11.51	15.01±4.19	12.96±4.51	11.58±3.36
	t		–1.466	–3.552	–0.174	–0.413	–2.687	–0.769	2.801
	P value		0.144	<0.001	0.862	0.680	0.008	0.443	0.005
COVID-19 history	Yes	90 (34.20)	2.26±1.00	3.70±3.03	8.83±4.20	32.05±9.38	12.19±4.66	9.24±3.31	10.62±4.55
	No	173 (65.80)	2.52±1.19	4.54±4.08	9.05±3.74	42.84±14.79	15.02±4.94	14.22±8.56	13.59±4.46
	Mann-Whitney U		7072.500	7237.500	7537.500	4019.500	5083.000	4222.000	5077.000
	P value		0.203	0.342	0.666	<0.001	<0.001	<0.001	<0.001
Having a relative with COVID-19	Yes	100 (38.00)	2.19±1.05	3.29±3.07	7.97±4.38	31.24±9.78	11.34±4.57	8.87±3.59	11.03±4.78
	No	163 (62.00)	2.58±1.17	4.83±4.04	9.58±3.45	43.99±14.27	15.70±4.56	14.76±8.49	13.53±4.42
	t		2.470	–3.262	–3.319	–8.572	–7.511	–6.578	–4.313
	P value		0.014	0.001	0.001	<0.001	<0.001	<0.001	<0.001

Coronavirus Anxiety Scale, DASS: Depression Anxiety Stress Scale, ISI: Insomnia Severity Index, MMAS: Morisky Medication Adherence Scale.

stores and shopping malls and using public transport. Most patients with DM also reported a reduction in the frequency of hospital presentations and attending regular control visits.

The mean score from the CAS was 4.25±3.76. The mean CAS scores were higher in the participants without a relative with a history of COVID-19 (p=0.001). The mean CAS scores were higher in the participants, who reported a decrease in the frequency of shopping, grocery/market visits, public transport use, presentation to hospital, and attending to routine controls during the pandemic (p<0.05). (*Table 1, 2, 3 and 4).*

The mean score from the ISI scale was 8.97±3.89. The mean scores from the DASS-21 scale were as follows: total scale (39.14±14.13), anxiety subdomain (14.05±5.02), depression subdomain (12.51±7.52), and stress subdomain (12.57±4.70). Furthermore, there was a significant positive correlation between the mean CAS score, the total score, and all the subdomain scores of the DASS-21 (p<0.05). *(Table 5)*

The effect of coronavirus anxiety on treatment compliance

The mean score for treatment compliance was 2.16±0.96. The treatment compliance scores were lower in the literate participants and those with relatives who contracted COVID-19 (p<0.05). There was a significant negative correlation between the mean CAS score and the treatment compliance score (p<0.05). In addition, the treatment compliance score decreased as DASS-21 scores increased (p<0.05).

The effect of coronavirus anxiety on metabolic condition

The PPBG values at data collection and during the previous year were 191.16±50.92 mg/dL and 146.46±30.34 mg/dL, respectively, and the difference was statistically significant (r=0.632, p<0.001). The difference between HbA1c values at the time of data collection and compared to the previous year in elderly DM patients was statistically significant (r=0.408, p<0.001). There was a significant relation between the mean CAS score and PPBG and HbA1c values (p<0.05).

DISCUSSION

During the pandemic, many elderly DM patients refrained from hospital visits due to both COVID-19-related anxiety and restrictions, potentially impacting their daily routines, treatment adherence, and metabolic health. This study aimed to assess the effects of novel coronavirus-related anxiety on daily life, treatment adherence and metabolic conditions in elderly DM patients.

The effect of coronavirus anxiety on daily life

As a result of the quarantine measures and restrictions, the elderly worldwide have been unable to leave their houses since the onset of the COVID-19 pandemic.[27] These restrictions and prohibitions led to increased social isolation for the individuals who enjoyed social contact only outside their homes (shopping, going to places of worship, or visiting family and friends, among other reasons).[28] In this study, most elderly DM patients have not visited their relatives, received guests, or eaten and drank out since the onset of the COVID-19 pandemic. Additionally, there has been a decrease in the frequency of going to a market, shopping, and using public transportation. This change in the behaviours of individuals may be attributed to the fear of contracting the disease and increased social isolation due to social restrictions.

Social and political messages released by governments affect how older adults feel about the risks of contracting the virus and the risks others pose to their health.[27] The social isolation of older adults is highly important due to its detrimental effect on their mental health.[29] In the present study, coronavirus anxiety was higher in the older adults, who went shopping, used public transport, presented to hospital, and attended routine controls less frequently during the pandemic period (p<0.05). Similarly, Santini *et al*.[29] reported in their study of 3,005 older adult individuals that social restrictions increased perceived social isolation and that higher perceived social isolation was associated with anxiety symptoms. A study by Kuan-Yu *et al*.[30] found that individuals with no chronic mental health disorders before the pandemic had increased anxiety and depression symptoms during the pandemic. The results of the present study are consistent with that of the literature. Increased social isolation may lead to coronavirus anxiety, and further, individuals with high coronavirus anxiety may isolate themselves from society out of fear of contracting the disease.

In the present study, coronavirus anxiety was higher in older adults who did not have a relative with a history of COVID-19. Similarly, a study by Montano and Acebes31 reported that participants with a

Table 3. Distribution of mean MMAS, CAS, ISI, and DASS-21 scores by the behaviors of diabetes mellitus patients

Behaviors from the beginning of COVID-19		n (%)	MMAS	CAS	ISI	DASS-21 Total score	DASS-21 Anxiety	DASS-21 Depression	DASS-21 Stress
Frequency of going out	Multiple times a day	45 (17.10)	2.60±1.03	2.53±3.15	9.37±4.72	43.80±22.12	15.44±7.33	15.64±14.93	12.71±4.88
	Once every day	66 (25.10)	1.91±1.22	2.68±2.64	7.44±4.48	34.71±11.14	11.98±3.64	10.14±4.58	12.59±4.59
	Every 2-3 days	32 (12.20)	2.56±1.34	4.50±3.55	10.00±4.74	34.81±13.86	13.94±6.56	10.53±5.13	10.34±4.51
	Once a week	26 (9.90)	3.19±0.89	4.15±3.07	9.50±4.22	36.65±13.78	13.50±4.93	11.42±5.36	11.73±4.96
	Less than once a week	94 (35.70)	2.46±0.94	6.11±4.12	9.37±1.90	42.20±9.35	15.03±3.23	13.67±3.61	13.50±4.47
	F		7.397	13.006	3.748	5.211	4.914	5.075	3.021
	P value		<0.001	<0.001	0.006	<0.001	0.001	0.001	0.018
Frequency of visiting relations	Yes	3 (1.10)	3.00±0.00	6.00±0.00	13.00±0.00	30.00±0.00	8.00±0.00	7.00±0.00	15.00±0.00
	No	176 (66.90)	2.34±1.18	4.84±3.88	8.98±3.81	38.89±9.85	14.35±4.50	11.56±3.89	12.98±4.35
	Sometimes	63 (24.00)	2.75±1.03	2.88±3.65	10.46±2.62	45.51±20.65	15.51±5.58	17.06±12.82	12.94±5.48
	Rarely	21 (8.00)	2.19±0.92	3.09±1.61	3.86±3.72	23.48±6.96	8.00±2.30	7.67±2.61	7.81±2.16
	$\chi2$		13.285	18.202	41.152	44.560	50.621	39.215	26.223
	P value		0.004	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Frequency of receiving guests	Yes	11 (4.20)	3.45±0.93	6.09±1.70	9.09±2.81	31.82±9.89	9.18±4.14	8.63±5.10	14.00±2.36
	No	148 (56.30)	2.07±0.98	4.69±3.63	8.91±3.93	39.13±9.15	14.81±4.49	11.66±3.66	12.65±3.87
	Sometimes	69 (26.20)	2.74±0.88	3.26±4.29	9.76±3.08	42.04±20.84	14.15±5.55	15.44±12.64	12.43±5.99
	Rarely	31 (11.80)	2.94±1.59	3.22±2.95	7.38±5.33	35.00±16.02	11.93±5.24	11.64±5.79	11.42±5.50
	Often	4 (1.50)	3.50±1.73	7.75±2.87	10.00±1.41	42.25±4.34	14.00±4.24	11.00±2.71	17.25±2.50
	$\chi2$		41.471	22.417	3.285	7.467	21.604	12.590	9.413
	P value		<0.001	<0.001	0.511	0.113	<0.001	0.013	0.052
Frequency of going out to a café/restaurant	Yes	3 (1.10)	4.00±0.00	10.00±0.00	11.00±0.00	44.00±0.00	18.00±0.00	13.00±0.00	13.00±0.00
	No	186 (70.70)	239±1.07	5.05±3.89	9.02±3.96	37.61±11.22	14.04±5.09	11.52±4.28	12.05±4.61
	Sometimes	14 (5.30)	3.50±1.50	3.07±3.49	9.64±3.47	37.64±17.23	13.85±6.49	12.50±6.59	11.28±5.57
	Rarely	60 (22.80)	2.23±1.09	1.75±1.59	8.58±3.87	44.01±19.83	13.93±4.52	15.60±13.22	14.48±4.44
	$\chi2$		14.671	43.038	6.211	1.750	5.314	2.218	20.264
	P value		0.002	<0.001	0.102	0.626	0.150	0.528	<0.001
Going on a holiday	Yes	37 (14.10)	1.78±1.29	2.29±2.43	10.97±1.38	38.73±8.28	12.70±2.32	10.81±3.88	15.21±3.23
	No	226 (85.90)	2.54±1.07	4.57±3.86	8.65±4.08	39.21±14.89	14.27±5.31	12.79±7.99	12.14±4.77
	Mann-Whitney U		2282.500	2830.000	1980.000	4173.500	3430.500	4114.000	2154.500
	P value		<0.001	0.001	<0.001	0.986	0.077	0.874	<0.001

CAS: Coronavirus Anxiety Scale, DASS: Depression Anxiety Stress Scale, ISI: Insomnia Severity Index, MMAS: Morisky Medication Adherence Scale.

Table 4. Distribution of mean MMAS, CAS, ISI, and DASS-21 scores by the habits of diabetes mellitus patients

Habits since the onset of COVID-19		n (%)	MMAS	CAS	ISI	DASS-21	DASS-21 Anxiety	DASS-21 Depression	DASS-21 Stress
Frequency of shopping	Increase	50 (19.00)	2.40±1.61	3.34±3.11	10.02±3.21	38.38±7.55	12.86±3.32	10.72±3.52	14.80±2.85
	Unchanged	36 (13.70)	3.08±1.46	4.92±3.38	8.97±4.56	39.06±12.05	14.17±5.01	11.75±5.31	13.14±5.44
	Decrease	177 (67.30)	2.31±0.81	4.37±3.98	8.68±3.89	39.38±15.89	14.37±5.38	13.18±8.65	11.84±4.77
	$\chi2$		8.589	44.836	3.168	10.571	7.698	16.608	1.817
	P value		0.014	<0.001	0.205	0.005	0.021	<0.001	0.403
Frequency of hand washing	Increase	153 (58.20)	2.48±1.29	2.92±3.16	8.90±4.00	38.14±16.26	13.35±5.45	12.16±9.33	12.62±4.77
	Unchanged	91 (34.60)	2.22±0.78	6.05±4.03	9.00±3.60	41.13±10.04	15.19±3.99	13.20±3.78	12.72±4.69
	Decrease	19 (7.20)	3.05±1.03	6.36±2.24	9.47±4.52	37.73±11.72	14.21±5.11	12.05±4.90	11.47±4.19
	$\chi2$		8.589	44.836	3.168	10.571	7.698	16.608	1.817
	P value		0.014	<0.001	0.205	0.005	0.021	<0.001	0.403
Frequency of going to a market	Increase	78 (29.70)	2.49±1.31	2.71±2.81	9.45±3.23	45.05±17.09	14.45±4.20	15.50±11.72	15.10±3.67
	Unchanged	41 (15.60)	2.66±1.59	4.07±4.01	6.21±5.60	34.12±12.25	12.56±5.58	10.04±4.61	11.51±4.89
	Decrease	144 (54.80)	2.33±0.85	5.14±3.89	9.51±3.29	37.38±11.71	14.26±5.21	11.60±4.22	11.51±4.64
	F		1.156	11.442	13.307	11.350	2.198	9.901	18.067
	P value		0.316	<0.001	<0.001	<0.001	0.113	<0.001	<0.001
Frequency of using public transport	Unchanged	51 (19.40)	3.08±1.46	5.64±4.41	9.43±5.11	38.92±12.72	14.63±5.24	11.96±5.05	12.33±5.07
	Decrease	212 (80.60)	2.27±0.98	3.91±3.52	8.86±3.54	39.20±14.47	13.92±4.96	12.65±8.06	12.63±4.62
	Mann-Whitney U		4011.000	4489.500	4726.000	5199.500	4893.000	5375.500	5197.500
	P value		0.003	0.056	0.155	0.670	0.288	0.949	0.665
Frequency of hospital presentations	Unchanged	59 (22.40)	3.32±1.11	4.00±4.09	11.19±3.88	48.17±17.90	15.78±4.78	17.41±11.19	14.98±4.68
	Decrease	146 (55.50)	2.09±0.96	4.06±3.61	8.33±3.54	35.75±10.77	13.03±4.56	10.87±4.03	11.85±4.41
	None at all	58 (22.10)	2.31±1.06	5.05±3.61	8.12±3.90	38.54±13.49	14.88±5.77	11.69±7.89	11.97±4.67
	F		33.000	3.454	9.509	18.474	7.689	18.206	10.702
	P value		<0.001	0.033	<0.001	<0.001	0.001	<0.001	<0.001
Frequency of attending to regular controls	Increase	8 (3.00)	3.42±1.31	6.91±4.75	13.16±3.99	47.13±9.67	17.37±4.68	15.12±4.48	14.63±5.31
	Unchanged	53 (20.20)	2.90±1.09	2.46±3.34	11.74±3.77	49.28±19.80	15.69±4.55	18.43±13.34	15.15±4.43
	Decrease	142 (54.00)	2.21±1.04	4.40±3.60	8.22±3.22	36.48±10.94	13.34±4.59	11.21±4.09	11.93±4.35
	None at all	60 (22.80)	2.44±1.18	5.07±3.82	7.28±4.09	35.43±10.57	13.83±5.95	10.03±3.54	11.56±4.84
	$\chi2$		46.511	11.646	33.598	25.415	20.055	29.995	27.934
	P value		<0.001	0.009	<0.001	<0.001	<0.001	<0.001	<0.001

CAS: Coronavirus Anxiety Scale, DASS: Depression Anxiety Stress Scale, ISI: Insomnia Severity Index, MMAS: Morisky Medication Adherence Scale.

Table 5. Correlation of certain characteristics of diabetes mellitus patients with mean MMAS, CAS, ISI, and DASS-21 scores

Characteristics of patients	CAS		MMAS		ISI		DASS-21	
	r	P value	r	P value	r	P value	r	P value
Age	0.055	0.376	–0.041	0.512	0.019	0.764	0.096	0.120
DM duration	0.113	0.067	0.048	0.439	–0.071	0.252	–0.024	0.696
PPBG	0.024	0.705	–0.021	0.737	0.037	0.564	–0.025	0.696
HbA1c	–0.071	0.263	–0.025	0.693	–0.025	0.697	–0.047	0.461
MMAS	–0.302	<0.001	-	-	–0.051	0.412	–0.308	<0.001
ISI	0.022	0.720	–0.051	0.412	-	-	0.399	<0.001
DASS-21	0.229	<0.001	–0.308	<0.001	0.399	<0.001	-	-
Depression	0.044	0.472	–0.125	0.043	0.247	<0.001	0.893	<0.001
Anxiety	0.266	<0.001	–0.288	<0.001	0.486	<0.001	0.749	<0.001
Stress	0.333	<0.001	–0.330	<0.001	0.281	<0.001	0.768	<0.001

CAS: coronavirus anxiety scale, DASS: depression anxiety stress scale, DM: diabetes mellitus, HbA1c: hemoglobin A1c, ISI: insomnia severity index, MMAS: Morisky medication adherence scale, PPBG: preprandial blood glucose.

COVID-19-positive family member had lower levels of anxiety. In contrast, certain studies reported that having a COVID-19-positive family member was associated with increased anxiety.[32,33] Different prognoses of COVID-19 in the participants' relatives might account for the different results in the studies above. The fact that having a relative with COVID-19 was associated with lower anxiety in the present study, may be due to a decrease in uncertainty about the disease and accordingly, an easier adaptation to the anxiety factor regarding contracting the disease.

In the present study, coronavirus anxiety increased as anxiety, stress, and depression increased. Similarly, relevant studies suggested that during the pandemic, the anxiety, stress, and depression levels significantly increased in the individuals[34]; and that the foregoing were positively correlated to each other.[35-37] Consistent with the previous studies with adult groups during the pandemic period, the anxiety, stress, and depression levels of DM patients during the pandemic were positively correlated with sleep problems.[38-40] Ahmed *et al*.[41] suggested in a cross-sectional study to assess the long-term impact of the COVID-19 pandemic that DM was a risk factor for mental health and sleep problems. A previous study reported that 87% of patients with type 2 DM were affected due to psychological stress during the quarantine period, where 27% experienced sleep deprivation.[42]

The effect of coronavirus anxiety on treatment compliance

Treatment compliance is essential for individuals with conditions including advanced age, DM, and exposure to COVID-19, which need to be controlled concurrently.[43] Uncontrolled blood glucose levels can significantly increase mortality as well as the incidence of complications. Therefore, patients must adhere to medical treatment and maintain a healthy lifestyle.[44] More than a third of older adults may fail to adhere to their treatment.[43] A study by Alshareef *et al*.[44] suggested that the treatment compliance levels of DM patients significantly decreased due to the COVID-19 pandemic. Another study with patients with type 2 DM reported lower treatment compliance levels in patients with anxiety and depression.[45] Similarly, the fact that lower treatment compliance levels in DM patients were associated with higher coronavirus anxiety, anxiety, stress, and depression levels in the present study was consistent with the relevant literature.

The effect of coronavirus anxiety on metabolic condition

DM patients are considered a high-risk population prone to a complex prognosis of COVID-19 and associated deaths. It was suggested that inevitable changes in daily life and behaviours due to the pandemic could affect DM's self-management and glycemic control.[46] Furthermore, ageing alone can make it challenging to manage DM, notwithstanding other factors.[47] A study by Falcetta *et al*.[48] reported that the age variable in the COVID-19 pandemic was one of the most significant risk factors for impaired glycemic control in DM patients. Consistently, the present study found that the PPBG and HbA1c values of DM patients were higher compared to that of the previous year ($p<0.05$). The deteriorating metabolic control during the pandemic may be associated with certain adverse situations, including degraded family economic status, limited access to healthy food due to restrictions, impaired diet,

inaccessibility of healthcare services due to restricted outpatient clinic services at the hospitals and fear of contracting the disease, decreased physical activity, restricted social activities, and increased stress.[49]

A study by Ruissen *et al*.[46] reported that the COVID-19 pandemic and quarantine measures increased anxiety in DM patients, resulting in weight gain and less physical exercise. Nevertheless, notwithstanding the above factors, there was no deterioration in glycemic control. Accordingly, there was no significant relationship between coronavirus anxiety and metabolic condition in the present study. However, it was observed that the pandemic had an overall adverse effect on the metabolic control of DM patients.

CONCLUSIONS

In conclusion, the present study demonstrated that the pandemic and coronavirus anxiety had an adverse effect on the daily life, treatment compliance, and metabolic control of elderly DM patients. The negative impact of the pandemics on the physiological and psychological well-being of individuals is still ongoing, albeit decremental, despite a certain period that has passed since its beginning. This long-term condition can further affect individuals with chronic diseases, especially DM, which needs to be well-controlled. Therefore, healthcare professionals should consider the need for regular check-ups of DM patients. Furthermore, healthcare professionals must exercise due care for the needs and emotions of the DM individuals and develop new ways to maintain patient control and training under extraordinary circumstances when face-to-face patient examination cannot be conducted. In the context thereof, ensuring continuous clinical support via phone or online calls, channelling patients to sources that provide original, up-to-date, and accurate health information, and using specific strategies such as telemonitoring are recommended. Accordingly, these steps may contribute to controlling anxiety and stress, improving daily life, increasing treatment compliance, and maintaining metabolic control in DM patients.

Acknowledgment

The authors are grateful to all patients with diabetes who participated in this study.

Conflict of Interests

The authors declare no conflict of interest.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Süleyman Demirel University, Scholl os Medicine, Isparta, Turkey. (Decision number: 158, date: 24.05.2022).

Authors' Contribution

Study Conception: SE, SP, ADA, MA, İHE; Study Design: SE, SP, DAD, MA, İHE; Literature Review: DAD, SE; Critical Review: SE, SP, DAD, MA, İHE; Data Collection and/or Processing: SE, MA, İHE,; Analysis and/or Data Interpretation: SE, SP; Manuscript preparing: DAD, SE, SP.

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TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Cardiovascular Medicine and Haematology, Clinical Oncology

Real-Life Data Comparing Weekly VCD and Twice-Weekly VCD Protocols in Newly Diagnosed Multiple Myeloma Patients

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ABSTRACT

Background This study aimed to evaluate the efficacy and side effects of bortezomib, cyclophosphamide and dexamethasone (VCD) treatment, which is frequently preferred in primary care in patients with multiple myeloma in our country, with two applications per week and one application per week.

Methods A total of 141 patients who received VCD in the induction treatment of newly diagnosed multiple myeloma were retrospectively reviewed and analysed. Both treatment groups were evaluated in terms of efficacy and side effects.

Results A total of 141 patients with newly diagnosed multiple myeloma who received VCD in induction therapy were included in the study. The median age was 62 years. Among 141 patients included in the study, 57 patients received treatment two days a week and 84 patients received treatment one day a week. Sixty-one (43.3%) patients were female and 80 (56.7%) were male. There was no significant difference between the two groups in terms of post-treatment response rates after 2nd cycle VCD regimen (p=0.378) and 4th cycle VCD regimen (p=0.965). Patients receiving weekly VCD regimen had a significantly higher rate of receiving other regimens, and additional VCD regimen of autologous stem cell transplant (ASCT) was significantly higher in patients who received a VCD regimen twice a week compared to the other group (p<0.001). ASCT was performed in 73% of the patients (n: 103). In 54 patients with ASCT at the end of 4th cycle VCD, there was no significant difference between very good partial response/complete response rates and partial response/sub responses between the two groups according to the 3rd month post-transplant responses (p=0.612). Neuropathy was observed in seven (12.3%) patients receiving twice-weekly VCD regimens, while neuropathy was observed in 16 (19.3%) and neutropenia in two (2.4%) patients receiving weekly VCD regimens. The two groups had no significant difference regarding side effects (p=0.387).

Conclusion Our study found no significant difference in the treatment response rates of patients receiving weekly VCD and twice-weekly VCD. The low rates of ASCT in the weekly VCD group were thought to be related to the fact that the patients receiving the weekly regimen were older than the other group and were unsuitable for ASCT due to age. No difference was observed between the two groups regarding the frequency of side effects.

Received: *August 28, 2023;* ***Accepted:*** *October 11, 2023;* ***Published Online:*** *29 January 2024*

How to cite this article: *Cengiz E, Can F, Güneş AK, Ceran F, Dağdaş S, Özet G, Dilek İ. Real-Life Data Comparing Weekly VCD and Twice-Weekly VCD Protocols in Newly Diagnosed Multiple Myeloma Patients. Turk J Int Med 2024;6(1):51-57. DOI: 10.46310/tjim.1350932*

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Turk J Int Med 2024;6(1):51-57
DOI: 10.46310/tjim.1350932
Original Article

Keywords: *Myeloma, induction, bortezomib, cyclophosphamide, dexamethasone*

INTRODUCTION

Combining bortezomib, cyclophosphamide and dexamethasone (VCD) is an effective and widely used induction protocol for newly diagnosed multiple myeloma patients.[1] Since it is difficult to reach the combination of bortezomib, lenalidomide, and dexamethasone in our country's first step of induction treatment, VCD combination is frequently preferred. Different protocols can be applied for VCD. In the weekly VCD protocol, bortezomib is administered subcutaneously once a week, whereas in the twice-weekly VCD protocol, bortezomib is administered twice-weekly.[2] Our study aimed to compare the side effects and response status between these two protocols in newly diagnosed multiple myeloma patients.

MATERIAL AND METHODS

In our study, 141 patients who applied to haematology outpatient clinics between March 2013 and March 2022 and received VCD in the induction treatment of newly diagnosed multiple myeloma were retrospectively screened and analysed. Approval for the study was received from the local ethics committee (dated 24/05/2023 and numbered E1-23-3619 decision).

Demographic data, comorbidities, genetic status at diagnosis, presence of hypercalcemia, renal failure, anaemia and lytic lesions at diagnosis were evaluated. The genetic status of the patients was classified as standard and high risk according to the Mayo Clinic mSMART classification. According to this classification, the presence of trisomy's, t(11;14), t(6;14) was considered standard risk, t(4;14), t(14;16), t(14;20), del 17p, p53 mutation was considered high risk. For prognosis scoring of the patients, the international scoring system (ISS) was calculated based on albumin and beta-2 microglobulin results and revised ISS (R-ISS) was calculated by adding genetic results and LDH values.

The presence of hypercalcemia was defined as a serum calcium level at least 1 mg/dL above the upper limit of the laboratory or, a serum calcium level above 11 mg/dL, a creatinine clearance below 40 mL/min or a serum creatinine value above 2 mg/dL was defined as the presence of renal insufficiency, a haemoglobin (Hb) level below 10 g/dL was defined as the presence of anaemia. An osteolytic lesion of 5 mm or larger on CT or PET-CT was defined as the presence of a lytic lesion. The presence of extramedullary disease at diagnosis was evaluated. Serum IgG, IgA, IgM, serum-free kappa, serum-free lambda, M protein and bone marrow plasma cell ratio were recorded. Response evaluation of patients receiving VCD at the end of 2nd cycle and 4th cycle according to International Myeloma Working Group (IMWG) criteria; 3rd-month post-transplant responses of patients who received autologous stem cell transplantation at the end of 4th cycle and 6th cycle VCD responses of patients who were not suitable for autologous stem cell transplantation were analysed. Bortezomib-related side effects were evaluated as neuropathy, febrile neutropenia and neuropathy. VCD weekly regimen was administered as cyclophosphamide 300 mg/m^2 intravenously (IV) weekly, dexamethasone 40 mg IV weekly, bortezomib 1.5 mg/m^2 subcutaneously (SC) and VCD twice-weekly regimen was administered as cyclophosphamide 300 mg/m2 IV weekly, dexamethasone 40 mg IV weekly, bortezomib 1.3 mg/m^2 SC.

Patients were divided into two groups: those receiving VCD weekly and those receiving VCD twice-weekly. Differences between the two groups regarding chemotherapy responses and side effects were compared.

Statistically analysis

All statistical analyses were performed using IBM SPSS version 29.0.1 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were presented as mean±SD in the tables. Some categorical variables were presented as numbers (n) and percentages (%), and some were presented in tables. The chi-square test was used for the comparison of categorical variables. Multivariate logistic regression analysis was

performed to determine the variables predicting side effects. P value <0.05 was considered statistically significant.

RESULTS

A total of 141 patients with newly diagnosed multiple myeloma receiving VCD in induction therapy were included in the study. The median age was 62 years (29-83). Among 141 patients included in the study, 57 received bortezomib 1.3 mg/m^2 SC on days 1, 4, 8, and 11, and 84 received bortezomib 1.3 mg/m^2 SC weekly. The median age between the two groups receiving weekly VCD and twice-weekly VCD was 60 and 64 years; according to this analysis, a statistically significant difference was found between age and VCD days (p=0.004). The age of the patients who received weekly VCD was higher. Sixty-one (43.3%) patients were female and 80 (56.7%) were male. According to the ISS staging system, 24.5% (n: 14) of the patients who received twice-weekly VCD regimen were stage I, 35% (n: 20) were stage II, 40.3% (n: 23) were stage III; 21.4% (n: 18) of the patients who received weekly VCD regimen were stage I, 30.9% (n: 26) were stage II, 47.6% were stage III. Only 8.5% (n: 12) of all patients included in the study had high genetic risk. The most common subtype was IgG kappa (30.5%). While 44.7% (n=63) of all patients had no comorbidity, the most common comorbidity was

Table 1. Comparison of clinical and sociodemographic data of patients (n: 141)

Variables	VCD twice a week (n: 57)	Weekly VCD (n: 84)	*P*-value
Gender (Male/Female)	34/23	46/38	0.565[b]
Median age (years)	60	64	0.004[a]
ISS			0.616[b]
I	14 (24.5%)	17 (20.7%)	
II	20 (35.1%)	25 (30.5%)	
III	23 (40.4%)	40 (48.8%)	
R-ISS			0.461[b]
I	11 (19.3%)	13 (15.9%)	
II	38 (66.7%)	62 (75.6%)	
III	8 (14%)	7 (8.5%)	
Genetic			0.494[b]
Standard	51 (89.5%)	77 (92.8%)	
High	6 (10.5%)	6 (7.2%)	
Diagnosis type			0.693[b]
IgA kappa	9 (15.8%)	8 (9.5%)	
IgA lambda	5 (8.8%)	12 (14.3%)	
IgG kappa	17 (29.8%)	26 (31%)	
IgG lambda	13 (22.8%)	16 (19%)	
Lambda light	9 (15.8%)	11 (13%)	
Kappa light	4 (7%)	10 (12%)	
IgM kappa	0	1 (1.2)	
M protein			0.515[b]
<3 g/dL	31	45	
≥3 g/dL	26	36	
Hypercalcemia (No/Yes)	45/12	73/11	0.209[b]
Renal failure (No/Yes)	36/21	57/27	0.563[b]
Anemia (No/Yes)	27/30	49/35	0.391[b]
Presence of lytic lesions (No/Yes)	13/44	24/60	0.445[b]
Extramedullary disease (No/Yes)	41/16	72/12	0.044[b]
Additional therapy before ASCT (No/Yes)	34/17	21/27	0.022[a]
ASCT (No/Yes)	5/52	33/51	<0.001[a]

VCD: bortezomib, cyclophosphamide and dexamethasone; ISS: International Staging System; R-ISS: Revised International Staging System; ASCT: autologous stem cell transplantation

[a] Mann Whitney U test, [b] Pearson Chi-square test.

Table 2. Comparison of chemotherapy response and side effect data and VCD days of patients (n: 141)

	VCD twice a week (n: 57)	Weekly VCD (n: 84)	*P*-value
After 2nd cycle VCD			0.378
CR	1 (1.8%)	0	
VGPR	27 (47.4%)	32 (38.1%)	
PR	27 (47.4%)	48 (57.1%)	
MR	2 (3.5%)	4 (4.8%)	
4th cycle VCD			0.965
CR	20 (35%)	25 (30%)	
VGPR	15 (26.3%)	23 (27.4%)	
PR	18 (31.6%)	28 (33.3%)	
MR	1 (1.8%)	2 (2.4%)	
SD	0	1 (1.2%)	
PD	3 (5.3%)	5 (6%)	
6th cycle VCD			0.445
CR	1 (12.5%)	10 (28.6%)	
VGPR	3 (37.5%)	15 (43%)	
PR	4 (50%)	10 (28.5%)	
After ASCT 3rd month			0.829
CR	22 (71%)	18 (78.3%)	
VGPR	7 (22.6%)	4 (17.4%)	
PR	2 (6.5%)	1 (4.3%)	
Side effect			0.254
None	50 (87.7%)	65 (78.3%)	
Neuropathy	7 (12.3%)	16 (19.3%)	
Neutropenia	0	2 (2.4%)	

VCD: bortezomib, cyclophosphamide and dexamethasone; CR: complete response; VGPR: very good partial response; PR: partial response; MR: minimal response; SD: stable disease; PD: progressive disease.

hypertension (n: 34, 24.1%). There was no significant difference between both groups in the presence of hypercalcemia (p=0.209), renal failure (p=0.563), anaemia (p=0.391) and presence of lytic lesions (p=0.445) at diagnosis. The number of patients with the extramedullary disease was higher in patients receiving twice-weekly VCD regimens compared to the other group (p=0.044). Table 1 showed the results of the analyses related to comparing various clinical and sociodemographic data of the patients with the days of VCD.

Response rates in twice-weekly VCD treatment group after two cycles were 1.8% complete response (CR), 47.4% very good partial response (VGPR) and 47.4% partial response (PR); these rates were 35%, 26.3% and 31.6%, respectively after four cycles of treatment. CR rate was 0%, VGPR was 38.1% and PR was 57.1% after two cycles in weekly treatment group; after four cycles 30% CR, 27.4% VGPR and 33.3% PR were achieved, respectively. There was no significant difference between the two groups in terms of therapy response after 2nd cycle VCD regimen (p=0.378) and 4th cycle VCD regimen (p=0.965). On the other hand; patients receiving weekly VCD regimen had a significantly higher rate of receiving other regimen and additional VCD regimen before autologous stem cell transplantation (ASCT) compared to the other group (p=0.022). The rate of ASCT was significantly higher in patients who received a VCD regimen twice a week compared to the other group (p<0.001). ASCT was performed in 73% of patients (n: 103). In 54 patients who had ASCT at the end of the 4th cycle VCD, responses three months after transplantation were analysed. No significant difference was found between the VGPR/CR response rates and PR/subresponses between the two groups (p=0.612).

Neuropathy was observed in seven (12.3%) patients receiving twice-weekly VCD regimens, while neuropathy was observed in 16 (19.3%) and neutropenia in two (2.4%) patients receiving weekly VCD regimens. The two groups had no significant difference regarding side effects (p=0.387). Table 2 compared chemotherapy responses and side effect data with VCD days.

DISCUSSION

Multiple myeloma accounts for approximately 17% of haematological malignancies.[3] In myeloma, the treatment goal for young and elderly patients should be to prolong survival by achieving the best possible treatment response without impairing quality of life. Studies have shown that weekly use of bortezomib and subcutaneous administration can be tolerated without any side effects on efficacy.[4,5] CR response after induction therapy and after ASCT is the most important predictor of long-term survival.[6] In recent studies, VCD induction regimens and doses are different and heterogeneous in multiple myeloma patients eligible for transplantation. It is a dose-dependent neuropathy that limits the use of bortezomib.[7] Studies have compared the combination of bortezomib, cyclophosphamide and dexamethasone (CyBorD or VCD) in induction therapy in multiple myeloma patients using different protocols. Most of these studies used bortezomib 1.3 mg/m^2 twice-weekly (days 1, 4, 8, 11) and IV.2,[8-12] Subcutaneous bortezomib has been shown to have similar efficacy with fewer side effects than IV administration, and administration of bortezomib weekly rather than twice-weekly has been associated with reduced toxicity with similar response rates.[2,13]

In a study by McCaughan *et al.*14, the treatment responses of patients receiving weekly VCD were analysed. Stable disease (SD), PR and VGPR responses were obtained in 23%, 43%, and 33% of the patients, respectively, and no progression was detected in any patient. When the response rates after ASCT were analysed, SD was 3%, PR was 35%, and VGPR and higher response rates were obtained in 59% of the patients. In the study by Reeder *et al.*[2], weekly and twice-weekly VCD protocols were compared. Thirty-three patients received VCD twice a week. PR or higher response was obtained in 88% of the patients, VGPR or higher response in 61%, and CR response in 39%. Since toxicity associated with high dose dexamethasone and bortezomib developed in the twice-weekly VCD protocol, the efficacy of the treatment decreased due to postponement/stopping of treatment. Thirty patients received weekly VCD. In the weekly VCD protocol, the bortezomib dose was 1.5 mg/m^2. PR or better response was obtained in 93% of the patients, VGPR or better response in 60%, and CR response in 43%. In this study, it was decided that weekly bortezomib treatment with low-dose dexamethasone should be the first choice protocol for induction in transplant-eligible newly diagnosed multiple myeloma patients.

Although the current treatment guidelines recommend triplet therapies containing a proteozome inhibitor with immunomodulatory drug and dexamethasone for the first line treatment in myeloma patients, this drug combination cannot be used in primary care in our country within the reimbursement conditions and indication list. It is even recommended to add a monoclonal antibody treatment to triplet therapy for especially high-risk patients suitable for ASCT.[15] Therefore, in our study, the differences in treatment response rates and side effects between once-weekly and twice-weekly administration of VCD treatment, which is still used in primary care, were investigated. Weekly treatment has the advantage of reducing the frequency of treatment compared to twice a week. We aimed to investigate whether this advantage differs in terms of response. The efficacy results of our study were similar to the studies in the literature, and no significant difference was found between the two protocols regarding response rates. In our study, the low rate of ASCT in the weekly VCD group was considered to be related to the fact that the patients receiving the weekly regimen were older than the other group and were not suitable for ASCT because of age.

Regarding side effects, the incidence of neuropathy and neutropenia was lower in our study compared to other studies. In the study by Li *et al.*[16], the incidence of neutropenia was 42%, and the incidence of neuropathy was 29%. The low toxicity incidence may be related to incomplete record keeping due to retrospective study.

Although our study was limited due to its retrospective nature and relatively low number of patients, it was thought to contribute to the literature since there was no prospective study data including many patients in our country.

CONCLUSIONS

In conclusion, our study showed no significant difference between weekly VCD and twice-weekly VCD protocols regarding response and side effects. Therefore, it has been shown that the weekly VCD protocol is feasible in induction treatment by reducing the number of hospital admissions in our country, where financial and regulatory constraints exist.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Ankara Bilkent City Hospital, Ankara, Turkey. (Decision number: E1-23-3619, date: 24.05.2023).

Authors' Contribution

Study Conception: EC, AKG; Study Design: FC, EC; Literature Review: EC, FC; Critical Review: EC, İD; Data Collection and/or Processing: ES,; Analysis and/or Data Interpretation: EC, GÖ; Manuscript preparing: EC.

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TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Internal Medicine

Combined Use and Side Effect Profile of Different Vaccine Models for COVID-19: Single Centre Experience

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ABSTRACT

Background Currently, the most effective method to combat the COVID-19 pandemic is vaccination. This study investigated whether the combined use of vaccines obtained by different methods affected the side-effect profile.

Methods This cross-sectional study evaluated 437 people (265 females, 172 males; mean age, 42.04±14.49 years) who applied to the emergency department due to side effects among 26,974 vaccinated people (13,460 females, 13,514 males). The complaints and outcomes of the patients who applied to the emergency department were recorded.

Results While the rate of admission to the emergency department due to post-vaccination side effects was 1.6% among all vaccinated participants, this rate was 3% in the mixed vaccination group. It was observed that hospitalisation was required in only two patients due to side effects. When vaccination methods were compared, the frequency of admission to the emergency department due to side effects was higher in the patients in the group in which the mRNA vaccine was mixed with the booster shot. However, it was not statistically significant (p=0.113).

Conclusion Different vaccine methods did not change the side effect profile, so different vaccine combinations could be used together if necessary.

Turk J Int Med 2024;6(1):58-63
DOI: 10.46310/tjim.1343477
Original Article

Keywords: *COVID-19, vaccine, side-effect*

Received: *August 15, 2023;* ***Accepted:*** *October 18, 2023;* ***Published Online:*** *29 January 2024*

How to cite this article: *Avcı A, Özer MR, Yurdakul MS, Ozer H, Baloglu İ. Combined Use and Side Effect Profile of Different Vaccine Models for COVID-19: Single Centre Experience. Turk J Int Med 2024;6(1):58-63. DOI: 10.46310/tjim.1343477.*

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INTRODUCTION

In December 2019, cases of pneumonia of unknown aetiology were mentioned in the city of Wuhan. In January 2020, the agent was identified as a new coronavirus (2019- nCoV) that has not been detected in humans before. Later, the name of the 2019-nCoV disease was accepted as COVID-19 and the virus was named SARS-CoV-2. WHO defined COVID-19 as a pandemic on 11 March due to the emergence, spread and severity of COVID-19 cases in 113 countries outside China.[1] The COVID-19 disease had a worldwide impact, causing more than 4.5 million deaths and unleashing the most significant global health crisis since the influenza pandemic of 1918.[2] Fighting this epidemic, all countries applied methods such as masks, social distance, and quarantine. In addition, vaccine studies have started with the aim and hope of controlling the outbreak.[3] With the approval of the Food and Drug Administration (FDA), two doses of the Pfizer-BioNTech COVID-19 vaccine started to be used in December 2020.[4] The Pfizer-BioNTech COVID-19 vaccine is a messenger RNA (mRNA) vaccine and enables cells to become immune by producing antibodies after vaccination.[5] The number of people who received the first dose of the Pfizer-BioNTech COVID-19 vaccine worldwide is increasing daily. Although the frequency of side effects after vaccination is 0.2%, very few are serious side effects, such as anaphylaxis.[6] Purified inactivated viruses can induce neutralising antibody responses and have been classically used for vaccine development. CoronaVac is an inactivated COVID-19 vaccine developed by Sinovac Life Sciences (Beijing, China). It showed that CoronaVac was well tolerated and induced humoral responses against SARS-CoV-2 in those aged 18-59 who received the CoronaVac vaccine. Studies have reported that doses starting from 1.5 µg up to 6 µg for vaccination in individuals over 60 years of age are safe and well tolerated.

In our country, within the scope of combating the pandemic, two doses of COVID-19 (inactivated) Vaccine manufactured by Sinovac were used at first. Then, as the vaccine's effectiveness decreased, it was recommended to apply an additional 3rd dose of vaccine as of July 1, 2021. In this study, we aimed to compare the complaints and their differences with other types of vaccine administration in terms of side effects of patients who applied to the hospital with early-stage side effects after two doses of Sinovac-manufactured COVID-19 vaccine and one booster shot of an mRNA vaccine.

MATERIAL AND METHODS

The study protocol was approved by the Medical Ethics Committee of Karaman Training and Research Hospital (10.09.2021/32053). This was a cross-sectional retrospective study evaluating 437 people (265 females, 172 males; mean age, 42.04±14.49 years) who applied to the emergency department due to side effects among 26,974 vaccinated people (13,460 females, 13,514 males) between July 1 and August 1, 2021.

Patients aged 18-80 who received at least one dose of the COVID-19 vaccine were included in the study. The patients were divided into three groups according to vaccine dose and type. Participants in the first group received the first dose of the Pfizer BionTech COVID-19 vaccine. Participants in the second group were administered two doses of the Pfizer BionTech COVID-19 vaccine. Participants in the third group were administered two doses of the COVID-19 (inactivated) vaccine produced by Sinovac and an mRNA vaccine booster shot.

A review of medical records (including information on age, sex, and application complaint) was undertaken. In addition, the hospitalization-discharge outcomes of the patients were examined. All precautions have been taken for the confidentiality of data.

Statistical analysis

The findings of our study were evaluated using the Statistical Package for Social Sciences for Windows version 21.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were given for each variable. Continuous data were expressed as mean ± standard deviation. Categorical data were expressed as frequency and percentages. Mixed ANOVA models were used to assess differences between groups in terms of continuous variables. A difference was considered statistically significant when p-value <0.05.

RESULTS

Demographic and clinical characteristics of participants were depicted in Table 1. It was observed

that 26,974 people were vaccinated in Karaman Training and Research Hospital between July 1 and August 1, 2021. All individuals had received their first Pfizer BionTech COVID-19 vaccine dose, while 17,152 (63.6%) individuals had received both doses. In addition, 3,595 (13.3%) individuals had a history of two doses of COVID-19 (inactivated) vaccine manufactured by Sinovac before the first dose of Pfizer BionTech COVID-19 vaccine.

Table 1. Demographic and clinical characteristics of participants

Parameters	Frequency n (%)
Inoculated vaccine dose	
1st dose	6,227 (23.1)
1st and 2nd dose	17,152 (63.6)
2nd sinovac plus 1st dose	3,595 (13.3)
Total	26,974 (100)
Gender (Female/Male)	
1st dose	3,305/2,922
1st and 2nd dose	8,274/8,878
2nd sinovac plus 1st dose	1,881/1,714
Total	13,460/13,514
Previous infection with SARS-CoV-2	
Infected	107 (24.5)
Non-infected	330 (75.5)
Onset of side effects	
1st dose	95 (21.7)
1st and 2nd dose	233 (53.3)
2nd sinovac plus 1st dose	109 (24.9)
Total	437 (100)

After vaccination, 437 people were admitted to our hospital due to various side effects. Among all vaccinated participants, the hospital admission rate due to side effects was 1.6%. While the rate of admission to the emergency department was 1.5% in patients vaccinated after the first dose of the Pfizer BionTech COVID-19 vaccine, this rate was 1.35% after two doses. The same rate was 3% in the mixed vaccination group. Muscle-joint pain was the most common side effect, regardless of vaccine dose and type (34.9%). Other than that, fever, malaise, nausea, headache, and flu-like symptoms were the most common side effects (18.8%, 9.2%, 10.8%, 7.1%, and 6.6%, respectively). The rarest side effects were myocarditis and seizure *(Table 2).* While hospitalisation was required for only two patients due to side effects, it was observed that all patients recovered without any sequelae.

When the mixed vaccine group was examined, the most common side effect was muscle-joint pain (25.7%). Other common reasons for admission in this group were fever, nausea, flu-like symptoms, and headache (19.3%, 15.6%, 11%, and 10.1%, respectively).

Table 2. Common side effects after getting a COVID-19 vaccine

Symptoms	Frequency n (%)
Muscle-joint pain	153 (35)
Fever	82 (18.8)
Nause	47 (10.8)
Malaise	40 (9.2)
Headache	31 (7.1)
Flu-like symptom	29 (6.6)
Injection site redness	19 (4.3)
Diarrhoea	16 (3.7)
Arm pain	13 (3.3)
Seizure	1 (0.2)
Myocarditis	1 (0.2)

We performed post hoc analysis with the Bonferroni method to compare the groups in terms of side effects. Although there was no difference in common side effects, the frequency of admission to the emergency department due to side effects was higher in patients in the group mixed with a booster shot of an mRNA vaccine. However, it was not statistically significant ($p<0.113$). We also observed that the same group was older ($p<0.05$) *(Table 3).*

DISCUSSION

This was the first study to evaluate for adverse events in patients who received two doses of Sinovac-Manufactured COVID-19 (inactive) Vaccine followed by an additional dose of Pfizer BionTech COVID-19 vaccine. The present study had two main findings. First, the frequency of admission to the emergency department for post-vaccine adverse events was higher, although not statistically significant, in people who received two doses of the COVID-19 (inactive) vaccine manufactured by Sinovac and a booster shot of an mRNA vaccine. Second, there was no difference in common side effects and side effect outcomes.

Currently, in the period following the outbreak, no specific treatment consensus has been reached for COVID-19, although various potential treatments have yielded more or less encouraging results.[7-10] Therefore, a global race has begun to develop an anti-COVID-19 vaccine in response to the COVID-19 pandemic. As of

Table 3. Comparison of the groups in terms of side effect profile

Variables	First group (n: 95)	Second group (n: 233)	Third group (n: 109)	*P*-value
Age (years)	33.86+11.97	40.86+13	51.79+14.21	<0.05
Gender (Female/Male)	63/32	141/92	61/48	0.321
Applying to the emergency room	95 (1.5)	233 (1.35)	109 (3.03)	0.113
Symptoms				
Muscle-joint pain	36 (37.9)	89 (38.2)	30 (27.5)	0.135
Fever	14 (14.7)	47 (20.2)	21 (19.3)	0.516
Nause	9 (9.5)	21 (9)	17 (15.6)	0.169
Malaise	8 (8.4)	23 (9.9)	9 (8.3)	0.857
Headache	5 (5.3)	15 (6.4)	11 (10.1)	0.348
Flu-like symptom	5 (5.3)	12 (5.2)	12 (11)	0.107
Injection site redness	7 (7.4)	9 (3.9)	3 (2.8)	0.238
Diarrhoea	6 (6.3)	8 (3.4)	2 (1.8)	0.228
Arm pain	4 (4.2)	5 (2.1)	4 (3.7)	0.540

Data were given as mean±SD or n (%).

April 19, 2021, according to the COVID-19 data of the Milken Institute, there are 252 vaccine options for use in the treatment of COVID-19 under different vaccine platforms and development stages around the world. These vaccines have been developed by different methods such as RNA-based, viral vector-mediated, virus-like particle, and inactivated virus. However, four COVID-19 vaccines specifically, BNT162, mRNA 1273, ChAdOx1 and Ad26.COV2-S have been authorised in all countries of the world. Other vaccines, such as Sputnik V, BBIBP-CorV, CoronaVac, and COVAXIN, have also completed phase III clinical trials and have been put into emergency use in many countries.[11] Many countries have developed their vaccination administration protocols. Our country used double-dose PfizerBioNTech, double-dose Sinovac plus single-dose Pfizer-BioNTech, or three-dose Sinovac vaccination protocols.[12]

In a study conducted by Hatmal *et al*.[13], 2213 participants (1,344 women and 869 men) were evaluated with a questionnaire regarding side effects after vaccination. In this study, Sinopharm 38.2% (845), AstraZeneca 31% (686), Pfizer-BioNTech 27.34% (605), and less frequently, Sputnik V, Moderna, Covaxin, and Johnson & Johnson vaccines were used for vaccination. They found that the most common side effect was pain and swelling at the injection site, and the participants who reported moderate to severe side effects were those frequently administered AstraZeneca, Pfizer-BioNTech, and Sinopharm vaccines. In addition, they also showed that the presence and number of post-vaccination side effects were significantly correlated with the number of doses received (p=0.01 and <0.001, respectively). In addition, Pormohammad *et al*.[14] showed that mRNA-based vaccines cause more side effects, and the Adenovirus vector vaccine causes more diarrhoea and arthralgia than other vaccines. The same study stated that after administering the mRNA-based vaccine, side effects such as redness, swelling, itching, general fever, chills, myalgia, joint pain, vomiting, fatigue and headache were observed in the vaccination area. In our study, while mild and moderate side effects such as muscle-joint pain, fever, nausea, weakness, headache, flu-like symptoms, rash at the injection site, diarrhoea, and arm pain were more common, in line with the literature, the most common side effect was muscle-joint pain.

Previous studies shown that the frequency of conditions that can be considered as severe side effects such as thrombocytopenia, thrombosis, anaphylaxis, myocarditis, acute myocardial infection, pulmonary embolism, deep vein thrombosis, intracranial bleeding is very low.[12-15] Barda *et al*.[16] recently demonstrated that the risk ratio of myocarditis after vaccination was 100,000/2.7, and adverse effects such as acute kidney injury, arrhythmia, deep vein thrombosis, intracranial haemorrhage, myocardial infarction, and pulmonary embolism were rare. While serious side effects were detected in only two of the participants in our study, this rate corresponded to 100,000/3.7 when considering the vaccinated ones, similar to the studies in the literature.

Due to the increase in hospitalisation rate due to COVID-19 in people who received two doses of inactive vaccine produced by Sinovac, an additional

3rd dose of vaccine was planned in our country. In our study, when the group that received two doses of COVID-19 (inactive) Vaccine produced by Sinovac and a booster shot of an mRNA vaccine, there was no significant difference in side effects when compared with the group that received only Pfizer BionTech vaccine. In addition, it was determined that the mixed-type vaccine group was older. This is because the vaccine is administered primarily to older adults in our country, and the first vaccines made in our country were produced by Sinovac since there were problems in the supply of vaccines when the pandemic first broke out. In addition, some rumours about mRNA vaccines, such as deterioration of the genetic structure and infertility, especially the religious concerns of the elderly population, may have caused the COVID-19 (inactive) vaccine produced by Sinovac to be chosen as the first choice in the elderly population.

There were several limitations in our study. First, our sample was not large enough as our study was designed as a single centre. Secondly, it should be considered that our results cannot be applied to all patients because of the differences between nationalities since almost all of the patients included in the study were Turkish. Finally, interventions and treatments for patients were not evaluated in this study.

CONCLUSIONS

In conclusion, mixed vaccination methods will be needed, especially as the pandemic progresses. In the present study, we demonstrated that although the frequency of admission to the emergency department due to post-vaccine side effects has increased in people who have received a mixed vaccine for COVID-19, the common side effects and outcomes were similar. Therefore, mixed vaccination methods can be used reliably for patients. Further randomized and controlled studies evaluating the mixed vaccination methods for COVID-19 are needed.

Conflicts of Interest

All authors declared that there was no conflict of interest in this study.

Informed Consent

Ethics committee approval was obtained from the institution for the study, and written consent was obtained from all patients.

Financial Disclosure

This study did not need financial funding.

Human Participants and/or Animal Rights

This article contains no unethical studies with human participants or animals performed by authors.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Karamanoğlu Mehmetbey University, Karaman, Turkey. (Decision number: 06/02, date: 19.00.2021).

Authors' Contribution

Study Conception: AA, IB; Study Design: AA, IB, HÖ; Literature Review: MRÖ, AA, HÖ; Critical Review: İB; Data Collection and/or Processing: AA, MRS, MSY; Analysis and/or Data Interpretation: İB, HÖ; Manuscript preparing: İB, HÖ.

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TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Cardiovascular Medicine and Haematology

A Case of Acute Lymphoblastic Leukaemia Complicated with Sinonasal Mucormycosis Infection

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ABSTRACT

Acute lymphoblastic leukaemia (ALL) is an aggressive hematologic malignancy of lymphoid progenitor cells. During treatment of ALL, the patients may be complicated by fatal infections such as sinonasal mucormycosis. In patients with immunocompromised conditions like haematologic malignancies, mucormycosis can be deadly. Once mucormycosis has been detected, it is critical to act quickly to begin treatment. Amphotericin B, posaconazole, or isavuconazole are the medications of choice. Effective treatment requires a long-term course of therapy. Switching to other effective medications should be considered when the preferred treatment is not working. The factors contributing to mucormycosis must also be treated, such as the underlying conditions (haematologic malignancies). Herein, we aimed to discuss a clinically stable ALL patient complicated with extensive sinonasal mucormycosis. She improved with amphotericin B (5 mg/kg/day) and oral posaconazol (300 mg/day) treatment.

Turk J Int Med 2024;6(1):64-68
DOI: 10.46310/tjim.1316471
Case Report

Keywords: *Acute lymphoblastic leukaemia, sinonasal mucormycosis, mucormycosis, amphotericin B, posaconazole*

Received: *June 19, 2023;* ***Accepted:*** *November 9, 2023;* ***Published Online:*** *29 January 2024*

How to cite this article: *Hacımustafaoğl AŞ, Orhan B, Ersal T, Özkocaman V, Özkalemkaş F. A Case of Acute Lymphoblastic Leukaemia Complicated with Sinonasal Mucormycosis Infection. Turk J Int Med 2024;6(1):64-68. DOI: 10.46310/tjim.1316471*

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INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is an aggressive neoplasm of lymphoid progenitor cells. The annual incidence of ALL is 1.7 cases per 100,000 people in the United States.1 Pediatric ALL is a highly curable disease with survival rates above 90%. In contrast, the long-term overall survival (OS) of ALL in adults is about 35-45%.[1] Mucormycosis is an infection with high mortality caused by filamentous mold fungi.[2] In Europe and America, mucormycosis cases are most commonly seen in hematologic malignancies (38-62%).[3] Invasive fungal infections in the paranasal sinuses have a progressive course and high mortality rates in immunocompromised patients.[4] The global guidelines for treating mucormycosis recommends controlling the underlying conditions (uncontrolled diabetes and immunosuppression), an early diagnosis and an effective treatment. This treatment includes systemic antifungal therapies with extensive surgical debridement.[5] We aimed to present a patient diagnosed with Pre-B-ALL who was complicated with sinonasal mucormycosis infection.

CASE REPORT

A 28-year-old woman, who received chemotherapy and radiotherapy for Ewing sarcoma nine years ago, was followed up in remission. She was diagnosed with pulmonary embolism after receiving the COVID-19 vaccine one year ago. Anti-cardiolipin IgM and IgG, anti-beta 2 glycoprotein IgM and IgG, and antiphospholipid IgM and IgG were negative. In the thyrombophilia panel, while MTHFR mutation was heterozygously positive, factor V Leiden and prothrombin mutations were negative. In whole blood count, platelet $100x10^9$/L, leukocyte $9.10x10^9$/L, lymphocyte $1.92x10^9$/L, haemoglobin 12.9 g/dL. Low molecular weight heparin (LMWH) was started to treat the pulmonary embolism. Thrombocytopenia ($18x10^9$/L) developed under LMWH treatment. Peripheral blood smear showed leukocyte $10.7x10^9$/L, neutrophil $5.24x10^9$/L, lymphocyte $4.78x10^9$/L, haemoglobin 10.1 g/dL, platelet $15.0x10^9$/L, and %40 lymphoblast. A bone marrow biopsy was performed, and 74% lymphoblastic infiltration was observed in the bone marrow aspirate (flow cytometry: CD19+, CD20+, CD22+). The Philadelphia (Ph) chromosome was negative in cytogenetic analysis. The patient was diagnosed with Ph(–) B-ALL. She was hospitalised for HYPER-CVAD (cyclophosphamide 900 mg/day, vincristine 2 mg/day, doxorubicin 75 mg/day, dexamethasone 40 mg/day, mesna 900 mg/day, methotrexate 1.5 g/day, cytarabine 9 g/day, rituximab 560 mg) treatment. After the first cycle of HYPER-CVAD, the patient went into remission and received four HYPER-CVAD chemotherapy cycles and five doses of intrathecal methotrexate therapies for CNS prophylaxis during 8-month period.

In April 2022, she was hospitalised for the fourth course of HYPER-CVAD chemotherapy. During HYPER-CVAD, she received prophylactic ciprofloxacin, fluconazole, acyclovir. She had complaints of headache and fullness in the ear. Skull base magnetic resonance imaging (MRI) was reported as oedema findings extending from Rosenmüller fossa, Meckel's cave, masticator cavity, and carotid cavity and contrast enhancement findings in the dynamic examination. There were signal intensity changes consistent with inflammation in the ethmoid cells, bilateral maxillary sinus, sphenoid sinus, and unstained area in the mucosa on the posterior wall of the sphenoid sinus on the right. The findings were consistent with mucormycosis-like invasive infection *(Figure 1)*. During otorhinolaryngology (ENT) examination, a mass lesion was observed in the nasopharynx. The serum galactomannan was negative. Liposomal amphotericin B was started at a high dose of 5 mg/kg/day because the patient had central nervous system involvement (Sphenoid sinuses were involved.). A biopsy was performed on the lesions in the nasopharynx. In the nasopharynx debridement material, there were hyphae, spores, and fungi formations that belong to the group of mucorales. The nasopharynx debridement biopsy results also revealed mucormycosis. After eight weeks of liposomal amphotericin B treatment, no mucor was detected in the nasal re-biopsy specimens. However, the appearance favoring mucormycosis infection was persisted in the control skull base MRI. The patient was discharged with 300 mg/day oral posaconazole treatment, and ALL maintenance treatment was postponed.

After two months of posaconazole treatment, cranial MRI revealed; "Intense inflammatory appearance and abscess formation (mucormycosis) over 4 cm extending into the pterygomaxillary fissure, orbital fissure, cavernosal sinus and infratemporal fossa on the right" *(Figure 1)*. Posaconazole medication was continued despite the demonstrated improvement over the last MRI. The patient was clinically stable

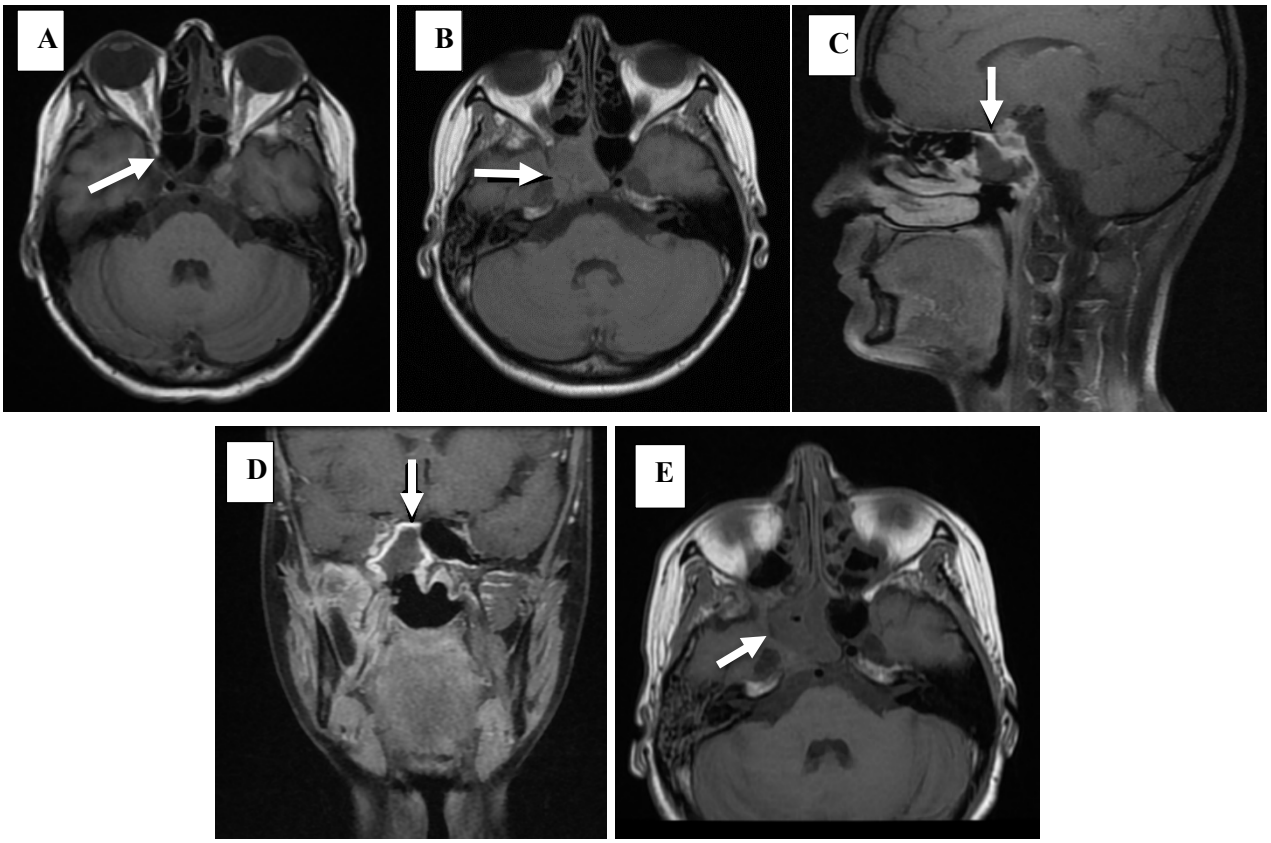

Figure 1. Cranial MRI findings at the onset of the first symptoms on 01.06.2022 (A), on the 69th day of liposomal amphotericin B treatment on 09.08.2022 (B, C and D) and on the 5th month of antifungal treatment on 02.11.2022 (E)

with no evidence of recurrence. It was decided to start ALL maintenance treatment (vincristine 2 mg/day, mercaptopurine 100 mg/day, methotrexate 15 mg/day) under 4th month of posaconazole treatment. The patient continued to be followed up with the infectious disease and ENT department under outpatient posaconazole maintenance treatment, and no signs or symptoms of mucormycosis infection were observed.

DISCUSSION

The diagnosis of ALL generally requires demonstration of ≥20% bone marrow lymphoblasts on hematopathology review of bone marrow aspirate and biopsy materials.[6] The most common treatment regimens include multiagent chemotherapy regimens. Hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate and cytarabine (Hyper-CVAD) is one of them. In general, the treatment phases of ALL can be grouped as induction, consolidation, and maintenance therapies. All treatment regimens for ALL include central nervous system (CNS) prophylaxis and/or treatment.[6] Our case had given HYPERCVAD regimen. Since she was CD20 positive in her flow cytometry, she received rituximab therapy.

Mucormycosis is an infection with high mortality caused by filamentous mold fungi. It requires long-term treatment.[4,7] It also requires extensive surgical debridement. According to the ESCMID/ECMM 2019 guidelines, both conventional amphotericin B or liposomal amphotericin B (at a dose of 5 mg/kg/day) are recommended for the first-line antifungal monotherapy for mucormycosis. When amphotericin B formulations are unavailable or in instances of fungal infections that are refractory or intolerant to amphotericin B, posaconazole or isavuconazole are strongly suggested as salvage therapy.[5] Treatment dose for oral isavuconazole is 200 mg three times a day (first two days), followed by 200 mg once a day maintenance dose, and for oral posaconazole is 300 mg twice a day g (first day), followed by 300 mg once a day maintenance dose.[9] In our case, after eight weeks of liposomal amphotericin B treatment, no mucormycosis was found in biopsy specimens, but findings in favour of

mucormycosis persisted in imaging studies. Therefore, posaconazole (300 mg/day oral) treatment and close clinical follow-up were planned at discharge. Posaconazole treatment was scheduled to be continued in the patient who was clinically responsive and had cranial MRI that could be in favor of mucormycosis.

Remission maintenance therapy is a standard component of the treatment of ALL after induction therapy. According to NCCN Guidelines, most maintenance regimens are based on a backbone of daily mercaptopurine (6-MP) and weekly methotrexate (typically with the addition of periodic vincristine and corticosteroids) for 2 to 3 years.[9] In our case, after four months of oral posaconazole treatment, the clinically stable patient was given maintenance ALL treatment (vincristine 2 mg/day, mercaptopurine 100 mg/day, methotrexate 15 mg/day) under posaconazole therapy. She was still under posaconazole treatment and had ALL maintenance treatments.

As in our case, cases of rhino-cerebral mucormycosis have been reported in the literature, but these cases are usually in the pediatric age group ALL.[8] Bonifaz *et al*.[7] conducted a retrospective study including 55 mucormycosis patients with oral involvement. This study has showed that the main comorbidity in patients infected with mucormycosis was diabetes (%71) and second most associated comorbidity was neutropenia (%27) mainly related to acute lymphocytic leukaemia.[7] In our case, the patient was having HYPER-CVAD therapy and was in neutropenia a week before being diagnosed with mucormycosis.

Liang *et al*.[5] reported a case of 11-year-old pulmonary mucormycosis treated with oral posaconazole. They continued the anticancer regimen during voriconazole treatment. Popa *et al*.[8] reported a 5-year-old girl diagnosed with severe rhino-cerebral mucormycosis (facial and cerebral structures were involved) after completing induction treatment of ALL, which discontinued leukaemia therapy during the episode of febrile mucormycosis. They then started chemotherapy as soon as the patient got better.[8] As in our case, we continued with posaconazole treatment for mucormycosis, and the patient was given ALL maintenance treatment under posaconazole treatment.

CONCLUSIONS

Our case is one of a few surviving cases of rhino-cerebral mucormycosis arising in patients with ALL reported in the literature. As Popa *et al*.[8] mentioned, the complete remission of leukaemia in our patient was a particular advantage. The mucormycosis infection was improved with posaconazole treatment. The importance of this case is being a self-limiting case of mucormycosis controlled with amphotericin B and posaconazole treatment. Our case highlights the importance of continuing oral regimens (posaconazole) if there is an unresponsiveness after parenteral amphotericin B. It is essential to cure underlying aetiology in mucormycosis treatment. That's why the clinicians should start maintenance therapies for underlying etiologies (like ALL) as soon as possible, the patient's infection is cured or stabilised.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: AŞH, BO; Study Design: AŞH, BO; Literature Review: AŞH, BO; Critical Review: BO, TE, VÖ, FÖ; Data Collection and/or Processing: AŞH, BO,; Analysis and/or Data Interpretation: AŞH, BO, TE, VÖ, FÖ; Manuscript preparing: AŞH, BO.

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TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Infectious Diseases

Severe Acute Respiratory Syndrome Coronavirus 2 Omicron Variant Kinetics in Natural Infection: A Case Study

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ABSTRACT

Background Omicron has become the mainstream epidemic variant of severe acute respiratory syndrome coronavirus 2 worldwide. One reason for the high infectivity of this variant is its ability to multiply rapidly in the human body. It has been speculated that, in general, the short period required for virus multiplication affects the incubation period and timing of viral shedding that begins during the incubation period. However, it is unclear whether these effects can be related to the Omicron variant. Similar to a recent human challenge study, in this study, patients with known timing of Omicron infection were followed up in a hospital before the onset of the disease.

Methods In two patients, the viral shedding was investigated and analysed along with symptoms before and after the disease onset.

Results The incubation period for Omicron was 30-36 h; this was shorter than the average incubation period of the alpha variant in the human challenge study and that reported in a systematic review and meta-analysis (3.5 days). Viral shedding at the nasal site began 19-22 h after infection, approximately 10 h before symptom onset.

Conclusion The results of this study demonstrated that in some instances with Omicron (BA.5), the time to viral shedding and the time to disease onset were considerably shorter after infection than those previously reported for Omicron and Alpha variants. We showed the importance of early detection of the viral antigen after viral exposure and early isolation initiation to prevent infection spread.

Turk J Int Med 2024;6(1):69-73
DOI: 10.46310/tjim.1352394
Case Report

Keywords: *SARS-CoV-2, Omicron variant, incubation period, viral shedding, infection, epidemic*

Received: *August 30, 2023;* ***Accepted:*** *December 13, 2023;* ***Published Online:*** *29 January 2024*

How to cite this article: *Tamura D, Yamagishi H, Koshu K, Tajima T, Osaka H. Severe Acute Respiratory Syndrome Coronavirus 2 Omicron Variant Kinetics in Natural Infection: A Case Study . Turk J Int Med 2024;6(1):69-73. DOI: 10.46310/tjim.1352394*

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected approximately 762 million people worldwide since the coronavirus disease (COVID-19) pandemic began and was associated with more than 6 M deaths worldwide by April 2023.[1] Since the emergence of the virus in Wuhan, China, in December 2019, various new variants have been identified. The high infectivity and transmissibility patterns of the virus have led to an increased vigilance for variants of concern (VOCs).[2] Omicron (B.1.1.529), a VOC that emerged in 2020, has become predominant within its short history, spreading worldwide at an unprecedented rate and generating new cases of infection. Several likely reasons have been suggested for the high infectivity of Omicron, one of which is its numerous mutations in high-infectivity regions.[3,4] Furthermore, mutations and deletions in its spike protein have led to a critical situation wherein specific therapies for patients infected with up to the delta variant level are not optimal for Omicron-infected patients.[5] One of the reasons for the rapid spread of Omicron is its increased adaptation to humans and rapid proliferation in the human body.[6,7] It has been suggested that increased viral replication may lead to earlier viral shedding and a shorter incubation period.[8] The mean incubation period of Omicron is 3.5-3.6 days[9,10], indicating a gradual reduction in the incubation period compared with those of the past epidemic variants. However, the timing of infection in infected individuals, the subject of these analyses, is only an estimate. Regarding the timing of viral shedding during incubation, a recent human challenge study on the alpha variant confirmed that viral shedding begins within two days after infection.[11] However, data for Omicron still need to be included. Due, in part, to the difficulty of obtaining specimens from infected patients before the onset of COVID-19 and to the difficulty of carrying out human challenge studies, the exact incubation period and the onset of viral excretion during the incubation period for the Omicron variant is still being.

As in the human challenge study, we had two patients in whom the time of infection with Omicron was precise, and the nasal viral load and clinical course were analysed over time immediately after infection. Although this is a case report, we compare the viral dynamics of Omicron during the incubation period with those reported previously and discuss the usefulness of viral antigen testing during the incubation period and the need to prevent the spread of infection.

CASE REPORT

Two patients who may have been infected with SARS-CoV-2 in December 2022 and January 2023 were included in this study. The patients were admitted to Jichi Children's Medical Center Tochigi and were asymptomatic immediately after the exposure to SARS-CoV-2. On admission, the film array of respiratory specimens, which was subjected to extensive screening tests, was negative for the virus and bacterial antigens. SARS-CoV-2-specific IgM and nucleocapsid IgG antibody tests using chemiluminescent enzyme immunoassay also tested negative. After admission, vital signs were measured multiple times daily; anterior nasal and nasopharyngeal nasal swab samples for viral load measurement and blood samples for antibody titer measurement were collected continuously.

Viral RNA was extracted from nasal specimens using QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany), and real-time polymerase chain reaction (RT-PCR) was performed using Reliance One-Step Multiplex Supermix (Bio-Rad Laboratories, California, USA) according to the National Institute of Infectious Disease protocol.[12] This study was approved by the Jichi Medical University Hospital Research Ethics Review Committee (approval number 21-100), and written informed consent was obtained from the participants. Written consent was obtained from a surrogate parent or guardian for the participant who was <18 years old.

Case 1 was an 18-year-old female patient with no history of COVID-19 and SARS-CoV-2 vaccination. She was exposed to a COVID-19 patient for approximately 2 h during lunch at home and was admitted to our hospital 5 h after the last contact (LC). On admission, SARS-CoV-2 RT-PCR results for the nasopharyngeal and anterior nasal samples were negative, and blood tests and chest radiographs showed no abnormal findings. SARS-CoV-2 RT-PCR result was negative until 12 h after the LC. The nasopharyngeal site sample tested positive for the SARS-CoV-2 antigen (lineage BA.5.2.1) for the first time 19 h after the LC, with a Cycle threshold (Ct) value of 36.9. Subsequently, 36 h after the LC, the patient developed a dry cough and sore throat, and 42 h after the LC, the patient developed a fever of 38.6 °C. The highest Ct values were 19.5 at 47 h after the LC for the anterior nasal sample and 17.3 at 64 h after the LC for the nasopharyngeal sample. We explained

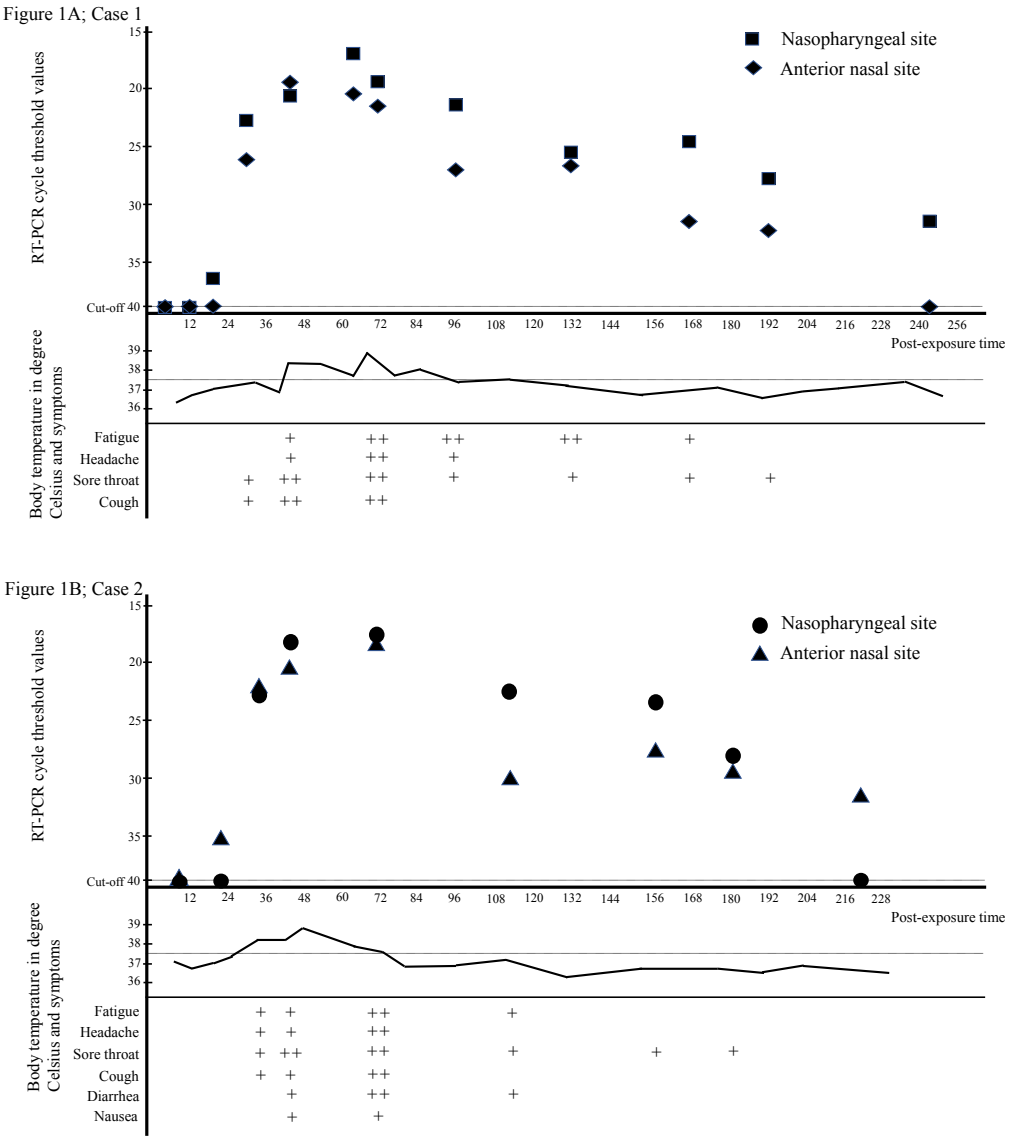

Figure 1. Viral dynamics and symptoms after Omicron variant infection in the two cases. Nasal specimens were collected from the anterior nasal and nasopharyngeal sites simultaneously. The cut-off value for RT-PCR was set at 40. Clinical symptoms were assessed at the time of specimen collection from the nasal cavity. One and two plus indicated mild and severe symptoms, respectively. No description was provided for asymptomatic patients. (A) Ct values for the anterior nasal site were shown using the diamond symbol, whereas those for the nasopharyngeal site are indicated as squares. (B) Ct value for the anterior nasal site was established as a triangle, whereas that for the nasopharyngeal site was established as a circle.

antivirals and other COVID-19 medications to the family and the patient; however, they expressed their reluctance to use any therapeutic agents other than antipyretics. Therefore, we used acetaminophen thrice a day as the maximum frequency of use when the patient complained of general malaise and headache at a body temperature ≥37.5 °C. Ninety-six hours after the LC, the fever resolved, and the symptoms rapidly improved. Subsequently, general malaise and sore throat persisted for >70 h. Viral shedding persisted for more than 240 h and 150 h after the LC and post-febrile, respectively *(Figure 1A).* Serum IgM tested positive 166 h after the LC, and serum IgG tested positive 192 h after the LC.

Case 2 was a 13-year-old female patient with no history of COVID-19 and SARS-CoV-2 vaccination. She was exposed to a COVID-19 patient during a 3-hour dinner party at home. She was admitted to the hospital 9 h after the LC. Upon admission, RT-PCR results for nasal specimens taken from anterior nasal and nasopharyngeal sites were negative, and blood tests and chest radiographs showed no abnormal findings. Twenty-two hours after the LC, the patient was asymptomatic; however, RT-PCR was positive for the SARS-CoV-2 antigen (lineage BA.5.2) for the anterior nasal specimen. The Ct value at this time was

35.0. We explained to the family and the patient the available COVID-19 medications of choice; however, they did not wish to use any other therapeutic agents except antipyretics. After that, the Ct values of both nasal samples decreased over time. The lowest Ct values were recorded at 71 h after the LC, 18.7 for the anterior nasal sample and 18.1 for the nasopharyngeal sample. Thirty-four hours after the LC, general malaise, fever of 38°C, dry cough, and sore throat developed. Seventy-one and 112 h after the LC, the fever had resolved and improved, respectively. Sore throat persisted for approximately 110 h after the resolution of the fever. Viral shedding continued for > 200 hours after the LC and 140 hours after the fever had broken *(Figure 1B)*. Furthermore, serum IgM tested positive 217 h after the LC; however, serum IgG did not test positive.

No radiographic or blood test abnormalities were found during hospitalisation for either patient.

DISCUSSION

Both the time to viral shedding and the incubation period after infection with the Omicron was short for both cases. The case results from the two cases highlight the importance of testing for viral antigens during the incubation period and initiating surgical masks and isolation as early as possible after viral exposure to prevent the spread of infection in home and group settings.

In our patients, viral shedding based on the nasal sample testing began during the 19-22 h incubation period after the LC. Compared with the alpha variant[11] for which viral shedding occurs 40 h after infection, in this study the Omicron variant shedding occurred earlier. This suggests that testing early after viral exposure, i.e., before the onset of disease, may be helpful; however, it should also be considered that at high Ct values, i.e., low viral loads, the possibility of false-negative result occurs with antigen-detection rapid diagnostic tests that do not amplify viral genes, although RT-PCR can provide an accurate diagnosis. The subsequent viral load trends were similar to those previously reported[13], with the nasopharyngeal site illustrating more viral shedding than the anterior nasal site; furthermore, viral shedding was observed for more than ten days after onset. A systematic review and meta-analysis reported the mean incubation period to be 3.5 days.[9] Although the reason is not apparent, it should be noted that some patients, like our patients, may be infected with the same variant of Omicron but with a much shorter incubation period of 30–36 h. A study by Ogata *et al*.[14], published several months prior, involving patients infected with Omicron, reported that the incubation period of Omicron had shortened to an average of about 2.6 days.

CONCLUSIONS

By inference, Omicron, which has been spreading since 2021, may have undergone genetic mutations[15] due to viral multiplication, resulting in increased efficiency of viral multiplication in the human body, which may be one of the reasons for early viral shedding after infection and shortened incubation period. Our results indicate that post-exposure measures must be taken sooner than before to prevent the spread of Omicron.

Conflict of Interest

The authors declare no conflicts of interest.

Funding

This work was supported by Sekisui Medical Co., Ltd. [grant number 4-2411-013].

Acknowledgments

We would like to thank the staff at the COVID-19 Ward 2A at Jichi Children's Medical Center, Tochigi, for caring for our patients.

Author Contributions

Conceptualization, D.T., H.Y.; materials, D.T., H.Y., K.K.; Patient care and specimen collection, D.T., H.Y., K.K.; Data collection, D.T.; Analysis, D.T.; Literature review, H.T., H.O.; Writing-original draft preparation, D.T., H.Y., K.K.; Critical review and editing, D.T., H.Y., K.K. H.T., H.O; Supervision, H.T., H.O.; Funding acquisition, D.T.

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