EISSN 2149-2530

Turkish Thoracic Journal

Official Journal of the Turkish Thoracic Society

ISSUE 2 APRIL 2017 VOLUME 18

Editorial

Original Articles

Case Reports

Consensus Report

Turkish Thoracic Journal

Official Journal of the Turkish Thoracic Society

ISSUE 2 APRIL 2017 VOLUME 18

Türk Toraks Derneği adına sahibi / Owner on behalf of the Turkish Thoracic Society: Fuat Kalyoncu • Yayın türü / Publication Type: Yerel süreli / Local periodical • Yayın tarihi / Publication Date: Ocak 2017 / January 2017 • Türk Toraks Derneği tarafından yayınlanmaktadır / Published by Turkish Thoracic Society, Turan Güneş Bulvarı Koyunlu Sitesi No: 175/19 Oran-Ankara, Turkey (+90 312 490 40 50)

AVES

Yayıncı
İbrahim KARA

Yayın Yönetmeni
Ali ŞAHİN

Yayın Yönetmeni Yardımcısı
Gökhan ÇİMEN

Yayın Koordinatörleri
Betül ÇİMEN
Zeynep YAKIŞIRER
Gizem KAYAN
Melike Buse ŞENAY

Yayın Sekreteri
Özlem ÇAKMAK

Proje Koordinatörü
Hakan ERTEN

Proje Asistanları
Aylin Atalay

Şükriye YILMAZ

Grafik Departmanı
Ünal ÖZER
Neslihan YAMAN
Deniz DURAN

Contact
Address: Büyükdere Cad. No: 105/9 34394
Mecidiyeköy, Şişli-İstanbul
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com

Turkish Thoracic Journal
Official journal of the Turkish Thoracic Society

Turkish Thoracic Journal

Official journal of the Turkish Thoracic Society

AIMS AND SCOPE

Turkish Thoracic Journal (Turk Thorac J 2017; 18:) is the double-blind, peer-reviewed, open access, international publication organ of Turkish Thoracic Society. The journal is a quarterly publication, published on January, April, July, and October and its publication language is English.

Turkish Thoracic Journal started its publication life following the merger of two journals which were published under the titles "Turkish Respiratory Journal" and "Toraks Journal" until 2007. Archives of both journals were passed on to the Turkish Thoracic Journal.

The aim of the journal is to convey scientific developments and to create a dynamic discussion platform about pulmonary diseases. With this intent, the journal accepts articles from all related scientific areas that address adult and pediatric pulmonary diseases, as well as thoracic imaging, environmental and occupational disorders, intensive care, sleep disorders and thoracic surgery. Clinical and research articles, reviews, statements of agreement or disagreement on controversial issues, national and international consensus reports, abstracts and comments of important international articles, interesting case reports, writings related to clinical and practical applications, letters to the editor, and editorials are accepted.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Turkish Thoracic Journal is indexed in Web of Science – Emerging Sources Citation Index, Scopus, EMBASE, EBSCO, CINAHL, Gale/Cengage Learning, ProQuest, DOAJ, and TUBITAK ULAKBIM TR Index.

Processing and publication are free of charge with the journal. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system, which is available at www.turkthoracj.org. The journal guidelines, technical information, and the required forms are available on the journal's web page.

All expenses of the journal are covered by the Turkish Thoracic Society. Potential advertisers should contact the Editorial Office. Advertisement images are published only upon the Editor-in-Chief's approval.

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the Turkish Thoracic Society, editors, editorial board, and/or publisher; the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

All published content is available online, free of charge at www.turkthoracj.org. Printed copies of the journal are distributed to the members of the Turkish Thoracic Society, free of charge.

Editors in Chief:
Prof. Oğuz KILINÇ
Prof. Metin AKGÜN
Address: Turan Güneş Bulvarı, Koyunlu Sitesi No: 175/19 Oran, Ankara, TURKEY
Phone: +90 (312) 490 40 50
Fax: +90 (312) 490 41 42
E-mail: toraks@toraks.org.tr

Publisher: AVES
Address: Büyükdere Cad., 105/9 34394 Mecidiyeköy, Şişli, İstanbul, TURKEY
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com
Web page: www.avesyayincilik.com

INFORMATION FOR THE AUTHORS

Turkish Thoracic Journal (Turk Thorac J 2017; 18:) is the double-blind, peer-reviewed, open access, international publication organ of Turkish Thoracic Society. The journal is a quarterly publication, published on January, April, July, and October and its publication language is English.

The aim of the journal is to convey scientific developments and to create a dynamic discussion platform about pulmonary diseases. With this intent, the journal accepts articles from all related scientific areas that address adult and pediatric pulmonary diseases, as well as thoracic imaging, environmental and occupational disorders, intensive care, sleep disorders and thoracic surgery. Clinical and research articles, reviews, statements of agreement or disagreement on controversial issues, national and international consensus reports, abstracts and comments of important international articles, interesting case reports, writings related to clinical and practical applications, letters to the editor, and editorials are accepted.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

Manuscripts submitted to Turkish Thoracic Journal will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions.

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. For photographs that may reveal the identity of the patients, releases signed by the patient or their legal representative should be enclosed.

All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

Each individual listed as an author should fulfil the authorship criteria recommended by the International Committee of Medical Journal Editors

(ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

1 Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2 Drafting the work or revising it critically for important intellectual content; AND
3 Final approval of the version to be published; AND
4 Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

Turkish Thoracic Journal requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through www.turkthoracj.org) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

Turkish Thoracic Journal requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional, that might lead to potential bias or a conflict of interest. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

When submitting a manuscript to Turkish Thoracic Journal, authors accept to assign the copyright of their manuscript to Turkish Thoracic So-

ciety. If rejected for publication, the copyright of the manuscript will be assigned back to the authors. Turkish Thoracic Journal requires each submission to be accompanied by a Copyright Transfer Form (available for download at www.turkthoracj.org). When using previously published content, including figures, tables, or any other material in both print and electronic formats, authors must obtain permission from the copyright holder. Legal, financial and criminal liabilities in this regard belong to the author(s).

Statements or opinions expressed in the manuscripts published in Turkish Thoracic Journal reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; the editors, the editorial board, and the publisher disclaim any responsibility or liability for such materials. The final responsibility in regard to the published content rests with the authors.

MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2016 - http://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behaviour.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.turkthoracj.org. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the following:
- Copyright Transfer Form,
- Author Contributions Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors)

during the initial submission. These forms are available for download at www.turkthoracj.org.

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions and this page should include:
- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, and highest academic degree(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: An English abstract should be submitted with all submissions except for Letters to the Editor. Submitting a Turkish abstract is not compulsory for international authors. The abstract of Original Articles should be structured with subheadings (Objective, Material and Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Material and Methods, Results, and Discussion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, and Discussion subheadings. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	35	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labelled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are three or fewer authors, all authors should be listed. If there are four or more authors, the first three authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Rankovic A, Rancic N, Jovanovic M, et al. Impact of imaging diagnostics on the budget – Are we spending too much? Vojnosanit Pregl 2013;70:709-11.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be cancelled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

Editors in Chief:
Prof. Oğuz KILINÇ
Prof. Metin AKGÜN
Address: Turan Güneş Bulvarı, Koyunlu Sitesi No: 175/19 Oran, Ankara, TURKEY
Phone: +90 (312) 490 40 50
Fax: +90 (312) 490 41 42
E-mail: toraks@toraks.org.tr

Publisher: AVES
Address: Büyükdere Cad. 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com
www.avesyayincilik.com

CONTENTS

Turk Thorac J 2017; 18: 27-8 DOI: 10.5152/TurkThoracJ.2017.17012

EDITORIAL

Primary Ciliary Dyskinesia: Ready for Quality of Life Assessment

Özge Yılmaz[1], Metin Akgün[2,3]

[1]Department of Pediatric Allergy and Pulmonology, Celal Bayar University School of Medicine, Manisa, Turkey
[2]Editor in Chief
[3]Department of Chest Diseases, Atatürk University School of Medicine, Erzurum, Turkey

Primary ciliary dyskinesia (PCD) is a chronic, inherited disease characterized by ciliary dysfunction leading to defects in mucociliary clearance, thus causing upper and lower respiratory problems such as sinusitis and bronchiectasis as well as infertility. Diagnostic workup includes a combination of different techniques such as nasal nitric oxide measurement, high-speed video microscopy analysis, electron microscopy, and genetic analysis because there is no single gold standard due to the genetic and phenotypic heterogeneity of the disease [1,2].

Due to the chronic nature of the disease, difficulty in expectorating respiratory secretions, chronic presence of symptoms such as productive cough, and requirement of daily treatment, this disease poses a burden on the patients and their families. PCD negatively impacts quality of life (QOL) because of disease complications as well as treatment burden. Moreover, treatment adherence decreases with time in patients, which might further deteriorate prognosis [3].

World Health Organization defines "health" as a complete state of physical, mental, and social well-being; thus, patient-reported outcomes, especially health-related QOL (HRQOL), are important components of health and need to be assessed as part of a routine care in chronic diseases such as PCD [4].

In the previous issue of the Turkish Thoracic Journal, Emiralioglu et al. described the translation procedure of PCD-specific HRQOL. Forward translation procedures followed international standards, where two independent and blinded translators fluent in English and Turkish participated. Backward translation into English was performed by a third independent translator. The final Turkish translations of the questionnaires were applied to five subjects from each age group: adult, adolescent, and pediatric PCD patients as well as five parents. After the subjects completed the questionnaire, a cognitive debriefing session was performed, where each item of the questionnaire was discussed by the subjects. Finally, all these information were used to achieve a final Turkish translation of the PCD-specific HRQOL that is ready for validation and reliability studies [5].

The PCD-QOL questionnaire developed by Lucas et al. has different domains for different age groups: pediatric, adolescent, and adult patients as well as parents. These domains mainly evaluate physical, emotional, and social aspects of PCD related to QOL. Moreover, there are different domains for various symptoms at different age groups. The total numbers of items in the questionnaires are 37 in the questionnaire for children, 43 in the one for adolescents, 49 in the one for adults, 41 in the parents' questionnaire [5-7]. Content validity of this questionnaire has been shown in English-speaking populations [6]. However, translations of QOL measures require cultural adaptation besides linguistic translation, and cognitive debriefing is one of the most important steps of this adaptation.

Assessment of QOL is an essential part of follow-up of children with chronic diseases such as PCD. Thus, it is important that we have a cultural adaptation of a Turkish PCD-QOL questionnaire. Next step shall include the demonstration of validity and reliability of this questionnaire in Turkish patient population.

Address for Correspondence: Özge Yılmaz, Celal Bayar Üniversitesi Tıp Fakültesi, Çocuk Allerji Bilim Dalı, Manisa, Türkiye
E-mail: oyilmaz_76@hotmail.com ***Available Online Date:*** *15.03.2017*

REFERENCES

1. Lucas JS, Barbato A, Collins SA, et al. European Respiratory Society guidelines for the diagnosis of primary ciliary dyskinesia. Eur Respir J 2017;49:pii: 1601090.
2. Goutaki M, Maurer E, Halbeisen FS, et al. The international primary ciliary dyskinesia cohort (iPCD Cohort): methods and first results. Eur Respir J 2017;49:pii: 1601181.
3. Pifferi M, Bush A, Di Cicco M, et al. Health-related quality of life and unmet needs in patients with primary ciliary dyskinesia. Eur Respir J 2010;35:787-94. [CrossRef]
4. Eiser C, Morse R. A review of measures of quality of life for children with chronic illness. Arch Dis Child 2001;84:205-11. [CrossRef]
5. Emiralioğlu N, Karadag B, Ozcelik U. Quality of Life Questionnaire for Turkish Patients with Primary Ciliary Dyskinesia. Turk Thorac J 2017; 18: 2017;18:19-22. [CrossRef]
6. Dell SD, Leigh MW, Lucas JS, et al. Primary ciliary dyskinesia: first health-related quality-of-life measures for pediatric patients. Ann Am Thorac Soc 2016;13:1726-35. [CrossRef]
7. Lucas JS, Behan L, Dunn Galvin A, et al. A quality-of-life measure for adults with primary ciliary dyskinesia: QOL-PCD. Eur Respir J 2015;46:375-83. [CrossRef]

Turk Thorac J 2017; 18: 29-32 DOI: 10.5152/TurkThoracJ.2017.16051

ORIGINAL ARTICLE

Influence of Statin Therapy on Exacerbation Frequency in Patients with Chronic Obstructive Pulmonary Disease

Şehnaz Olgun Yıldızeli[1], Baran Balcan[2], Emel Eryüksel[1], Berrin Bağcı Ceyhan[1], Sait Karakurt[1], Turgay Çelikel[1]

[1]Department of Pulmonolgy and Intensive Care, Marmara University School of Medicine, İstanbul, Turkey
[2]Department of Pulmonolgy, Başkent University School of Medicine, Ankara, Turkey

Abstract

OBJECTIVES: Chronic obstructive pulmonary disease (COPD) is an inflammatory disease, in which chronic and systemic inflammation plays an important role. By decreasing neutrophil infiltration and cytokine production, statins have anti-inflammatory mechanisms.

MATERIALS AND METHODS: Fifty-seven patients who had diagnosis of chronic obstructive pulmonary disease according to GOLD guideline were included in the study; 20 of them were statin users. Statin users group were patients being under medication with regular simvastatin, atorvastatin or rosuvastatin 20 mg per day for at least the past 1 year.

RESULTS: There was statistically no significant difference between patients with or without statin treatment with respect to; age, female-male ratio, COPD severity level, medication used for COPD, pulmonary function tests results and smoking habits. COPD exacerbation frequency in patients using statins was significantly less than patients not using statins ($p<0.05$). Patient number with COPD exacerbation, antibiotic treatment and outpatient clinic administration and outpatient clinic administration frequency was significantly lower in statin using patients ($p<0.05$).

CONCLUSION: COPD patients receiving statins have a lower frequency of COPD exacarbations, hospital administration and antibiotic treatment compared to patients not receiving statins.

KEYWORDS: Statin, COPD, exacerbations

Received: *04.12.2016* ***Accepted:*** *15.02.2017* ***Available Online Date:*** *15.03.2017*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease of the lungs characterized by progressive airway obstruction [1]. Some studies have proposed a significant association between smoking and pulmonary inflammation [2,3]. However, recent studies have shown an increase in systemic inflammatory markers in non-smokers, suggesting a possible association with systemic inflammation rather than solitary pulmonary inflammation [4]. Deterioration in pulmonary functions may result in decreased functional capacity, frequent hospitalization, increase in hospitalization rates, and early mortality [5]. Currently, COPD is the fourth leading cause of mortality worldwide and is projected to be the third by 2020 [6]. The economic burden of the disease is high due to close follow-up requirements, hospitalization due to exacerbations, and long-term treatments of the disease. However, the only available options that increase survival rate are oxygen treatment and smoking cessation [7,8].

Chronic and systemic inflammation plays an important role in the pathogenesis of COPD. Statins are a class of drugs that inhibit cholesterol production in the liver by blocking the mevalonate pathway. Currently, these drugs are used in the prevention of cardiovascular diseases. In addition to their cholesterol-lowering effects, recent studies have shown that they also possess immune modulatory and pleiotropic effects [9,10]. Decrease in neutrophil infiltration and cytokine production, blockage of matrix remodelling, and slow-down in endothelial and epithelial integrity and apoptosis are the antiinflammatory mechanisms of statins in COPD patients [11]. Recently, studies have reported significant reduction in mortality [12,13] and hospitalization rates in patients receiving statins [14].

This study aimed to evaluate the possible effect of statins on the annual exacerbation frequency of COPD patients.

MATERIALS AND METHODS

Patient Selection

The study was conducted between January 2009 and September 2011 on patients with COPD visiting our outpatient clinic for routine clinical follow-up. All patients had a history of at least 20 packets per year smoking habit with some of them

Address for Correspondence: Baran Balcan, Başkent Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Ankara, Türkiye
E-mail: drbaranbalcan@yahoo.com

being ex-smokers. Spirometric tests performed in all patients, immediately prior to inclusion in this study, were in accordance with the GOLD guideline [15]. All patients' medical treatment included long acting beta-2 agonists, tiotropium bromur, and inhaled corticosteroids. Patients with asthma, bronchiectasis, pulmonary fibrosis, pulmonary embolism, congestive heart failure, or any organ malignancy and patients being treated with oral steroids, angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARB) were excluded from the study.

Study Design

Patients without the mentioned exclusion criteria were included in the study. The possible effects of statin use on clinical COPD exacerbation was assessed with questionnaires. All research procedures were designed according to declaration of Helsinki, and all participants provided written consent for the study. Patients who had exacerbations in past one year period were included in the study. Demographic data such as height, age, sex, and body weight of these patients were recorded. Disease severity was assessed with pulmonary function tests (PFT) undertaken during the stable period of the disease prior to inclusion in the study. All spirometric assessments were performed according to the American Thoracic Society's suggestions and the same device was used in all patients [16]. Forced expiratory volume (FEV_1), forced expiratory capacity (FVC), FEV_1/FVC ratio, and forced expiratory mid-flow (FEF_{25-75}) were recorded during the first second. Disease severity was classified as FEV_1>80% (low), 50%>FEV_1<80% (moderate), 30%>FEV_1<50% (severe), and FEV_1<30% or respiratory insufficiency with FEV_1<50%, according to the GOLD guideline [15].

Patients eligible for the study were asked about statin use. Statin users included patients under medication with regular simvastatin, atorvastatin, or rosuvastatin 20 mg per day for at least the past 1 year. Patients with irregular statin use or alterations made in dosage or type were not included in the study. COPD patients treated according to GOLD criteria were grouped as statin users or non-users.

Subsequent to spirometric assessment and inclusion in the study, patients were asked to fill in a questionnaire to evaluate COPD exacerbations during the past 1year. The questionnaire included an evaluation of worsening of breathing difficulty, coughing, sputum, or change in sputum nature during the past 1 year. Beside routine clinical follow-ups, outpatient and emergency clinic administration, antibiotic treatment due to exacerbations, and hospitalization episodes during the past 1 year were also assessed. Anthonisen criteria were used to define COPD exacerbations. The presence of any two of worsening of breathing difficulty, coughing, sputum, or change in sputum nature was accepted as COPD exacerbations.

Data were filled into a chart and grouped as statin users versus non-statin users. Group-wise comparisons were made to detect whether or not statin use is associated with COPD exacerbation and hospitalization.

RESULTS

Sixty-five patients filled in questionnaires, and eight of them were excluded from the study due to missing data. The final number of patients included in the study was 57 [statin users, n=20 (35%); non-statin users, n=37 (65%)]. The mean age of patients was 67.3 (range, 37-92) and male:female ratio was 0.5. There were statistically no significant differences between statin users and non-statin users with respect to age, male:female ratio, COPD severity, medication used for COPD, PFT results, and smoking habits (Table 1). Both groups were comparable. Outpatient clinic administration out of scheduled controls was reported seven times in statin users. However, in only two cases, COPD exacerbation criteria were fulfilled. The number of non-statin users applying to the outpatient clinic out of schedule and emergency was 18 (48%) and 6 (16%), respectively. COPD exacerbation criteria were fulfilled in 24 patients from this group. COPD exacerbation frequency in statin users (0.8 exacerbations per year) was significantly less than that in non-statin users (1.2 exacerbations per year) (p<0.05). The number of patients with COPD exacerbation, antibiotic treatment, and outpatient clinic administration and outpatient clinic administration frequency were significantly lower in statin users (p<0.05). Clinical results of patients are explained in detail in Table 2.

Table 1. Patient characteristics from both groups

	Statin (+)	Statin (–)	p
Patient number	20	37	>0.05
Male/female	0.53	0.4	>0.05
Mean age	67.3 (52–90)	64.3 (37–92)	>0.05
Mean packets per year smoking	33.2	34.9	>0.05
Active smokers	16 (80%)	34 (91%)	>0.05
Mean FEV_1/FVC	68.75	64.7	>0.05
Mean FEV_1	76.95	75.8	>0.05
Mean FVC	85.95	90.1	>0.05
Mean MMEF	53.75	46.4	>0.05

FEV: forced expiratory volume, FVC: Forced vital capacity, MMEF: Maximum mid-expiratory flow

Table 2. Clinical results of statin users vs. non-statin users

	Statin users	Statin non-users	
Patients with COPD exacerbation:	2 (10%)	24 (64%)	<0.05*
Patients requiring steroid treatment	0	5 (13%)	>0.05
Patients requiring antibiotic treatment	2 (10%)	20 (%54)	<0.05*
Patient number of out of schedule outpatient clinic administration	2 (10%)	18(48%)	<0.05*
Total outpatient clinic administration	4 (20%)	32 (94%)	<0.05
Hospitalized patients	0	4 (10%)	>0.05
Emergency clinic administration	0	6 (16%)	>0.05

COPD: chronic obstructive pulmonary disease, *statistically significant

DISCUSSION

Our study showed that COPD patients may benefit from statins. The 1-year retrospective evaluation of COPD patients showed that frequency of exacerbations, out of schedule hospital administration, and antibiotic treatment due to exacerbations were significantly lower in statin users than in non-statin users.

Similar to our study results, in the study of Mancini et al.[14] a lower frequency of hospitalization and mortality were reported in COPD patients receiving statins. Furthermore, Mancini et al.[14] proposed that ACEi and ARB have similar outcomes. Recently, Wang et al.[17] showed that statin use was associated with a 30% decreased risk of COPD exacerbation, and this correlated with drug dose but was independent of the duration of therapy. In our study, patients using ACEi and ARB were not included in order to have a homogenous group and focus on the assessment of statins. In a recent study, statin use in patients hospitalized for COPD exacerbation was associated with a lower risk of subsequent and severe COPD exacerbation [18]. These results are consistent with our study results that less frequent exacerbations are seen in patients receiving statins. In addition to a lower frequency of exacerbations, a lower rate of exacerbation episodes and requirement of intubations have been reported in COPD patients receiving statins [17]. In a retrospective and population-based study, a decrease in the rate of COPD-related mortality was reported [19]. Furthermore, the study has reported a decrease in pulmonary disease- and pneumonia-related mortality. In correspondence with the literature, the non-statin users in our study had a significantly higher frequency of exacerbations. In particular, emergency ward admission in non-statin users were seen in nearly half of the patients, whereas in statin users, this ratio remained as low as 10%. A further evidence of the clinically relevant information showing a more serious clinical picture in non-statin users was the significantly higher rate of medical treatment (antibiotics, steroids) required due to the secondary effects of COPD.

Studies have assessed the effect of statins on COPD severity and progression by evaluating PFTs. Independent of smoking status, some studies have reported a reduced decline in FEV_1 for statin users compared with non-users [20,21]. However, a reduced decline in FEV_1 was not observed by the Heart Protection Study Collaborative Group while assessing the effect of simvastatin on mortality due to various diseases [22]. The lowered COPD mortality rates in simvastatin users were also seen in the study group's results. As we did not perform control PFTs in our study, the possible outcomes could not be evaluated.

The current literature supports the idea of inflammation playing an important role in the pathogenesis of COPD [4,23]. Particularly, disease severity has been shown to be related with the underlying inflammation [24]. Neutrophil accumulation in the airway results in the expression of pro-inflammatory cytokines (especially TNF-alpha and interleukins), which are a fundamental part of the pathogenesis. In a recent experimental animal study evaluating the effect of simvastatin on airway inflammation in COPD, decreases in inflammatory markers such as leukocytes, macrophages, eosinophils, TNF-alpha, IL-4, and IL-13 were reported [25]. In another study evaluating the cardiovascular risk of COPD patients, an increase in C-reactive protein (CRP) was found to be related to COPD severity [26]. Although inhaled corticosteroids are beneficial in decreasing inflammation occurring in the airways, it was found to be associated with an increased risk of pneumonia [27]. The discovery of the anti-inflammatory effects of statins independent of their cardioprotective effect [28] has led to the investigations on their possible benefits in inflammatory diseases [29,30]. Although we did not evaluate the inflammatory markers of COPD patients in this study, the decrease in the frequency of exacerbations may be due to the anti-inflammatory effect of statins; similar observations have been made by Blamoun et al.[31]. Recent literature reviews have suggested that the anti-inflammatory effect of statins on the airways is independent of inhaled corticosteroid treatments [11,19,32,33]. In our study, to overcome the possible bias that would arise from different medical treatment regimens, all patients received inhaled corticosteroid treatment.

The main limitations of our study were the small sample size and no follow-up of the FEV_1 and CRP values due to the retrospective nature of the study. However, our study has objected to evaluate only one topic without causing any confusion. The study mainly aimed to assess the possible effect of statins on exacerbation frequency and its medical management.

In conclusion, this study shows that COPD patients receiving statins have a lower frequency of COPD exacerbations, hospitalization, and antibiotic treatment compared with patients not receiving statins. Further randomized prospective studies with larger sample size need to be conducted to confirm the results of this study.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.K., B.B.C., E.E.; Design - B.B.C., T.Ç.; Supervision - T.Ç.; Resources - T.Ç.; Materials - T.Ç.; Data Collection and/or Processing - T.Ç.; Analysis and/or Interpretation - B.B., Ş.O.Y.; Literature Search - B.B., Ş.O.Y.; Writing Manuscript - Ş.O., B.B.; Critical Review - T.Ç., S.K., E.E., B.B.C.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Walsh GM. Defective apoptotic cell clearance in asthma and copd--a new drug target for statins? Trends Pharmacol Sci 2008;29:6-11.
2. Stockley RA. Neutrophils and the pathogenesis of copd. Chest 2002;121:151S-5S.

3. Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: Molecular and cellular mechanisms. Eur Respir J 2003;22:672-88. [CrossRef]
4. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: A systematic review and a meta-analysis. Thorax 2004;59:574-80. [CrossRef]
5. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of copd (the bold study): A population-based prevalence study. Lancet 2007;370:741-50. [CrossRef]
6. Murray CJ, Lopez AD. Evidence-based health policy--lessons from the global burden of disease study. Science 1996;274:740-3. [CrossRef]
7. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: A clinical trial. Nocturnal oxygen therapy trial group. Ann Intern Med 1980;93:391-8.
8. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the medical research council working party. Lancet. 1981;1:681-6.
9. Undas A, Brummel-Ziedins KE, Mann KG. Statins and blood coagulation. Arterioscler Thromb Vasc Biol 2005;25:287-94. [CrossRef]
10. Arnaud C, Burger F, Steffens S, et al. Statins reduce interleukin-6-induced c-reactive protein in human hepatocytes: New evidence for direct antiinflammatory effects of statins. Arterioscler Thromb Vasc Biol 2005;25:1231-6. [CrossRef]
11. Young RP, Hopkins R, Eaton TE. Potential benefits of statins on morbidity and mortality in chronic obstructive pulmonary disease: A review of the evidence. Postgrad Med J 2009;85:414-21. [CrossRef]
12. Soyseth V, Brekke PH, Smith P, Omland T. Statin use is associated with reduced mortality in copd. Eur Respir J 2007;29:279-83. [CrossRef]
13. Ishida W, Kajiwara T, Ishii M, et al. Decrease in mortality rate of chronic obstructive pulmonary disease (copd) with statin use: A population-based analysis in japan. Tohoku J Exp Med 2007;212:265-73. [CrossRef]
14. Mancini GB, Etminan M, Zhang B, et al. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. J Am Coll Cardiol 2006;47:2554-60. [CrossRef]
15. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Gold executive summary. Am J Respir Crit Care Med 2007;176:532-55. [CrossRef]
16. Standardization of spirometry, 1994 update. American thoracic society. Am J Respir Crit Care Med 1995;152:1107-36.
17. Wang MT, Lo YW, Tsai CL, et al. Statin use and risk of copd exacerbation requiring hospitalization. Am J Med 2013;126:598-606. [CrossRef]
18. Horita N, Miyazawa N, Kojima R, et al. Statins reduce all-cause mortality in chronic obstructive pulmonary disease: A systematic review and meta-analysis of observational studies. Respir Res 2014;15:80.
19. Lahousse L, Loth DW, Joos GF, et al. Statins, systemic inflammation and risk of death in copd: The rotterdam study. Pulm Pharmacol Ther 2013;26:212-7. [CrossRef]
20. Keddissi JI, Younis WG, Chbeir EA, et al. The use of statins and lung function in current and former smokers. Chest 2007;132:1764-71. [CrossRef]
21. Alexeeff SE, Litonjua AA, Sparrow D, et al. Statin use reduces decline in lung function: Va normative aging study. Am J Respir Crit Care Med 2007;176:742-7. [CrossRef]
22. Heart Protection Study Collaborative Group. The effects of cholesterol lowering with simvastatin on cause-specific mortality and on cancer incidence in 20,536 high-risk people: A randomised placebo-controlled trial [ISRCTN48489393]. BMC Med 2005;3:6.
23. MacNee W. Systemic inflammatory biomarkers and co-morbidities of chronic obstructive pulmonary disease. Ann Med 2013;45:291-300. [CrossRef]
24. Vanfleteren LE, Spruit MA, Groenen M, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;187:728-35. [CrossRef]
25. Zeki AA, Franzi L, Last J, Kenyon NJ. Simvastatin inhibits airway hyperreactivity: Implications for the mevalonate pathway and beyond. Am J Respir Crit Care Med 2009;180:731-40. [CrossRef]
26. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation 2003;107:1514-9. [CrossRef]
27. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775-89. [CrossRef]
28. Schonbeck U, Libby P. Inflammation, immunity, and hmg-coa reductase inhibitors: Statins as antiinflammatory agents? Circulation 2004;109:II18-26.
29. Morimoto K, Janssen WJ, Fessler MB, et al. Lovastatin enhances clearance of apoptotic cells (efferocytosis) with implications for chronic obstructive pulmonary disease. J Immunol 2006;176:7657-65. [CrossRef]
30. Forrester JS, Libby P. The inflammation hypothesis and its potential relevance to statin therapy. Am J Cardiol 2007;99:732-8. [CrossRef]
31. Blamoun AI, Batty GN, DeBari VA, et al. Statins may reduce episodes of exacerbation and the requirement for intubation in patients with copd: Evidence from a retrospective cohort study. Int J Clin Pract 2008;62:1373-8. [CrossRef]
32. Janda S, Park K, FitzGerald JM, et al. Statins in copd: A systematic review. Chest 2009;136:734-43. [CrossRef]
33. Dobler CC, Wong KK, Marks GB. Associations between statins and copd: A systematic review. BMC Pulm Med 2009;9:32.[CrossRef]

Turk Thorac J 2017; 18: 33-9 DOI: 10.5152/TurkThoracJ.2017.16016

ORIGINAL ARTICLE

To Investigate the Effects of Air Pollution (PM10 and SO_2) on the Respiratory Diseases Asthma and Chronic Obstructive Pulmonary Disease

Mustafa Saygın[1], Taner Gonca[2], Önder Öztürk[3], Mehmet Has[4], Sadettin Çalışkan[5], Zehra Güliz Has[6], Ahmet Akkaya[3]

[1]Department of Physiology, Süleyman Demirel University School of Medicine, Isparta, Turkey
[2]Clinic of Chest Diseases, Isparta State Hospital, Isparta, Turkey
[3]Department of Chest Diseases, Süleyman Demirel University School of Medicine, Isparta, Turkey
[4]Clinic of Chest Diseases, Şanlıurfa Training and Research Hospital, Şanlıurfa, Turkey
[5]Department of Physiology, Pamukkale University School of Medicine, Denizli, Turkey
[6]Provincial Department of Environment, Şanlıurfa, Turkey

Abstract

OBJECTIVES: Effects of air pollution parameters of sulfur dioxide (SO2) and particulate matter (PM10) values on the respiratory system were investigated.

MATERIAL AND METHODS: Data of SO_2 and PM10 were obtained daily for air pollution and classified into two groups: Group I (2006–2007), coal burning years and Group II (2008–2009), natural gas+ coal burning. Groups I and II were divided into two subgroups according to the months of combustion as combustible (November-April) and noncombustible (May-October). The number of patients with asthma and chronic obstructive pulmonary disorder (COPD) was recorded between 2006 and 2009.

RESULTS: There was no statistically significant difference between Groups I and II for PM10 and SO_2 ($p>0.05$). Within the years, the values of SO_2 and PM10 were statistically different between the groups defined by month ($p<0.01$). The number of patients in the combustible and noncombustible subgroups were found to be different for every 4 years, and the numbers of patients with COPD or asthma were not changed through the years. There was a strong correlation between PM10 and COPD ($r=0.59$, $p<0.01$) and a weak correlation between PM10 and asthma ($r=0.25$, $p>0.05$). A correlation was found between SO_2 and COPD ($p<0.01$) but not between SO_2 and asthma ($p>0.05$). The number of visits for COPD and asthma was statistically different between combustible and noncombustible subgroups (X2:58.61, p=0.000; X2:34.55, p=0.000, respectively). The r2 values for SO_2 and PM10 for COPD patients were 17% and 24%, respectively, in contrast to 8% and 5%, respectivley for asthma patients.

CONCLUSION: Air pollution is known to increase respiratory disease occurrences. With decrease in the usage of solid fuel, air pollution could be reduced and may be effective in preventing respiratory diseases.

KEYWORDS: Air pollution, respiratory system disease, PM10, SO_2, asthma, COPD

Received: *12.05.2016* ***Accepted:*** *03.02.2017* ***Available Online Date:*** *15.03.2017*

INTRODUCTION

Inhalation of toxic particles and gases increases epithelial permeability, which is one of natural defense mechanisms of the lungs; decreases mucociliary activity; and depresses macrophage functions. These substances render toxic effects in healthy or unhealthy individuals and can be a component of molecular events that commonly develop [1]. *In vitro* experimental studies conducted on humans and animals showed that the damages caused increased inflammatory cellular activation (e.g., neutrophils, T lymphocytes, macrophages, and mast cells), increased production of inflammatory cell proteins (cytokines and chemokines), increased oxidative stress with free radical formation [2] (superoxide, hydrogen peroxide, and hydroxyl radicals), and decreased antioxidant enzyme levels (glutathione transferase and superoxide dismutase) [3].

Several studies have shown that particulate matter (PM) in the air affect short- and long-term health. In many studies, there is evidence of effects of PM10 and PM2.5 (PM diameter of 10 or 2.5 μm) on asthma and chronic obstructive pulmonary disease (COPD) and on the increased rate of hospitalization [4]. Studies have shown that particle pollution in the air has negative effects on many parameters, particularly on respiratory function tests [5], patient's symptoms, and the rate of hospitalization [6-8].

Chronic obstructive pulmonary disease presents with progressive inflammation of the airways, pulmonary veins, and pulmonary parenchyma [9,10] and irreversibly causes airflow restriction [11]. Among all pulmonary diseases, COPD is believed to be strongly associated with exposure to polluted air, in particular to PM (black smoke, total mass, PM10 or PM2.5 μm in diameter) [12]. Epidemiological data suggest that increased level of PM pollution elevates the number of admissions to the emergency unit due to previously existing COPD or the rate of hospitalization [13,14]. According

Address for Correspondence: Mustafa Saygın, Süleyman Demirel Üniversitesi Tıp Fakültesi, Fizyoloji Anabilim Dalı, Isparta, Türkiye
E-mail: fizyolog@gmail.com

to the estimates of World Health Organization (WHO), the number of deaths due to exposure to smoke from solid fuels is approximately 1.6 million per year. Of these 693000 are associated with COPD and 910000 with acute lower respiratory tract infections [15].

Sulfur dioxide (SO_2) pollution is caused by combustion of fossil fuels including sulfur and by pollutants resulting from heating and released from smokestacks. In contrast, PM pollution is mostly caused by industrial regions and partially by fossil fuels used for heating [16]. Exposure to SO_2 was found to be associated with increased prevalence of respiratory symptoms, such as wheezing and shortness of breath; total and respiratory mortality [17]; increased risk of asthma [18]; and exacerbation of a previously occurred respiratory disease [19], increased prevalence of respiratory symptoms, such as wheezing and shortness of breath [20].

The aim of the study was firstly to determine the relationship between the use of solid fuels, which causes increased particles and harmful gases in air, and respiratory tract diseases and secondly to determine the effect of PM10 and SO_2 in air pollution on the exacerbation of asthma and COPD, which are among the respiratory tract diseases.

MATERIAL AND METHODS

This was a retrospective observational study, and the values of SO_2 and PM10 were obtained from Isparta Provincial Directorate of Environment in order to determine daily air pollution between 2006 and 2009. Data were recorded as daily measurements in the measurement station at Isparta and were evaluated considering daily SO_2 and PM10 values for all years.

The protocols for the research project and survey have been approved by a suitably constituted ethics committee of our institution and conform to the provisions of the Declaration of Helsinki (as revised in Edinburgh 2000).

Of the patients who were admitted with a complaint of a respiratory tract disease to the emergency unit of the Suleyman Demirel University hospital between 2006 and 2009, data of adults (aged >15 years) with asthma and COPD attack were assessed retrospectively. The diagnosis and staging process were performed in accordance with the guidelines of Global Initiative for Asthma (GINA) for asthma patients and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for COPD patients [21,22]. The attacks were initially assessed by emergency medicine and chest diseases research assistants and on-call chest diseases professors in the emergency medical unit. The coexistence of clinical and physiological findings, such as speech disorder, agitation, confusion, cyanosis, respiratory rate >30/minute, pulse rate >120/minute, involvement of accessory respiratory muscles, oxygen saturation below 91%-92%, and CO_2 retention was accepted as asthma and COPD attack [23,24]. Patients admitted to hospital were classified in accordance with the International Classification of Diseases, Revision 10 (ICD 10-CM, code J44-KOAH and J45-ASTHMA). Inclusion criteria were patients with asthma and COPD and admitted to the emergency unit for exacerbation; however, those admitted to the emergency unit due to other upper respiratory tract diseases and with coexistent cardiac diseases were excluded from the study.

Study groups were designed as follows:

Group I: According to heating state, November-April was accepted as one period and May-October as the other period. The periods were further classified based on the months in which solid fuels was used (November-April) and not used (May-October), and monthly data were subsequently evaluated between 2006 and 2007.

Group II: In addition to solid fuel usage, the periods were classified based on the months in which fuel was used (November-April) and not used (May-October) between 2008 and 2009 when natural gas usage was initiated, and monthly data were evaluated.

According to data obtained from Torosgaz at the time of the study, there were a total of 94000 houses across Isparta, and 7000 active subscribers began the use natural gas. The measurement station was downtown and there were 550 houses, 23 official institutions, and a central heating system. In the region where the measurement was performed, the total number of houses was 4000, and 1477 houses used natural gas, with the fuel usage rate of 36.9%, whereas this rate was 7.4% across the province. According to these results, the rate of natural gas use is defined as partial transition to natural gas and the use of solid fuel continues in the same region.

The mean SO_2 and PM10 values for each month in the determined groups and asthma and COPD patients admitted with a complaint of respiratory tract diseases to the emergency unit of Suleyman Demirel University hospital in the related months were included in the study. Of the admissions, air pollution data of the city center where the study was performed were evaluated. In case of an attack, necessary treatment could be received in the emergency unit of any hospital. Therefore, the patients included in the study were those who were admitted in the region where air pollution was evaluated.

Statistical Analysis

The Kolmogorov-Smirnov test was used to determine whether data displayed normal distribution. The nonparametric Kruskal-Wallis test was employed to compare the months in which solid fuel was and was not used and to assess the differences. The numbers of patients were compared using ANOVA according to the months in which solid fuel was used or not used by considering even the year. Since variances were not homogeneous, patient numbers were compared using the Kruskal-Wallis test according to the months in which solid fuel was used and not used. Depending on the absence of nonhomogeneous variance, patient numbers were compared using the F-test variance analysis as years and months in which solid fuel was and was not used. Because the variance range was extremely wide, variations were found to be homogeneous as a result of homogeneous square root transformation in the F test, and the data were made reliable. In statistical evaluations, the value of $p<0.05$ was accepted to be significant.

RESULTS

Table 1 presents the numbers of asthma and COPD patients from those admitted due to respiratory tract diseases to the emergency unit in 2006-2007 (Group I) and 2008-2009 (Group II) and the evaluation of PM10 and SO_2 values according to the months in which solid fuel was used and not used. PM10 and SO_2 levels showed a statistically significant difference in the months ($p<0.001$). According to these findings, the levels of PM10 and SO_2 significantly increased in the months in which solid fuel was used. Considering the months in which solid fuel was used and not used in a year, PM10 and SO_2 levels were found to differ significantly ($p<0.001$), and there was a decrease in the months in which solid fuel was not used. Similarly, there was a statistically significant decrease in the frequency of asthma ($p<0.001$) and COPD ($p<0.001$) occurrence in the months in which solid fuel was not used (Table 1).

Table 1. Numbers of patients admitted to the emergency unit due to respiratory tract diseases in 2006–2008 (Group I) and 2008–2009 (Group II) and the evaluation of PM10 and SO_2 values according to the months in which solid fuel was and was not used

	PM10 (μg/m³) (mean±SD)	SO_2 (μg/m³) (mean±SD)
Group I	83.49±51.66	55.76±56.52
Months in which solid fuel was used	121.19±49.04[b]	91.26±58.32[a]
Months in which solid fuel was not used	45.79±0.63	16.72±9.32
Group II	87.09±63.95	52.56±57.16
Months in which solid fuel+natural gas was used	123.94±54.91[b]	95.38±51.70[a]
Months in which solid fuel+ natural gas was not used	50.23±50.72	9.75±12.27

According to months in which fuel was not used; [a]$p<0.05$ for PM, [b]$p<0.05$ for SO_2

Table 2. PM10 and SO_2 values according to year group. Group I: 2006–2007 and Group II: 2008–2009

Year group	PM10 (n=24)	SO2 (n=20)
Group I		
2006-2007	83.50±51.66	55.77±56.53
Group II		
2008-2009	87.09±63.95	52.56±57.16
p value	0.831	0.851

For Group II, when PM10 ($p<0.001$) and SO_2 ($p<0.001$) values were compared between the months in which solid fuel+natural gas were used and solid fuel+natural gas were not used, there was a statistically significant difference, and the values decreased in the months in which solid fuel+natural gas was not used.

Regardless of the classification, no significant difference was found between the groups When comparing air pollution based on the year (Table 2). When data were compared using t test, no statistically significant difference was detected ($p>0.05$).

There was a significant difference between the months in which solid fuel was used and not used in terms of the number of COPD ($p<0.001$) and asthma ($p<0.001$) admissions. The number of patient admissions was significantly decreased in months in which solid fuel was not used.

According to single factor analysis of variance, the number of COPD patients in months in which solid fuel was used and not used differed at the same level in all years. There was a statistically significant difference between the months in which solid fuel was used and not used in terms of the number of COPD and asthma patients admitted to hospital ($p<0.001$ and $p<0.05$, respectively), and the numbers of COPD patients and asthma patients were lower in the months in which solid fuel was not used (Table 3).

The presence of a linear relationship between PM10 and SO_2 values and the numbers of patients with asthma and COPD was evaluated through correlation analysis. There was an increasing linear relationship between PM10 and SO_2 values, PM10 and COPD, and SO_2 and COPD. There was an increasing linear relationship between PM10 and asthma and between SO_2 and asthma. However, their statistical significance level was low.

A high correlation was observed between PM10 and the number of COPD patients ($r=0.59$, $p<0.001$). There was a correlation between PM10 and SO_2 ($r=0.025$, $p<0.001$). The correlation between PM10 and asthma ($r=0.25$, $p=0.123$) was found to be statistically nonsignificant. While a correlation was observed between SO_2 and COPD ($p<0.05$), there was no significant correlation between SO_2 and asthma ($p>0.05$). The distribution graphs for the correlation analysis between

Table 3. Comparison of the numbers of patients admitted to the emergency unit in months in which fuel was used and not used according to years

	2006-2007		2008-2009	
	COPD mean±SD	Asthma mean±SD	COPD mean±SD	Asthma mean±SD
Months in which solid fuel (+natural gas) was used	13.08±7.40[a]	2.16±1.89[b]	12.33±5.08[a]	3.66±3.14[b]
Months in which solid fuel (+natural gas) was not used	5.66±2.67	1.33±1.07	4.66±3.77	1.00±1.41
p value	0.001	0.001	0.05	0.05

One-factor variance analysis was performed. According to months in which fuel was not used; [a]$p<0.05$ for COPD, [b]$p<0.05$ for asthma

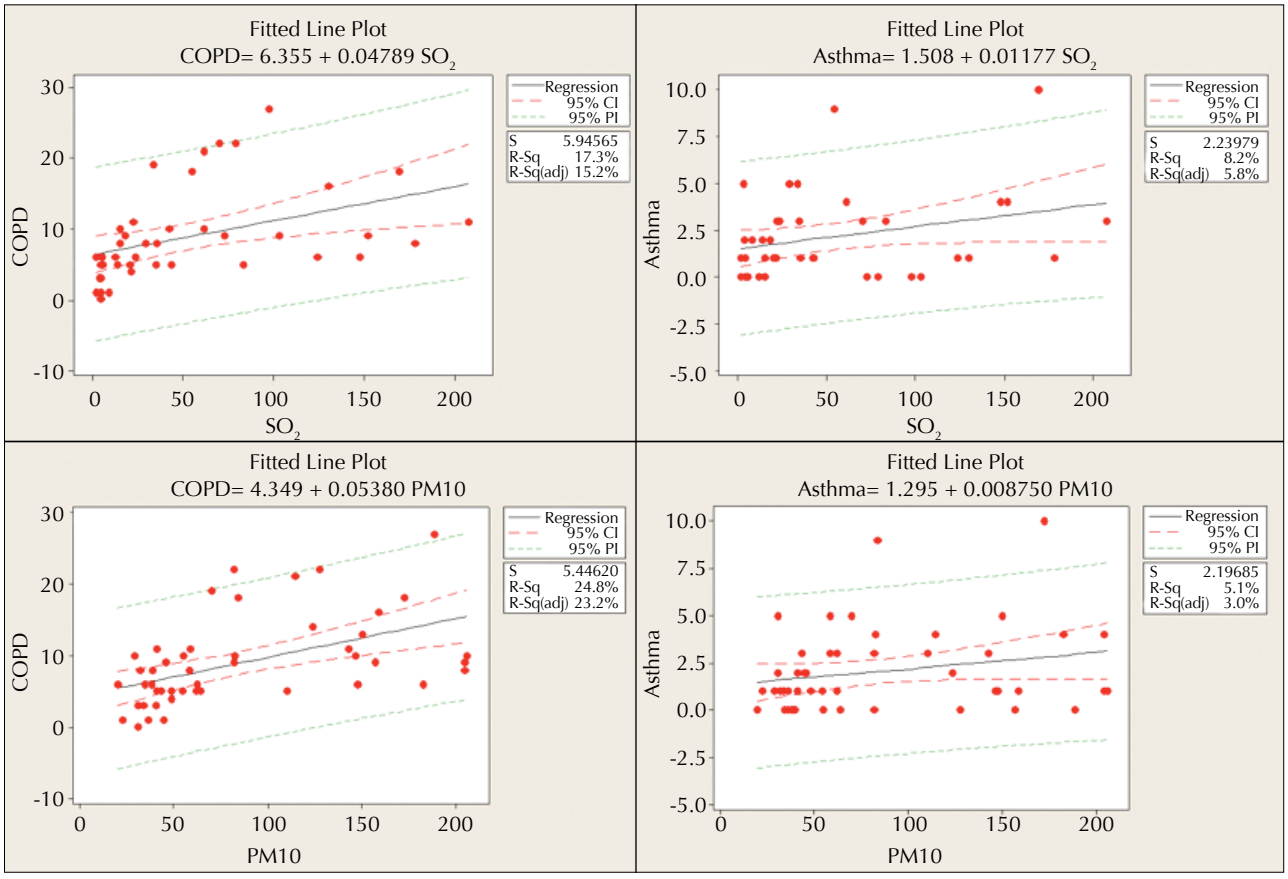

Figure 1. SO_2 and PM10 and asthma and COPD scatter graphs and regression models (regression analyses were performed for determining SO_2 and PM10 values and the predictability of having asthma and COPD, and the results are presented in Figure 1. Coefficients of determination were ranged between 5% and 25%. Although the predictability of models is not high, they provide information that shows that they are assessable

SO_2 and PM10 values and asthma and COPD variables are presented in Figure 1.

Regression Analysis

Linear regression analyses were performed for predicting SO_2 and PM10 values and the numbers of COPD and asthma patients. The r^2 values were 17% for SO_2 and COPD (6,355+0,04789xSO_2), 8% for SO_2 and asthma (1,508+0,01177xSO_2), 24% for PM10 and COPD (4,349+0,005380xPM10), and 5% for PM10 and asthma (1,295+0,008750xPM10). The coefficients of determination for regression models indicated that the predictive value of the model is low. However, it partially explains the relationship between the related variables (Figure 1).

DISCUSSION

Our study revealed that an increase in air pollution and accordingly in respiratory tract diseases development occurred in association with the use of solid fuels.

The relationship between the level of daily air pollution in the center of Sivas and the diagnostic rates of COPD and bronchial asthma in patients hospitalized in Sivas Chest Diseases Hospital between October 1, 1998, and September 30, 2000, was investigated. No statistically significant relationship was found in the study between daily SO_2 values and all patients hospitalized at the same period and patients diagnosed with bronchial asthma and COPD. A significant relationship was found between total daily particle values and hospitalized COPD patients residing within the borders of the municipality (r=0.5, p=0.013) [25]. A study evaluating the use of coal banned in 1990, 1995, and 1998 and the patient admission rates before and after the ban in Ireland revealed that the number of admissions due to respiratory tract diseases continuously decreased after the ban, and a decrease was observed in the numbers of pneumonia, COPD, and asthma patients [26]. Similarly, a study investigating SO_2- and PM-induced air pollution and the admissions of asthma and COPD patients to the emergency unit showed that high SO_2 values were found to be associated with admission to the emergency unit [27]. A study by Rumana et al. [28] examined the relationship between the levels of PM2.5, PM10, nitrogen oxides (NOx), SO_2, ammonia (NH_3), and ozone (O_3), urbanization, and air pollution and emergent respiratory and cardiac diseases and revealed that respiratory infections (25%) and the prevalence of asthma/COPD (4%) were associated with increased air pollution. In literature, studies have demonstrated a linear relationship between air pollution and respiratory tract diseases. Similar findings were obtained in our study. However, harmful effects on respiratory health will be reduced with widespread use of natural gas and elimination of other pollutants contributing to air pollution.

The current degree of air pollution was evaluated in the province of Diyarbakir. It was observed that the annual SO_2 and PM concentrations were approximately 110 μg/m^3 in 2000-2001, which increased in 2002 and declined in 2003. Ac-

cording 2004 data, the values of SO_2 and PM increased to 134 and 137 μg/m^3, respectively, in January; the values were 115 and 120 μg/m^3, respectively, in December. These values were above the targeted limit determined by the Turkish Air Quality Protection Regulation and WHO. Similar to our study, it is observed that the factors causing air pollution are the use of solid fuels, exhaust gas, and factory emissions [29]. In the example of the province of Van, air pollution parameters (SO_2 and PM10) before the use of natural gas and after transition to natural gas were examined. Coal, fuel oil, and diesel fuel were used for heating in the province. Natural gas use was initiated as of March 2008. With the use of natural gas, the use of other fuels decreased. Thus, the study thus revealed that while the SO_2 value of 250 μg/m^3 stated in the Air Quality Evaluation and Management Regulation (AQEMR) was exceeded in some months before transition to the use of natural gas, the value did not exceed the limit after initiation of natural gas usage. It was observed that the PM10 value exceeded the 200 μg/m^3 value stated in the regulation in winter and reached 267 μg/m^3. With transition to natural gas usage in March 2008, a decrease was observed in the PM10 value again [30]. The data obtained from this study, which are consistent with those in literature, show that solid fuel-induced air pollution significantly decreased with partial transition to natural gas.

Sunyer et al. [31] evaluated the admissions to the emergency unit due to COPD and daily air pollution in Barcelona, which is a Mediterranean city where motor vehicles were commonly used in 1991. They found a positive relationship between the admissions for COPD and black smoke, SO_2, and carbon monoxide (CO). In other studies conducted in the USA and Canada, the significant relationship between admission or hospitalization in the emergency unit due to respiratory diseases and asthma and particles and O_3 was emphasized [32-37]. These results indicate a relationship between the levels of PM and SO_2 and the admissions for asthma and COPD, similar to our study.

Stieb et al. [38] evaluated 400000 emergency service visits in 14 hospitals in seven different cities between 1990 and 2000 and examined the levels of CO, NO_2, SO_2, PM10, and PM2.5. The levels of PM10 and PM2.5 were found to be associated with asthma attacks. In the study conducted by Canova et al. [39] regarding the effect of PM10 on hospitalization rate and its relationship with asthma and COPD, it was found that the high level of PM10 was related to hospital admission, and short-term exposure to PM10 decreased antioxidants in the blood samples of patients and increased exacerbations.

In İzmir, the relationship between asthma cases and the levels of SO_2 and PM10 was investigated in six districts between 2007 and 2010. A significant correlation was noted between air pollution in the province and the number of asthma cases [40]. In an analysis conducted on adults and children in London, it was shown that PM10 and SO_2 had strong effects on asthma and other lower respiratory tract diseases [41]. In our study, the findings revealed an increasing linear relationship between the levels of PM10 and SO_2 and the number of patient admissions for COPD. "A study in Tokyo examining the acute effect of air pollution on pulmonary functions and airway inflammation in healthy volunteers showed that the mean 4-day PM10 concentrations increased, and PM10 was significantly associated with forced expiratory volume in 1 second (FEV_1) values. In relationship with the history of asthma, the level of exhaled nitric oxide (FeNO) was found to be increased. While high level of PM10 was associated with decreased FEV_1, it was emphasized that the patients with rhinitis and asthma are more susceptible to air pollution [42]. In a study investigating the effect of PM2.5 on asthma-related mortality and morbidity, experimental asthma was induced with ovalbumin in rats in two cities of the USA, and the rats were exposed to air pollution for 16 hours. Subsequently, PM2.5 analyses were performed (mass, size, fraction, and main component analyses, and trace element content), the lung lobe was removed through bronchoalveolar lavage (BAL), and airway inflammation and mucus response were evaluated. The concentration of PM, which was similar in two cities, did not cause any effect in nonasthmatic rats. On the contrary, 200% airway mucus, 250% neutrophil, and 90% eosinophil increases in BAL and 300% total protein increase were noted in the asthmatic rats. It was concluded that increased PM caused exacerbation in asthma patients sensitive to it, and exposure to PM should be considered for the protection of public health [43]. In the Italian part of the EpiAir Project, the effect of air pollution on hospital admissions was investigated in nine cities between 2001 and 2005. The relationship between PM10 and gases (NO_2 and O_3) and respiratory tract diseases was examined, and three pollutants were found to be associated with hospitalization for different levels of asthma, COPD, and respiratory tract infections. A high relationship was detected between NO_2 and asthma, particularly in children [44]. In our study, there was an increasing linear relationship between admissions due to asthma attack and the levels of PM10 and SO_2; however, the significance value was low, which could be because of increasing linear relationship can be explained with that the number of asthma patients was same in all months and pollens increased attacks as well as air pollution.

In fact, while this pollution is more associated with secondary transformation and long-range transport in hot periods, particle pollution in Isparta is strongly influenced by local traffic and factories. Moreover, high levels of PM and SO_2 even in the months in which solid fuel is not used can be associated with air pollution produced by large factories downtown and near city centers as well as exhaust gases. In this case, in addition to traffic and industrial sectors, the numbers of asthma and COPD attacks increased in parallel with increased air pollution in the months in which solid fuel was used. In this study, the particles measured during the study period in Isparta were found to be a risk factor, particularly for COPD. This is associated with air pollution caused by the use of solid fuel especially in winters, exhaust gases, and smokestacks of factories. The results show that exposure to oxidants (particles) leads to exacerbation of inflammatory response symptoms that develop against infections and an increase in the number of hospitalizations due to infection [45,46].

Our study provides valuable data with regard to the relationship between air pollution and respiratory tract diseases in our country. However, it has some limitations. Data on air

pollution in the study reflect the state of the center of Isparta. It cannot be certainly assumed that the patients admitted to the emergency unit due to acute exacerbation were those exposed to air pollution in the city center. However, considering that respiratory emergencies triggered by air pollution could be intervened in any medical service, patients included in the study could indeed belong to the region where the study was conducted, which is one of the restrictions of the study. The misleading factor is that the measurement of air pollution was performed at specific regions of the city, and the data obtained were adapted to the whole city. In this situation, distinguishing patients from regions with and without air pollution may be difficult. Another limitation of the study is that PM2.5 could not be evaluated instead of PM10. This was attributed to the capacity of the measurement station.

In addition to its contribution to the pathogenesis of asthma and COPD, air pollution is a risk factor for those with a history of asthma and COPD. It affects individual quality of life and has a serious economic impact. This issue should be dealt with regard to public health. To ensure a comfortable and healthy life of the members of a society, local and national authorized institutions should take necessary measures, and the society should be aware of the situation. The detection of the amount and development of this pollution (exposure to pollutants and oxidative stress) will be inestimable for the correct evaluation of the efficiency of air quality policies and for decreasing the effects of air pollution on respiratory tract diseases.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: The number of patients used only from the application, was not take a consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.S., T.G., Ö.Ö.; Design - M.S., T.G., Ö.Ö.; Supervision - S.Ç., A.K.; Resources - M.H., Z.G.H.; Materials - M.S., T.G.; Data Collection and/or Processing - M.S., T.G.; Analysis and/or Interpretation - M.S., T.G., Ö.Ö.; Literature Search - M.S., T.G., M.H.; Writing Manuscript - M.S., Ö.Ö.; Critical Review - Ö.Ö., S.Ç., A.K.; Other - M.H., Z.G.H.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Andersen ZJ, Wahlin P, Raaschou-Nielsen O, et al. Size distribution and total number concentration of ultrafine and accumulation mode particles and hospitaladmissions in children and the elderly in Copenhagen, Denmark. Occup Environ Med 2008;65:458-66. [CrossRef]
2. Mudway IS, Stenfors N, Duggan ST, et al. An in vitro and in vivo investigation of the effects of diesel exhaust on human airway lining fluid antioxidants. Arch Biochem Biophys 2004;423:200-13. [CrossRef]
3. Behndig A, Mudway IS, Brown JL, et al. Airway antioxidant and inflammatory responses to diesel exhaust exposure in healthy humans. European Respir J 2006;27:359-65. [CrossRef]
4. Pope CA 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. J Air Waste Manag Assoc 2006;56:709-42. [CrossRef]
5. Penttinen P, Vallius M, Tiittanen P, et al. Source-specific fine particles in urban air and respiratory function among adult asthmatics. Inhal Toxicol 2006;18:191-8. [CrossRef]
6. Meng YY, Rull RP, Wilhelm M, et al. Outdoor air pollution and uncontrolled asthma in the San Joaquin Valley, California. J Epidemiol Community Health 2010;64:142-7. [CrossRef]
7. Halonen JI, Lanki T, Yli-Tuomi T, et al. Urban air pollution, and asthma and COPD hospital emergency room visits. Thorax 2008;63:635-41. [CrossRef]
8. Kelly FJ, Fussell JC. Air pollution and airway disease. Clin Exp Allergy 2011;41:1059-71. [CrossRef]
9. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. Lancet 2004;364:709-21. [CrossRef]
10. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med 2004;350:2645-53. [CrossRef]
11. Pauwels R. Global initiative for chronic obstructive lung diseases (GOLD): time to act. Eur Respir J 2001;18:901-2. [CrossRef]
12. Sunyer J, Basagana X. Particles, and not gases, are associated with the risk of death in patients with chronic obstructive pulmonary disease. Int J Epidemiol 2001;30:1138-40. [CrossRef]
13. Pope CA 3rd, Kanner RE. Acute effects of PM10 pollution on pulmonary function of smokers with mild to moderate chronic obstructive pulmonary disease. Am Rev Respir Dis 1993;147:1336-40. [CrossRef]
14. Ko FW, Tam W, Wong TW, et al. Temporal relationship between air pollutants and hospital admissions for chronic obstructive pulmonary disease in Hong Kong. Thorax 2007;62:780-5. [CrossRef]
15. Smith K, Mehta S, Maeusezahl-Feuz M. Indoor air pollution from household use of solid fuels. In: Ezzati M, Lopez A, Rodgers A, Murray C, eds. Comparative quantifi cation of health risks. Global and regional burden of disease attributable to s elected major risk factors. Geneva, Switzerland: World Health Organization, 2004: pp 1435-93.
16. Bayram H. Türkiye'de Hava Kirliliği Sorunu: Nedenleri, Alınan Önlemler ve Mevcut Durum. Turk Thorac J 2017; 18: 2005;6:159-65.
17. Chen R, Huang W, Wong CM, et al. Shortterm exposure to sulfur dioxide and daily mortality in 17 Chinese cities: the China air pollution and health effects study (CAPES). Environ Res 2012;118:65-71. [CrossRef]
18. Clark NA, Demers PA, Karr CJ, et al. Effect of early life exposure to air-pollution on development of childhood asthma. Environ. Health Perspect 2010;118:284-90. [CrossRef]
19. Chen TM, Gokhale J, Shofer S, et al. Outdoor air pollution: nitrogen dioxide, sulfur dioxide, and carbon monoxide health effects. Am J Med Sci 2007;333:249-56. [CrossRef]
20. Zhao Z, Zhang Z, Wang Z, et al. Asthmatic symptoms among pupils in relation to winter indoor and outdoor air pollution in schools in Taiyuan, China. Environ Health Perspect 2008;116:90-7. [CrossRef]
21. Boulet LP, FitzGerald JM, Reddel HK. The revised 2014 GINA strategy report: opportunities for change. Curr Opin Pulm Med 2015;21:1-7. [CrossRef]
22. Lange P, Marott JL, Vestbo J, et al. Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population. Am J Respir Crit Care Med 2012;186:975-81. [CrossRef]

23. Watase H, Hagiwara Y, Chiba T, et al. Japanese Emergency Medicine Network Investigators. Multicentre observational study of adults with asthma exacerbations: who are the frequent users of theemergency department in Japan? BMJ Open 2015;5:e007435. [CrossRef]
24. Chow L, Parulekar AD, Hanania NA. Hospital management of acute exacerbations of chronic obstructive pulmonary disease. J Hosp Med 2015;10:328-39. [CrossRef]
25. Koç Y, Karagöz N, Seven AS. Hava kirliliğinin Sivas Göğüs Hastalıkları Hastanesine yatışlar üzerine etkisi. J Kartal TR 2002;13:75-8.
26. Dockery DW, Rich DQ, Goodman PG, et al. Effect of air pollution control on mortality and hospital admissions in Ireland. Res Rep Health Eff Inst 2013;176:109.
27. Guillén Pérez JJ, Guillén Grima F, Medrano Tortosa J, et al. Unusual attendance at Hospital Emergency Services for asthma and chronic obstructive pulmonary disease andSO2 air pollution in Cartagena (Spain). Rev Esp Salud Publica 1995;69:305-14.
28. Rumana HS, Sharma RC, Beniwal V, et al. A retrospective approach to assess human health risks associated with growing air pollution in urbanized area ofThar Desert, western Rajasthan, India. J Environ Health Sci Eng 2014;12:23. [CrossRef]
29. Bayram H, Dörtbudak Z, Fişekçi FE, ve ark. Hava Kirliliğinin İnsan Sağlığına Etkileri, Dünyada, Ülkemizde ve Bölgemizde Hava Kirliliği Sorunu" Paneli Ardından. Tıp Dergisi 2006;33:105-12.
30. Çay Y. Yıldız A. Fosil Kaynaklı Yakıtların Neden Olduğu Hava Kirliliğinin Doğal Gaz Kullanımı İle Değişimi, Van İli Örneği. Makine Teknolojileri Elektronik Dergisi 2011;8:45-52.
31. Sunyer J, Anto JM, Murillo C, et al. Effects of urban air pollution on emergency room admissions for chronic obstructive pulmonary disease. Am J Epidemiol 1991;134:277-86. [CrossRef]
32. Health effects of outdoor air pollution. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. Am J Respir Crit Care Med 1996;153:3-50. [CrossRef]
33. Schwartz J. Air pollution and hospital admissions for the elderly in Birmingham, Alabama. Am J Epidemiol 1994;139:589-98. [CrossRef]
34. Schwartz J. Air pollution end hospital admissions for the elderly in Detroit, Michigan. Am J Resp Crit Care Med 1994;150:648-55. [CrossRef]
35. Schwartz J. PM10, ozone and hospital admissions for the elderly in Minneapolis-St Paul, Minnesota. Arch Environ Health 1994;49:366-74. [CrossRef]
36. Burnen RT, Dales R, Kreuski D, et al. Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. Am J Epidemiol 1995;142:15-22. [CrossRef]
37. Schwartz J. Air pollution and hospital admissions for respiratory disease. Epidemiology 1996;7:20-8. [CrossRef]
38. Stieb DM, Szyszkowicz M, Rowe BH, et al. Air pollution and emergency department visits for cardiac and respiratory conditions: a multi-city time-seriesanalysis. Environ Health 2009;8:25. [CrossRef]
39. Canova C, Dunster C, Kelly FJ, et al. PM10-induced hospital admissions for asthma and chronic obstructive pulmonary disease: the modifying effectof individual characteristics. Epidemiology 2012;23:607-15. [CrossRef]
40. Ozcan NS, Cubukcu KM. Evaluation of Air Pollution Effects on Asthma Disease: The case of Izmir. Procedia - Social and Behavioral Sciences 2015;202:448-55. [CrossRef]
41. Hajat S, Haines A, Goubet SA, et al. Association of air pollution with daily GP consultations for asthma and other lower respiratory conditions in London. Thorax 1999;54:597-605. [CrossRef]
42. Yoda Y, Otani N, Sakurai S, et al. Acute effects of summer air pollution on pulmonary function and airway inflammation in healthy young women. J Epidemiol 2014;24:312-20. [CrossRef]
43. Wagner JG, Morishita M, Keeler GJ, et al. Divergent effects of urban particulate air pollution on allergic airway responses in experimental asthma: acomparison of field exposure studies. Environ Health 2012;11:45. [CrossRef]
44. Colais P, Serinelli M, Faustini A, et al. Air pollution and urgent hospital admissions in nine Italian cities. Results of the EpiAir Project. Epidemiol Prev 2009; 33(6 Suppl 1):77-94.
45. Chauhan AJ, Krishna MT, Frew AJ, et al. Exposure to nitrogen dioxide (NO2) and respiratory disease risk. Rev Environ Health 1998;13:73-90.
46. Becker S, Soukup JM. Exposure to urban air particulates alters the macrophage-mediated inflammatory response to respiratory viral infection. J Toxicol Environ Health 1999;13:445-57.

Turk Thorac J 2017; 18: 40-6 DOI: 10.5152/TurkThoracJ.2017.16036

ORIGINAL ARTICLE

Is There a Link Between Obstructive Sleep Apnea Syndrome and Fibromyalgia Syndrome?

Handan İnönü Köseoğlu[1], Ahmet İnanır[2], Asiye Kanbay[3], Sevil Okan[2], Osman Demir[4], Osman Çeçen[2], Sema İnanır[5]

[1]Department of Pulmonary Diseases, Gaziosmanpaşa University School of Medicine, Tokat, Turkey
[2]Department of Physical Medicine and Rehabilitation, Gaziosmanpaşa University School of Medicine, Tokat, Turkey
[3]Department of Pulmonary Diseases, Medeniyet University, İstanbul, Turkey
[4]Department of Biostatistics and Medical Informatics, Gaziosmanpaşa University School of Medicine, Tokat, Turkey
[5]Department of Mental Health and Diseases, Gaziosmanpaşa University School of Medicine, Tokat, Turkey

Abstract

OBJECTIVES: Fibromyalgia syndrome (FMS) is characterized by complaints of chronic musculoskeletal pain, fatigue, and difficulty in falling asleep. Obstructive sleep apnea syndrome (OSAS) is associated with symptoms, such as morning fatigueness and unrefreshing sleep. We aimed to investigate the presence of OSAS and objectively demonstrate changes in sleep pattern in patients with FMS.

MATERIAL AND METHODS: Polysomnographic investigations were performed on 24 patients with FMS. Patients were divided into two groups: patients with and without OSAS (Group 1 and Group 2, respectively). A total of 40 patients without FMS who presented to the sleep disorders polyclinic with an initial diagnosis of OSAS were included in Group 3. Based on their apnea hypopnea index (AHI), OSAS in the patients were categorized as mild (AHI, 5-15), moderate (30), or severe (>30).

RESULTS: OSAS was detected in 50% of patients with FMS. The most prominent clinical findings were morning fatigue and sleep disorder, which were similar in three groups. In polysomnography (PSG) evaluation, patients with FMS had mild (33%), moderate (25%), and severe (42%) OSAS. In correlation analyses, negative correlations were observed between fibromyalgia impact questionnaire (FIQ) and mean oxygen saturation, visual analogue scale (VAS), and minimum oxygen saturation, whereas a positive correlation was found between FIQ and desaturation times in patients with FMS.

CONCLUSION: Detection of OSAS in 50% of the patients with FMS, and similar rates of complaints of sleep disorder and morning fatigue of OSAS and FMS cases are important results. Detection of correlation between the severity of hypoxemia and FIQ and VAS scores are significant because it signifies the contribution of increased tissue hypoxemia to the deterioration of clinical status. Diagnosis and treatment of OSAS associated with FMS are important because of their favorable contributions to the improvement of the clinical picture of FMS.

KEYWORDS: Obstructive sleep apnea syndrome, fibromyalgia syndrome, polysomnography, sleep disorders, apnea hypopnea index, hypoxemia

Received: *25.08.2016* ***Accepted:*** *06.02.2017* ***Available Online Date:*** *01.03.2017*

INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic health problem that presents with pain all over the body, with other symptoms, such as tenderness of the affected joints, muscles fatigue, sleep problems (waking up unrefreshed and excessive daytime sleepiness), and cognitive impairment [1]. Since its etiology is not fully known, its treatment is symptomatic. Patients with FMS are usually treated with various combinations of physiotherapy, psychotherapy, psychotrophic drugs, and analgesics. Treatment effectiveness in FMS is limited, and these patients frequently lead their lives with symptoms of chronic insomnia, sleep problems, fatigue, and pain [2].

Obstructive sleep apnea syndrome (OSAS) is a pathology with systemic effects that are characterized by associated symptoms of recurrent episodes of upper respiratory tract obstruction, hypoxemia, arousals during sleep, morning fatigue because of impaired sleep quality, morning headache, unrefreshing sleep, attention defict during daytime, impaired concentration, cognitive dysfunction, and depression [3]. Because of the similarities between the symptoms of FMS and OSAS, we aimed the presence of OSAS and objectively demonstrated the changes in sleep pattern in patients with FMS in this study.

MATERIAL AND METHODS

Cases and Study Design

This was a cross-sectional study and was performed between April 2013 and June 2014. Polysomnographic evaluation was performed on 24 patients who had predominantly complained of sleep disorder and were diagnosed with FMS in

Address for Correspondence: Handan İnönü Köseoğlu, Gaziaosmanpaşa Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Tokat, Türkiye
E-mail: handaninonu@gmail.com

The Clinics of Physical Therapy and Rehabilitation in our hospital. Patients with FMS were divided into two groups: patients with and without OSAS (Group 1 and Group 2, respectively). A total of 40 patients who were evaluated with the an initial diagnosis of OSAS in the clinics of sleep disorder but were found to be devoid of FMS following assessments performed in the Department of Physical Therapy and Rehabilitation were determined as the control group (Group 3). Diagnosis of FMS was based on the criteria established by The American College of Rheumatology [4]. Data related to demographic characteristics, sleep patterns, medical history, medication use, and habits were retrieved using a standardized questionnaire survey administered before the sleep study.

For evaluating pain, the visual analogue scale (VAS) was used. Pain threshold was evaluated using an algometer. The pressure algometer used in this study (JTECH, Commander™) was connected to a dial that can measure pressure in kg or libres with a round rubber pressure measurement tip in the form of a disk of 1 cm diameter. By holding the dial, the operator can apply pressure on the predetermined points. During the assessments, at the first instance of pressure pain felt by the patient, the algometer was taken away from the body, and the value displayed on the indicator was recorded. Measurements were repeated for three times, and the average of these values was taken into consideration.

Back depression scale (BDS), back anxiety scale (BAS), and fibromyalgia impact questionnaire (FIQ) forms were completed by the study groups. BDS, which consists of a total of 21 questions, was developed in the year 1967 by Beck, and it is based on the evaluation of somatic, affective, and cognitive functions of the patient. It is designed in a questionnaire form, and the patients were requested to choose the responses most suitable to their condition. Each item consists of four sentences. These sentences are listed from neutral (0 point) to the most severe state (3 points). The maximum score is 63 points [5]. According to Beck et al., depression levels were classified based on BDS scores as follows: 0-13 points, no depression; 14-19 points, mild; 20-28 points, moderate; and 29-63 points, severe depression [6]. BAS is a Likert-type assessment scale consisting of 21 items, which measures the frequency of anxiety symptoms experienced by an individual. Each item is rated between 0 and 3 points. Higher total scores indicate the severity of anxiety experienced by an individual. Its validation and reliability studies have been performed in our country [7]. Based on BAS scores, 0-17 points, 18-24 points, and ≥25 points indicate mild, moderate, and severe degrees of anxiety, respectively. FIQ was developed by Burchardt et al. to measure the functional state of patients with FMS [8]. It measures physical function, feeling oneself good, inability to go to work, feeling uneasy at work, pain, fatigueness, morning fatigueness, stiffness, anxiety, and depression. Apart from feeling oneself good, lower scores indicate recovery or mild impact of the disease on the patient. FIQ is completed by the patient and takes approximately 5 min to complete. Validation and reliability studies of FIQ have been performed [9]. This study was in compliance with the principles outlined in the Declaration of Helsinki and was approved by the Local Ethical Committee. Written informed consent was obtained from all the patients.

PSG Evaluation

Overnight PSG was performed in all patients using a 55-channel polysomnograph (Alice® Sleepware, Philips Respironics, PA, USA) and included the following variables: electrooculograms (two channels), electroencephalograms (four channels), electromyograms of the submental muscles (one channel) and anterior tibialis muscle of both legs (two channels), electrocardiograms, airflow measurements (with oronasal thermistor and nasal cannula pressure transducer), body position sensor that discerns changes in the body position during sleep, and a snore sensor for the detection of snoring vibrations. Respiratory efforts of chest and abdominal muscles (two channels) were recorded using piezoelectric belts and arterial oxyhemoglobin saturation (SaO_2: one channel) using pulse oximetry with a finger probe. The recordings were scored according to the standard criteria of American Academy of Sleep Medicine (AASM). Apnea was defined as ≥90% decrease in the air flow amplitude persisting for at least 10 s relative to the baseline amplitude. AASM has provided two definitions for hypopnea. The recommended definition is a ≥30% decrease in the air flow amplitude relative to the baseline values associated with ≥4% oxygen desaturation, all sustaining for at least 10 s. Alternative definition is expressed as ≥50% decrease in the air flow amplitude relative to the baseline values associated with a ≥3% oxygen desaturation or arousal from sleep, all sustaining for at least 10 s. In our study, hypopnea was determined according to the alternative definition [10]. Apnea hypopnea index (AHI) was calculated as the number of apneic plus hypopneic episodes per hour of sleep. Patients with AHI of ≥5 events/h were diagnosed with OSAS. Based on their AHI scores, the patients were categorized into mild (AHI, 5-15), moderate (AHI, 15-30), and severe OSAS (AHI, >30) groups according to the AASM Task Force criteria [11]. Oxygen desaturation index (ODI) was defined as the total number of measurements of oxyhemoglobin desaturation of ≥4% within ≥10 s-<3 min from the baseline divided by the total sleep time.

Statistical Analysis

Chi-square tests were used to investigate the correlations (if any) between qualitative variables. Quantitative variables were presented as arithmetic mean ± standard deviation and qualitative variables as numbers and percentages. For the difference between the groups, the independent Samples t-test was used, and for the correlation analysis, the Pearson correlation coefficient was used. Covariance analysis was used to compare the differences among the groups. For multiple comparison, the Bonferroni test was used. P values were adjusted according to age and body mass index (BMI) values. P values less than 0.05 were considered to be statistically significant. Calculations were performed using a pre-prepared statistical software (IBM SPSS Statistics 19, (IBM SPSS; IBM Co., Somers, NY, USA).

RESULTS

A total of 64 patients (females, n=28, 44% and males, n=36, 56%) were included in the study. Mean age (48.39±9.47 years) and mean BMI (48.39±9.47 kg/m^2) of all the groups were also calculated. Groups 1, 2, and 3 consisted of 12, 12, and 40 patients, respectively. A significant intergroup difference was observed in terms of gender, age, and BMI of the patients. In this study, p values were adjusted according to age and BMI values. In patients with FMS (Groups 1 and 2), higher mean VAS, tender points, FIQ, and Beck anxiety-depression scores but lower mean algometry scores were found compared with those in patients without FMS (Group 3). The most predominant clinical findings were complaints of morning fatigue and sleep disorder, which were at similar rates in the three groups. No intergroup difference was detected for additional concomitant diseases, including diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, and goiter (p>0.05). Demographic characteristics and FMS-related symptoms are indicated in Table 1.

The groups were compared with respect to PSG findings, and longer sleep latencies were seen in Group 2 (FMS positive, OSAS negative group) (p=0.004). Stages of non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep were similar between the groups with respect to their duration and percentages (p>0.05). Mean AHI and arousal index (ARI) scores were significantly different between the three groups (p<0.001), but mean AHI and ARI were similar between Group 1 (FMS positive, OSAS positive group) and Group 3 (FMS negative, OSAS positive group). OSAS has been detected in 50% of patients with FMS. Patients with FMS had mild (33%), moderate (25%), and severe (42%) OSAS (Group 1). In Group 3 (OSAS positive, FMS negative group), mild, moderate, and severe OSAS were seen in 15%, 20%, and 65% of the patients, respectively. PSG findings of the groups are shown in v 2. PSG findings of patients with FMS were evaluated, and alpha intrusions were detected in 11 of 24 patients. These activations were seen in NREM stages 2 and 3.

In correlation analyses, negative correlation was observed in all cases between sleep latencies and algometry scores (r=-0.28, p=0.022) (Figure 1). In patients with FMS, negative

Table 1. Demographic and clinical findings of study groups

	Group 1 FMS (+) OSAS(+) (n=12)	Group 2 FMS (+) OSAS(-) (n=12)	Group 3 FMS(-) OSAS (+) (n=40)	p
Age (year)[a]	51.75±8.00[a]	39.92±8.25[b]	50.88±8.3[a]	<0.001
Gender				
Female, n (%)	9 (75)[a]	12 (100)[a]	7 (17.5)[b]	<0.001
Male, n (%)	3 (25)[a]	0 (0)[a]	33 (82.5)[b]	
BMI (kg/m^2)*	40.66±11.53[a]	28.65±5.20[b]	32.28±5.42[b]	<0.001
Chronic pain duration (year)*	6.00±4.54	2.46±2.71	2.3±5.98	0.122
VAS*	7.00±1.00[a]	7.00±1.00[a]	2.00±3.00[b]	<0.001
TP*	14.00±3.00[a]	15.00±3.00[a]	2.00±3.00[b]	<0.001
Algometry*	19.07±4.06[a]	18.28±4.96[a]	21.95±3.54[b]	0.007
FIQ*	80.19±16.22[a]	69.31±14.15[a]	25.38±23.2[b]	<0.001
BDS*	19.00±7.00[a]	20.00±12.00[a]	6.00±5.00[b]	<0.001
BAS*	19.00±7.00[a]	31.00±14.00[a]	10.00±7.00[b]	<0.001
Symptoms, n(%)				
Chronic widespread pain	10 (90.9)[a]	10 (83.3)[a]	8 (20)[b]	<0.001
Sleep disorder	11 (100)	10 (83.3)	35 (87.5)	0.401
Fatigue, weakness	11 (100)[a]	12 (100)[a]	23 (57.5)[b]	0.001
Concentration disturbance	8 (72.7)[a]	8 (66.7)[ab]	12 (30)[b]	0.009
Headache	9 (81.8)[a]	12 (100)[a]	16 (40)[b]	<0.001
Paresthesia	8 (72.7)	6 (50)	18 (45)	0.265
Stiffness	8 (72.7)[a]	10 (83.3)[a]	10 (25)[b]	<0.001
Swelling sensation	9 (81.8)[a]	10 (83.3)[a]	9 (22.5)[b]	<0.001
Morning fatigue	11 (91.6)	10 (83.3)	26 (65)	0.064

*Mean±standard deviation. FMS: fibromyalgia syndrome; BMI: Body Mass Index; VAS: visual analogue scale; TP: tender points; FIQ: fibromyalgia impact questionnaire; BDS: Back depression scale; BAS: Back anxiety scale

[a,b]Each different superscript indicates the statistical significance

Table 2. Polysomnographic findings of study groups

	Group 1 FMS (+) OSAS(+) (n=12)	Group 2 FMS (+) OSAS(-) (n=12)	Group 3 FMS(-) OSAS (+) (n=40)	p
Total sleep time (minute)	377.42±52.65	353.04±61.78	363.34±53.35	0.551
Sleep latency (minute)	15.00±11.66[a]	31.88±28.07[b]	14.88±10.32[a]	0.004
REM (minute)*	62.67±31.93	56.71±21.39	64.23±30.15	0.736
(%)	16.09±7.43	16.18±6.05	17.05±7.12	0.879
Stage 1 (minute)*	40.08±21.42	26.33±12.89	45.98±28.57	0.067
(%)	10.95±5.71	8.01±5.07	12.86±8.48	0.147
Stage 2 (minute)*	153.13±21.12	148.21±35.2	151.44±45.9	0.954
(%)	41.22±7.53	42.02±7.23	41.62±10.73	0.980
Stage 3 (minute)*	121.54±48.28	121.79±48.8	101.94±47.31	0.285
(%)	31.73±10.51	33.82±11.37	28.12±12.99	0.320
Sleep Efficiency (%)	82.13±12.1	78.06±12.19	79.07±11.03	0.646
AHI	33.86±28.93[a]	2.09±1.72[b]	43.83±26.68[a]	<0.001
ARI	36.49±22.25[a]	7.12±3.48[b]	49.57±23.65[a]	0.001
Desaturation (%)	23.15±31.87	0.16±0.33	12.82±23.53	0.062
ODI	31.43±28.41[a]	2.21±1.98[b]	38.78±32.43[a]	0.001
Minimum O_2 saturation in night (%)	73.25±14.39[a]	90.42±3.82[b]	76.45±13.48[a]	0.002
Average O_2 saturation in night (%)	91.42±5.82[a]	95.67±1.07[b]	92.25±4.07[a]	0.025
Severity of OSAS n (%)				
Mild	4 (33)	-	6 (15)	
Moderate	3 (25)	-	8 (20)	0.277
Severe	5 (42)	-	26 (65)	

*Sleep stages are given as minute and % of total sleep time. REM: Rapid Eye Movement; AHI: Apnea-Hypopnea Index; ARI: Arousal Index; ODI: oxygen desaturation index; Desaturation (%): Sleep time of SpO_2<90%

[a,b]Each different superscript indicates the statistical significance

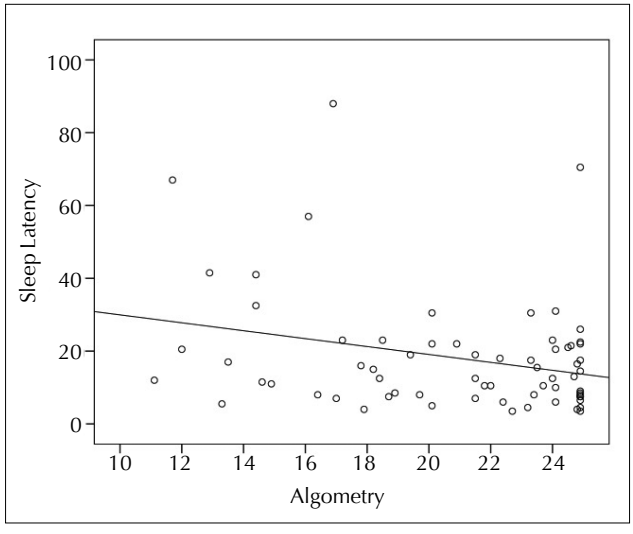

Figure 1. Correlation between sleep latency and algometry

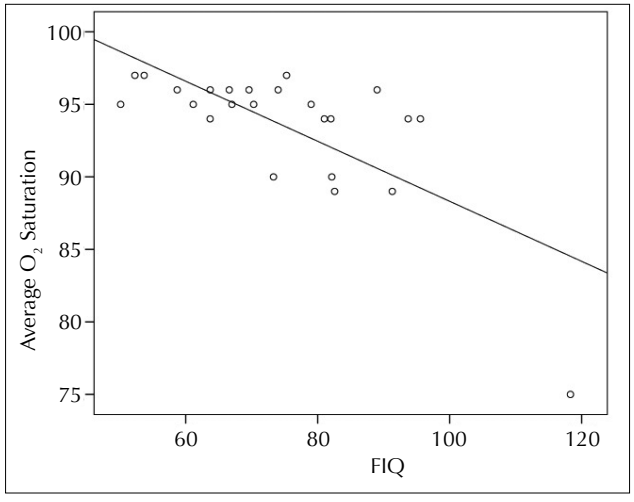

Figure 2. Correlation between average O_2 saturation and FIQ
FIQ: fibromyalgia impact questionnaire

correlations were observed in FIQ and average oxygen saturation (r=-0.71; p<0.001) (Figure 2), VAS and average oxygen saturations (r=-0.458, p=0.02), and VAS and minimum oxygen saturations (r=-0.438, p=0.032) (Figure 3), while a positive correlation was observed between FIQ and desaturation times (r=0.69, p<0.001) (Figure 4).

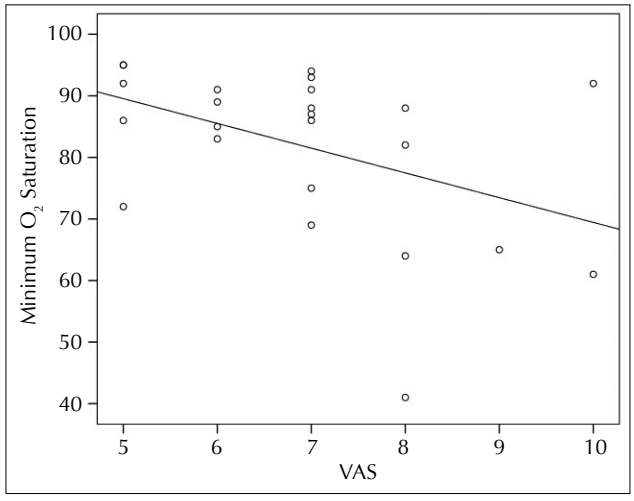

Figure 3. Correlation between minimum O_2 saturation and VAS
VAS: visual analogue scale

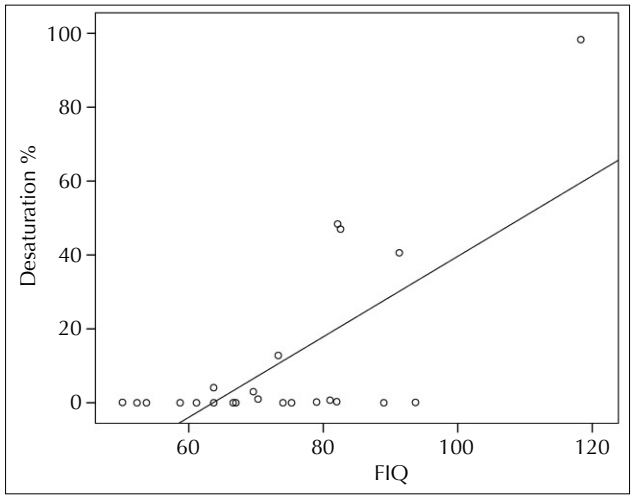

Figure 4. Correlation between desaturation times and FIQ
FIQ: fibromyalgia impact questionnaire

DISCUSSION

The salient findings of the present study are as follows. First, OSAS was detected in 50% of patients with FMS. The second outcome is distraction of attention to common symptoms of sleep disorder and morning fatigue in both FMS (Group 1, Group 2) and OSAS (Group 3). The third result is the detection of a significant correlation between the degree and severity of hypoxemia as retrieved from the records of PSG, FIQ, and VAS scores, which are characteristic measures of FMS. These outcomes were significant because they demonstrated the contribution of increased tissue hypoxia to clinical deterioration in FMS.

Fibromyalgia syndrome is a chronic painful condition with unknown etiology characterized by tender trigger points, with painful response to pressure, widespread pain, and muscular hypersensitivity [12]. Other frequently seen concomitant symptoms include fatigue, joint stiffness, sleep disorders, depression, and anxiety [13]. Fibromyalgia syndrome can affect the quality of life via induction of functional impairment [14]. Its prevalence is estimated to range between 2% and 4% [15-18]. It is observed in 3.4%-4.9% of females and 0.5%-1.6% of male patients with a female/male ratio of 6-9/1 [15,19].

In FMS, non-restorative sleep and morning fatigue are the most prominent symptoms [20-22]. The patients indicated their sleep as unrefreshening when they woke up, which signifies impaired sleep quality even if their sleep duration was normal. Impaired sleep quality is associated with fibromyalgia pain. Dysfunctional changes in the central nervous system (CNS) caused by chronic pain have been held responsible for sleep disorder. It has been suggested that in FMS, increased sympathetic activity in CNS and release of proinflammatory cytokines from glial cells adversely affects sleep quality. On the other hand, sleep has been suggested to have an impact on fibromyalgia symptoms, with an underlying immunological pathogenesis, and effects of mediator cytokines, such as TNF-α and IL1-β, involved in the sleep regulating regions of CNS on the the emergence of FMS symptoms have also been indicated [23]. In our study, complaints of sleep disorders were found in similar patients with FMS and OSAS. Similarly, the rates of morning fatigue, which is one of the most predominant symptoms of FMS, were not different between the groups. It should not be forgotten that the complaints of sleep disorder and morning fatigue, which are common symptoms of both FMS and OSAS, are extremely important because they are not related only to the underlying disease but are associated with other pathologies. Another outcome of our study is that sleep architecture is impaired in patients with FMS. PSG findings of the groups were compared, and longer sleep latencies were detected in patients with FMS and in those without OSAS (Group 2). In other words, these patients had difficulty in falling asleep, which is thought to be related to fibromyalgia pain. Indeed, in correlation analyses, a negative and significant correlation was observed between the algometry (pain threshold) and sleep latency, and the patients experienced difficulties in falling asleep as their pain threshold lowered. Similar distribution rates for NREM and REM stages of sleep in all groups were also remarkable. Indeed, increased duration of superficial sleep at the expence of deep (slow wave) sleep in patients with FMS demonstrates impaired sleep quality in these patients.

In patients with FMS, impairment of especially NREM stage of sleep is seen [24]. First, in the year 1975, PSG reports indicated the presence of alpha intrusions in NREM deep sleep in patients with FMS [25]. Phasic alpha activity, which causes sleep fragmentation, is seen in 50% of the patients [26]. In addition, cyclic alternating pattern episodes observed in these patients were found to be correlated with the severity of fibromyalgia symptoms, such as pain, fatigue, unrefreshing sleep, and depressive mood [27]. In our study, PSG findings of patients with FMS were evaluated and alpha intrusions were detected in 11 of 24 patients. These activations were seen in NREM stages 2 and 3. Another outcome related to this finding is the detection of mean ARI scores that were higher than the mean AHI scores, which defied any correlation in patients with FMS. Arousals often occur after apnea-hypopnea during sleep. It is a phenomenon that causes disruption of sleep continuity. In our study, higher number of arousals unrelated to respiratory events was detected in patients with FMS. These findings signified that this phenomenon leads to sleep fragmentation with ensuing impairment of sleep quality.

In FMS, increased sympathetic activity is seen, which is sustained during the sleep period [28]. In records of actigraphy, in addition to impaired sleep pattern, increase in nighttime activity was seen similar to daytime activity [29]. In OSAS, autonomic dysfunction and increased sympathetic discharge were also observed [30]. In conclusion, both pathologies impair sleep quality and abnormally increase heart rate variability, which will lead to emergence of vitally important pathologies. Therefore, OSAS and FMS concomitancy is an extremely important association because in addition to its adverse effects on the quality of life, it contributes to the mortality rates. In our study, detection of OSAS in 50% of the patients with FMS indicates the importance of this association.

In patients with FMS, the effect of hypoxia on tensile strength of muscles was investigated. The data obtained suggested that tissue hypoxia develops because of increased capillary perfusion and increase in the demand for oxygen by muscle tissue rather than enhanced muscle strain [31]. In another study, muscle metabolism was evaluated during aerobic and anaerobic exercises and lower maximum oxygen consumption was detected in patients with FMS. Besides, in these patients, muscles used aerobic metabolism less frequently and reached anaerobic threshold earlier [32]. These outcomes emphasize tissue oxygenation in fibromyalgia. In our study, patients with FMS had severe oxygen desaturations. Another outcome of our study is the detection of a positive correlation between FIQ and desaturation times (the time interval where nocturnal oxygen saturation is below 90%) and a negative correlation between mean and minimum oxygen saturation in patients with FMS. As mean and minimum oxygen saturation drops and desaturation time increases (ie. as oxygenation deteriorates), FIQ scores increase. This result was important because it emphasized the contribution of increased tissue hypoxia with resultant muscular dysfunction to clinical deterioration. Similar correlations were also observed between VAS and average and minimum oxygen saturations. We did not evaluate the contribution of effective OSAS treatment (ie. continuos positive airway pressure, CPAP) on the improvement of symptoms in patients with FMS associated with OSAS, which constituted the most important limitation of our study. This condition was stemmed from the scarce number of patients requiring CPAP treatment. Other limitation of this study is that the data was collected from a single region and the study had a small sample size.

In conclusion, because of similar symptoms, patients with FMS should be evaluated for OSAS. Also, FMS might occur in patients with OSAS. Additional contributions of diagnosis and treatment of concomitant OSAS to the treatment of patients with FMS can be suggested. Prospective studies with larger patient population that will evaluate treatment efficacy will shed light on this subject.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziosmanpaşa University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.İ.K., A.İ., A.K.; Design - H.İ.K., A.İ.; Supervision - H.İ.K., A.K.; Resources - S.O., O.Ç., S.İ.; Materials - S.O., O.Ç., S.İ.; Data Collection and/or Processing - H.İ.K., A.İ., S.O.; Analysis and/or Interpretation - O.D., H.İ.K., A.İ., A.K., S.İ.; Literature Search - H.İ.K., A.İ., A.K., S.İ., S.O., O.Ç.; Writing Manuscript - H.İ.K., A.İ., A.K., S.İ., O.D.; Critical Review - A.K., A.İ., O.D.; Other - S.O., O.Ç., S.İ., O.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Pejovic S, Natelson BH, Basta M, et al. Chronic fatigue syndrome and fibromyalgia in diagnosed sleep disorders: a further test of the 'unitary' hypothesis. BMC Neurol 2015;15:53. [CrossRef]
2. Goldenberg DL. Fibromyalgia syndrome a decade later: what have we learned? Arch Intern Med 1999;159:777-85.
3. Köktürk O. Obstrüktif Uyku Apne Sendromu Sonuçları. Tüberk Toraks Derg 2000;48:273-89.
4. Wolfe F, Smythe HA, Yunus MB, et al. The American college of rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum 1990;33:160-72. [CrossRef]
5. Moldofsky H, Lue FA, Mously C, et al. The effect of zolpidem in patients with fibromyalgia: a dose ranging, double blind, placebo controlled, modified crossover study. J Rheumatol 1996;23:529-33.
6. Jesse DE, Graham M. Are you often sad and depressed? Brief measures to ıdentify women at risk for depression in pregnancy. MCN Am J Matern Child Nurs 2005;30:40-5.
7. Ulusoy M, Sahin NH, Erkmen H. Turkish version of the Beck Anxiety Inventory: Psychometric properties. J Cogn Psychother 1998;12:163-72.
8. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol 1991;18:728-33.
9. Sarmer S, Ergin S, Yavuzer G. The validity and reliability of the Turkish version of the Fibromyalgia Impact Questionnaire. Rheumatol Int 2000;20:9-12. [CrossRef]
10. Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specification, 1st ed. American Academy of Sleep Medicine, Westchester, 2007.
11. Sleep-Related Breathing Disorders in Adults. Recommendations for Syndrome Definition and Measurement Techniques in Clinical Research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22:667-89.
12. Wilke WS. New developments in the diagnosis of fibromyalgia syndrome: say goodbye to tender points? Cleve Clin J Med 2009;76:345-52.
13. Clauw DJ. Fibromyalgia. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH; eds. Rheumatology. Mosby, Philadelphia 2004:701-11.
14. Wolfe F, Anderson J, Harkness D, et al. Work and disability status of persons with fibromyalgia. J Rheumatol 1997;24:1171-8.
15. Prins MA, Woertman L, Kool MB, Geenen R. Sexual functioning of women with fibromyalgia. Clin Exp Rheumatol 2006;24:555-61.
16. Ryan S, Hill J, Thwaites C, Dawes P. Assessing the effect of fibromyalgia on patients' sexual activity. Nurs Stand 2008;23:35-41. [CrossRef]
17. Shaver JL, Wilbur J, Robinson FP, et al. Women's health issues with fibromyalgia syndrome. J Womens Health (Larchmt) 2006;15:1035-45. [CrossRef]

18. De Costa ED, Kneubil MC, Leao WC, The KB. Assessment of sexual satisfaction in fibromyalgia patients. Einstein 2004;2:177-81.
19. Castro I, Barrantes F, Tuna M, et al. Prevalence of abuse in fibromyalgia and other rheumatic disorders at a specialized clinic in rheumatic diseases in Guatemala city. J Clin Rheumatol 2005;11:140-5. [CrossRef]
20. Gupta A, Silman AJ, Ray D, et al. The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study. Rheumatology (Oxford) 2007;46:666-71. [CrossRef]
21. Bennett RM, Jones J, Turk DC, et al. An internet survey of 2,596 people with fibromyalgia. BMC Musculoskelet Disord 2007;8:27. [CrossRef]
22. Cappelleri JC, Bushmakin AG, McDermott AM, et al. Measurement properties of the Medical Outcomes Study Sleep Scale in patients with fibromyalgia. Sleep Med 2009;10:766-70. [CrossRef]
23. Roizenblatt S, Neto NS, Tufik S. Sleep disorders and fibromyalgia. Curr Pain Headache Rep 2011;15:347-57. [CrossRef]
24. Moldofsky H, Scarisbrick P, England R, Smythe H. Musculoskeletal symptoms and non-REM sleep disturbance in patients with "Wbrositis syndrome" and healthy subjects. Psychosom Med 1975;37:341-51. [CrossRef]
25. Rosenfeld VW, Rutledge DN, Stern JM. Polysomnography with quantitative EEG in patients with and without fibromyalgia. J Clin Neurophysiol 2015;32:164-70. [CrossRef]
26. Lentz MJ, Landis CA, Rothermel J, Shaver JL. Effects of selective slow wave sleep disruption on musculoskeletal pain and fatigue in middle aged women. J Rheumatol 1999;26:1586-92.
27. Rizzi M, Sarzi-Puttini P, Atzeni F, et al. Cyclic alternating pattern: a new marker of sleep alteration in patients with fibromyalgia? J Rheumatol 2004;31:1193-9.
28. Chervin RD, Teodorescu M, Kushwaha R, et al. Objective measures of disordered sleep in fibromyalgia. J Rheumatol 2009;36:2009-16. [CrossRef]
29. Korszun A, Young EA, Engleberg NC, et al. Use of actigraphy for monitoring sleep and activity levels in patients with fibromyalgia and depression. J Psychosom Res 2002;52:439-43. [CrossRef]
30. Coy TV, Dimsdale JE, Ancoli-Israel S, Clausen J. Sleep apnoea and sympathetic nervous system activity: a review. J Sleep Res 1996;5:42-50. [CrossRef]
31. Strobel ES, Krapf M, Suckfüll M, et al. Tissue oxygen measurement and 31P magnetic resonance spectroscopy in patients with muscle tension and fibromyalgia. Rheumatol Int 1997;16:175-80. [CrossRef]
32. Lund E, Kendall SA, Janerot-Sjøberg B, Bengtsson A. Muscle metabolism in fibromyalgia studied by P-31 magnetic resonance spectroscopy during aerobic and anaerobic exercise. Scand J Rheumatol 2003;32:138-45.[CrossRef]

Turk Thorac J 2017; 18: 47-51 DOI: 10.5152/TurkThoracJ.2017.16008

ORIGINAL ARTICLE

Presence of Headache and Migraine in Asthma Patients

Muzaffer Onur Turan[1], Çiğdem Çelik Susuz[2], Pakize Ayşe Turan[3]

[1]Department of Chest Diseases, İzmir Katip Çelebi University Atatürk Training and Research Hospital, İzmir, Turkey
[2]Clinic of Neurology, Afyonkarahisar State Hospital, Afyon, Turkey
[3]Clinic of Chest Diseases, Menemen State Hospital, İzmir, Turkey

Abstract

OBJECTIVES: Migraine is a diseases characterized with severe headaches, with neurological and systemic findings. The purpose of this study is to investigate the prevalence of migraine and to examine whether there is a relationship between atopic disorders, parental history and migraine in asthma patients.

MATERIAL AND METHODS: A total of 288 asthma outpatients, who had the diagnosis by an early or late test of reversibility showing a reversible airway obstruction according to hospital database were included. The presence of headache, atopic symptoms and parental history about asthma, atopic disorders and migraine were asked. The patients with headache were consultated by neurology department and investigated about the presence of migraine. The diagnosis of migraine headache was made if patients fulfilled the International Headache Society (IHS) criteria.

RESULTS: 60.4% of patients described a headache. There were 94 patients (32.6%) with headaches meeting the IHS criteria for migraine. Only 12 patients had migraine with aura. There were atopic symptoms in 86.8% of patients. According to parental history, there were asthma in 47.9%, atopic symptoms in 39.6% and migraine in 22.2% of parents. Patients with atopic symptoms were found to have significantly high rate of headaches (65.3%) "p=0.007". The prevalence of migraine was significantly high in patients with parental atopic symptoms (54%) "p=0.002". Multiple logistic regression analysis identified that gender, parental history of asthma, allergia and migraine, and smoking were independent risk factors for presence of migraine in asthmatics.

CONCLUSION: There is a high prevalence of migraine headaches in patients with asthma. The coexistence of asthma and headaches may be related with a similar pathophysiological mechanism; parental history, common genetic compounds and smoking may play role in this mechanism. The headaches in asthma patients, atopic symptoms and family history should be questioned, and clinicians should be careful about the presence of migraine.

KEYWORDS: Asthma, migraine, headache

Received: *11.05.2016* ***Accepted:*** *05.03.2017*

INTRODUCTION

Headache is the common name for pain felt in the head and sometimes in the neck and in the upper area of the back. Headaches can occur without any underlying disease (primary), or they can develop in association with many different conditions or diseases (secondary). The International Headache Society (IHS) has classified headaches in 14 main groups and many subgroups and defined their causes based on etiological factors [1].

Migraine is a primary headache disorder accompanied by neurological and systemic findings and characterized by severe headaches, and neurological, vascular, and genetic factors play a role in its etiology [2]. Its diagnosis is established in accordance with the criteria determined by the IHS (Appendix 1a and 1b). Its prevalence is reported to be 6-8% among males and 15-18% among females [3].

Similarities resulting from pathophysiological mechanisms exist between asthma and migraine [4]. Some mediators such as tumor necrosis factor-alpha (TNF-a) and interleukin-1 beta (IL-1b) have a role both in the pathogenesis of asthma and in the development of migraine [5].

Allergic rhinitis is defined as inflammation of the nasal mucosa, and it is characterized by nasal itching, sneezing, nasal congestion, and rhinorrhea. The most important risk factor for allergic rhinitis is familial atopy. Another common feature of asthma and migraine is the presence of atopic characteristics that can be observed in patients. In a previous study, the prevalence of atopy in migraine patients was found to be near that in asthma patients [6].

Address for Correspondence: Muzaffer Onur Turan, İzmir Katip Çelebi Üniversitesi Atatürk Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Anabilim Dalı, İzmir, Türkiye
E-mail: onurtura@yahoo.com

The common coexistence of migraine and allergic diseases suggests that allergic mechanisms have a role in the pathophysiology of migraine. In this study, it was aimed to investigate the prevalence of migraine in patients diagnosed with asthma and the relationship between allergic rhinitis symptoms in asthma patients and their families and the presence of migraine.

MATERIAL AND METHODS

The study included 288 patients with the diagnosis of asthma who were admitted to the outpatient clinic of Chest Diseases in Afyon Bolvadin State Hospital during a 6-month period in 2013 and whose early or late positive reversibility in the respiratory function test was confirmed by the recording system at the hospital.

Patients with a history of head or cerebral trauma, cranial or cervical vascular disease, substance abuse, cranial or facial structural impairments and infections, extravascular intracranial disease, psychiatric disorders, arterial hypertension, and homeostasis disorders such as hypothyroidism, which can lead to secondary headache, were excluded. Moreover, patients who used montelukast and antihistamine drugs, which could suppress allergic complaints and cause an incorrect anamnesis, were excluded.

Sociodemographic data of included patients were recorded. The presence of asthma and migraine in patients and their first-degree families was questioned. The patients were asked about whether they and their first-degree families had allergic complaints such as nasal congestion, sneezing, nasal itching, and nasal and post-nasal drainage, and related responses were recorded.

Asthma patients included in the study were asked about the presence of headache. Patients who had headache were referred to the Department of Neurology. Those who met the diagnostic criteria of IHS were considered to have migraine-type headache [1]. The presence of aura was investigated in patients having migraine, and patients were classified as those having migraine with aura and without aura.

The sample size was calculated as 264, with an α value of 0.05 and study power of 90%. Accepting that a loss ratio of 10% would occur, a study with 288 patients was planned.

Statistical Analysis

While evaluating the data obtained from the study, statistical analysis was performed using Statistical Package for Social Sciences for Windows 15.0 (SPSS Inc; Chicago, IL, USA). The chi-square test was used in the comparison of qualitative data. For evaluating the variance of slopes, chi-square and T-tests were used. The results were assessed with a confidence interval of 95% and a significance level of $p<0.05$. In descriptive statistics, continuous variables were presented as mean and standard deviation and categorical variables as number and percentage. Multiple logistic regression analysis was performed for revealing the relationship between migraine, which was the dependent variable, and independent variables by calculating the odds ratio and 95% confidence interval.

RESULTS

Of 288 asthma patients included in the study, 236 (81.9%) were females and 52 (18.1%) were males, and their mean age was 42.9±11.6 years (minimum, 17 years; maximum, 77 years).

Considering disease control, asthma patients were classified as controlled (49.3%), partially controlled (21.6%), and uncontrolled (29.1%). While 175 (60.8%) patients were nonsmokers, 113 (39.2%) were smokers. Except the comorbidities included in the exclusion criteria, 27.8% of patients had additional comorbidities (mostly diabetes mellitus).

Allergic symptoms (nasal itching: 56%, sneezing: 42%, rhinorrhea: 30%, and nasal congestion: 27%) were present in 86.8% of the patients.

The complaint of headache was observed in 60.4% of the patients (after ruling out the causes of secondary headache). The number of patients who met the criteria for the diagnosis of migraine was 94 (32.6%). Only 12 patients had migraine with aura. The mean age of patients diagnosed with migraine was 44.3±12.0 years (Table 1).

No statistically significant difference was found between the mean ages in the groups of patients with and without migraine (p=0.918). While 39% of females and 16.7% of males had migraine-type headache, the rate of primary headache and the diagnosis of migraine were significantly higher among females than among males ($p<0.001$ and p=0.002, respectively). The existence of migraine was observed to be more common in patients who were smokers (p=0.046).

The patients had family histories of asthma, allergic complaints, and migraine at rates of 47.9%, 39.6%, and 22.2%, respectively, in their first-degree relatives. In patients with allergic complaints, the frequency of headache was quite high (65.3%) (p=0.007). The rate of the presence of migraine

Table 1. Information on the presence of headache and migraine in asthma patients

Patient characteristics	Number of patients n (%)
Presence of headache	174 (60.4)
Presence of migraine	94 (32.6)
Headache	
Unilateral headache	58 (33.3)
Type of pain	
Throbbing	99 (57)
Compressive	75 (43)
Aura	12 (7)
Aggravation with physical	93 (53.5)
Activity	
Nausea-vomiting	71 (41.2)
Photopsia	12 (7)
Disturbed by light and	69 (39.5)
Noise	
Visual loss	12 (7)

Table 2. Multiple logistic regression analysis of independent variables that can be associated with migraine

		(95% confidence interval)		
Independent variables	**OR**	**Lowest**	**Highest**	**p**
Gender (female)	2.229	1.089	4.143	0.005*
Age (continuous variable)	1.012	0.992	1.033	0.251
Allergy (+ or -)	1.108	0.427	2.871	0.834
Familial history of asthma (+ or -)	1.501	0.754	3.385	0.045*
Familial history of allergy (+ or -)	5.019	2.538	9.924	<0.001*
Familial history of migraine (+ or -)	2.108	1.085	4.094	0.028*
Smoking (+ or -)	6.961	2.091	23.172	0.002*

OR: odds ratio; *statistically significant

was found to be significantly high in patients with a familial history of allergic symptoms (54%) (p=0.002). A statistically significant relationship was detected between the complaint of headache and the presence of the familial histories of asthma, migraine, and allergic symptoms [42% (p=0.01), 80.6% (p=0.015), and 71.4% (p=0.038), respectively]. The complaint of headache was significantly common in patients having allergic symptoms (p=0.007). A significant relationship was found between the presence of the familial histories of asthma, migraine, and allergic symptoms and headache in asthma patients (p=0.01, p=0.015, and p=0.038). In patients having a familial history of allergic symptoms, the rate of migraine was significantly high (p=0.002).

Logistic regression analysis revealed that gender (female), smoking, and the presence of familial histories of asthma, allergic complaints, or migraine were independent risk factors for migraine in asthma patients (Table 2).

DISCUSSION

Headache is a disorder that is commonly defined in asthma patients and that negatively affects the quality of life. The relationship of headache and migraine with migraine was investigated in many studies. According to the results of the "Head Hunt" study, the frequency of asthma and chronic bronchitis was 1.5-times higher in patients with migraine and non-migraine headaches than in the normal population and the presence of asthma and bronchitis was found to be associated with the frequency of headache [7]. The fact that approximately 60% of our patients had headache indicates the high frequency of headache in asthma patients.

In our study, the prevalence of migraine was found to be 32.6% in asthma patients. In the literature, there are a few studies investigating the prevalence of migraine. Martin et al. [8] reported the rate of chronic migraine to be 5.4% in patients diagnosed with asthma. In a study conducted in Turkey on the prevalence of migraine, migraine was detected in 16.4% of the population (24.6% in females and 8.5% in males) [9]. This shows that migraine-type headache can be more commonly seen in asthma patients than in the normal population.

In our study, the frequencies of both migraine and primary headache were found to be higher in females than in males (2.3- and 1.8-times higher, respectively). Other studies have also demonstrated that the rate of migraine was 2-3 times higher in females [10]. Therefore, more attention should be paid to female asthma patients in terms of the existence of migraine, and it should always be kept in mind that the possibility of migraine is higher in females.

It has been suggested that the coexistence of asthma and migraine and headache can result from a common pathophysiological mechanism and familial history and that common genetic components have a role in this common pathogenesis [11]. It was reported that the risk of the development of asthma was higher in children whose parents had migraine [12]. In our study, the relationship between familial histories of asthma, migraine, and allergic symptoms and headache and migraine in asthma patients was significant, and it was recommended to examine the presence of headache and migraine in asthma patients with such a familial anamnesis.

In our study, it was observed that headache and migraine were more common in atopic patients. The presence of an independent relationship between allergic diseases and migraine is known [13]. It is specified in the literature that there is a strong relationship among asthma, allergic rhinitis, and migraine and that increased levels of histamine have a role in the basis of this relationship [14]. A study conducted by Gazerani et al. [15] revealed high levels of serum histamine and IgE in patients having allergy accompanied by migraine. Allergic rhinitis is a chronic disease characterized by seasonal and perennial symptoms, and it affects the nasal mucosa in particular with IgE-dependent inflammation [16]. These results indicate a biochemical mechanism that represents atopy in the relationship among allergy, asthma, and migraine. A similar relationship was also detected in our study.

Although it is known that smoking can lead to migraine attacks, there are insufficient data on it being a risk factor for the development of migraine [17]. Chen et al.[18] reported that the rate of smoking was higher in women with migraine than in women without migraine. The theory that the frequency of migraine can increase due to decreased nitric oxide synthesis in smokers has been focused on [19]. In our study, it was found that the prevalence of migraine was higher in smoking asthma patients and that smoking was not only a trigger but also a risk factor for migraine.

One of the important limitations in our study was that the decision on patient selection was made by only considering existent diseases, although there were many causes that could cause secondary-type headache. Another limitation was that patients were selected from the hospital recording system. Moreover, the investigation of the prevalence of patients admitted to the outpatient clinic might have posed a problem and affected the results. In addition, considering subjective complaints such as headache and allergic symptoms and familial histories of asthma and migraine, which were verbally stated in the anamnesis, is another limitation. Better results

can be obtained using objective criteria such as IgE levels in the blood and the skin prick test for investigating the presence of allergic rhinitis, a health committee report for obtaining a positive familial history, or proof on the presence of these diagnoses in a patient's history.

In conclusion, migraine can frequently be seen in asthma patients. The coexistence of asthma and headache has been suggested to result from a common pathophysiological mechanism. Moreover, familial history, the presence of common genetic components, and smoking can have a role in this coexistence. Headache and migraine can be more frequently encountered in atopic patients. Therefore, in asthma patients, the following should be kept in mind: the complaint of headache should be thoroughly examined, familial history and allergic symptoms should be questioned while taking anamnesis, and attention should be paid with regard to the presence of migraine.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Afyonkarahisar Kocatepe University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.O.T.; Design - M.O.T., Ç.Ç.S.; Supervision - M.O.T.; Resources - M.O.T.; Materials - M.O.T., Ç.Ç.S.; Data Collection and/or Processing - M.O.T.; Analysis and/or Interpretation - M.O.T.; Literature Search - M.O.T., P.A.K.; Writing Manuscript - M.O.T.; Critical Review - M.O.T.

Conflict of Interest: No conflict of interest was declared by the author.

Financial Disclosure: The author declared that this study has received no financial support.

REFERENCES

1. Headache Classification Subcommittee of the International Headache Society. Classification of Headache Disorders, 2nd Edition. Cephalalgia 2004;24:(Suppl 1):1-151.
2. Edvinsson L, Uddman R. Neurobiology in primary headaches. Brain Res Brain Res Rev 2005;48:438-56. [CrossRef]
3. Katsarava Z, Buse DC, Manack AN, et al. Defining the differences between episodic migraine and chronic migraine. Curr Pain Headache Rep 2012;16:86-92. [CrossRef]
4. Davey G, Sedgwick P, Maier W, et al. Association between migraine and asthma: matched case-control study. Br J Gen Pract 2002;52:723-7.
5. Yilmaz IA, Ozge A, Erdal ME, et al. Cytokine polymorphism in patients with migraine: some suggestive clues of migraine and inflammation. Pain Med 2010;11:492-7. [CrossRef]
6. Ozge A, Ozge C, Oztürk C, et al. The relationship between migraine and atopic disorders-the contribution of pulmonary function tests and immunological screening. Cephalalgia 2006;26:172-9. [CrossRef]
7. Aamodt AH Stovner, LJ, Langhammer A, et al. Is headache related to asthma, hay fever, and chronic bronchitis? The Head-HUNT Study. Headache 2007;47:204-12. [CrossRef]
8. Martin VT, Fanning KM, Serrano D, et al. Asthma is a risk factor for new onset chronic migraine: Results from the American migraine prevalence and prevention study. Headache 2016;56:118-31. [CrossRef]
9. Ertas M, Baykan B, Kocasoy Orhan E, et al. One-year prevalence and the impact of migraine and tensiontype headache in Turkey: a nationwide home-based study in adults. J Headache Pain 2012;13:147-57. [CrossRef]
10. Breslau N, Rasmussen BK. The impact of migraine. Epidemiology, risk factors, and co-morbidities. Neurology 2001;56:4-12. [CrossRef]
11. Ku M, Silverman B, Prifti N, et al. Prevalence of migraine headaches in patients with allergic rhinitis. Ann Allergy Asthma Immunol 2006;97:226-30. [CrossRef]
12. Chen TC, Leviton A. Asthma and eczema in children born to women with migraine. Arch Neurol 1990;47:1227-30. [CrossRef]
13. Alehan F, Ozçay F, Erol I, et al. Increased risk for coeliac disease in paediatric patients with migraine. Cephalalgia 2008;28:945-9. [CrossRef]
14. Heatley RV, Denburg JA, Bayer N, et al. Increased plasma histamine levels in migraine patients. Clin Allergy 1982;12:145-9. [CrossRef]
15. Gazerani P, Pourpak Z, Ahmadiani A, et al. Correlation between migraine, histamine and immunoglobulin E. Scand J Immunol 2003;57:286-90. [CrossRef]
16. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. J Allergy Clin Immunol 2001;108:2-8. [CrossRef]
17. Rozen TD. A history of cigarette smoking is associated with the development of cranial autonomic symptoms with migraine headaches. Headache 2011;51:85-91. [CrossRef]
18. Chen TC, Leviton A, Edelstein S, et al. Migraine and other diseases in women of reproductive age. The influence of smoking on observed association. Arch Neurol 1987;44:1024-8. [CrossRef]
19. Lassen LH, Ashina M, Christiansen I, et al. Nitric oxide synthase inhibition in migraine. Lancet 1997;349:401-2. [CrossRef]

Appendix 1a: Diagnostic criteria for migraine without aura (1)

A) At least five attacks including B–D items
B) Headache lasting for 4–72 h
C) Headache having at least two of the following characteristics
    1. Unilateral location
    2. Pulsating quality
    3. Moderate or severe pain intensity
    4. Aggravation by routine physical activity (walking, etc.)
D) During headache, at least one of the following
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia
E) Headache not attributed to another disorder

Appendix 1b: Diagnostic criteria for migraine with aura (1)

A) At least two attacks including B–D items
B) Aura including at least one of the following, but not motor weakness:
    1. Reversible visual symptoms with positive or negative features
    2. Reversible sensory symptoms with positive or negative features
    3. Fully reversible dysphasic speech disturbance
C) At least two of the following:
    1. Homonymous visual symptoms and/or unilateral sensory symptoms
    2. Aura symptoms develop in approximately 5 min, and different aura symptoms develop at 5-min intervals.
    3. Each symptom lasts for ≥5 and ≤60 min.
D) Headache beginning during aura or following aura within 60 min and fulfilling the criteria for migraine without aura
E) Headache not attributed to another disorder

Turk Thorac J 2017; 18: 52-3 DOI: 10.5152/TurkThoracJ.2017.16038

CASE REPORT

Spontaneous Splenic Rupture in the Early Postoperative Period to After Lobectomy

Ayşe Gül Ergönül, Tevfik İlker Akçam, Ali Özdil, Ufuk Çağırıcı

Department of Thoracic Surgery, Ege University School of Medicine, İzmir, Turkey

Abstract

Spontaneous splenic rupture is a quite rare entity that may develop secondary to some special situations (lymphoma, post-abdominal surgey etc). In the literature, the case of a patient has been reported following thoracic surgery. In a patient who had undergone right upper lobectomy for pulmonary carcinoma, signs of acute abdomen and low levels in the hemogram were detected on the fifth postoperative day; therefore, the patient underwent further investigations. A radiological evaluation revealed splenic rupture, and the patient was operated on. A case is presented that may be fatal and requires emergency response and that has to be kept in mind, although it is extremely rare. A case of spontaneous splenic rupture has been presented that may be fatal and requires emergency response; this should be kept in mind, although it is extremely rare.

KEYWORDS: Lung cancer pulmonary mass, splenic rupture, thoracic surgery pulmonary resection

Received: *27.09.2016* ***Accepted:*** *06.02.2017* ***Available Online Date:*** *01.03.2017*

INTRODUCTION

Splenic rupture is a fatal situation that commonly develops after trauma. A ruptured spleen in the absence of trauma is referred to as spontaneous splenic rupture [1,2]. It is quite rare, and its frequency has been reported to be 0.1% to 0.5% [3]. Spontaneous splenic rupture may be related to malignancies, endoscopic surgeries, use of anticlotting medications, or infections, and it may also exist idiopathically in the absence of any cause [4]. Hemodynamic support and emergency splenectomy are essential when it is diagnosed. We present a case with spontaneous splenic rupture that developed in the early postoperative period following right upper lobectomy and that had a fatal course. This case report serves as a discussion on and reminder of this hazardous complication.

CASE PRESENTATION

A 69-year-old male presented with complaints of coughing and bloody sputum; his chest X-ray revealed pathological signs, and he underwent thoracic computed tomography (CT). A 4-cm diameter mass was detected adjacent to the pleura in the anterior right upper lobe and had an irregular contour (Figure 1). Pozitron emission tomography (PET) 18-FDG for staging revealed a mass with FDG trapping in the right surrenal gland, in addition to the pulmonary mass. Transthoracic needle biopsy was performed for making a diagnosis. A diagnosis could not be made with the biopsy result; therefore, the mass in the surrenal gland was removed by endoscopic surgery. The pathological diagnosis of metastasis of an epithelial tumor was made. The period between laparoscopy and pulmonary resection was three weeks and was without any complication. With these signs, the patient was hospitalized in our clinic for the resection of the pulmonary mass. The patient provided written informed consent. He underwent mediastinoscopy, and the results of frozen section biopsy of the nodal stations 4R and 4L were reported as benign. Right upper lobectomy and mediastinal lymph node sampling were performed in the same session. The postoperative period was uneventful; apical and basal drains were removed on the fourth and fifth days, respectively. The patient was going to be discharged from the hospital during the day; however, there was a sudden (in a few minute) drop in his arterial blood pressure in the morning. Rapid investigations revealed his Hgb levels and Hct to be 7.9 g/dL and 23.8%, respectively. A chest X-ray was performed to evaluate the possibility of hemorrhage on the side of the resection; however, no signs of thoracic bleeding were observed. The patient consulted with members of the General Surgery Department because of the development of abdominal pain and distention during this time this procedure. Left bundle branch block and tachycardia developed, and he was evaluated by cardiologists. The patient's condition was partially stabilized, and he underwent abdominal CT, as recommended by general surgeon the department of general surgery. This investigation revealed free fluid in the abdomen and a hematoma around the spleen

Address for Correspondence: Tevfik İlker Akçam, Ege Üniversitesi Tıp Fakültesi, Göğüs Cerrahisi Anabilim Dalı, İzmir, Türkiye
E-mail: tevfikilkerakcam@hotmail.com

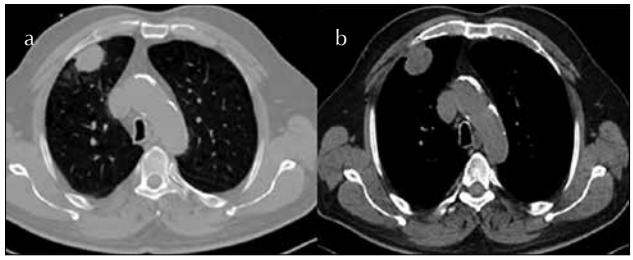

Figure 1. a, b. Computed tomography image: A 4-cm lesion in the right upper lobe

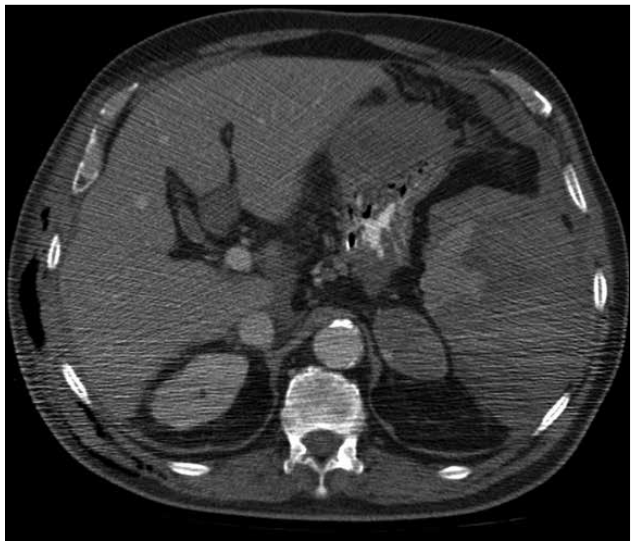

Figure 2. Computed tomography image: Abdominal free fluid and a hematoma around the splenic area

(Figure 2). The patient was therefore referred to the General Surgery Department again, and he underwent emergent splenectomy with laparotomy. He developed cardiac arrest in the early postoperative period. His heartbeat returned with resuscitation, and he was referred to the Anesthesia Intensive Care Unit. Pneumonia, empyema, and renal failure developed during his intensive care unit stay, and he died on the 12th postoperative day.

DISCUSSION

Spontaneous splenic rupture is quite rare; however, it must be considered in case of sudden drop in arterial blood pressure during early postoperative period due to its fatal consequences. Malignancies, infectious diseases, and systemic diseases play roles in its etiology. In particular, hematological malignancies form a wide group in this regard [1,4]. Although the available data are limited, its frequency has been reported to be 0.1% to 0.5%. Cases of spontaneous splenic rupture commonly in the literature as case reports; however, in the study by Kocael et al. [5], including a series of 12 cases, the most frequent cause of spontaneous splenic rupture has been reported to be the use of anticoagulants. Systemic diseases (amyloidosis, hepatitis, etc.) and malignancies play roles in its etiology. Further, there are idiopathic cases without any cause [5]. Hemodynamic support and emergency splenectomy are primarily recommended as soon as a diagnosis has been made, according to the clinical situation of a patient. The rate of splenectomy in these cases has been reported to be approximately 84.1% [1]. Nevertheless, in a ruptured spleen, particularly in cases related to infectious conditions and those that are not life threatening, clinical conservative approaches may also be performed. However, a patient must be closely followed up. Studies have reported a mortality rate of approximately 12.2% https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4254229/ however, in patients with a malignancy, splenomegaly, advanced age, and delayed diagnosis, the risk of mortality further increases [1,5].

In the literature, there is a single case with spontaneous splenic rupture in the early postoperative period following thoracotomy, and a malignancy was also present in this case [6]. The current patient with a malignant disease underwent laparoscopic right surrenalectomy for the metastatic lesion three weeks before pulmonary resection. Anticoagulant agents were administered for prophylaxis in the pre- and postoperative periods. All these conditions are risk factors for spontaneous splenic rupture in our patient, but we considered that the splenic rupture was not associated with these risk factors because the time interval between the two procedures (laparoscopic right surrenalectomy and pulmonary resection) was three weeks. The patient died due to additional complications that had developed during his intensive care unit stay despite urgent and successful splenectomy in the early postoperative period. This study aimed to serve as a reminder of this rare complication. The emergent evaluation and surgical approach may be lifesaving if splenic rupture is considered, when symptoms such as hypotension, tachycardia, and abdominal pain develop in the post-operative period, particularly in patients with a malignancy.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.G.E., U.Ç.; Design - A.G.E., T.İ.A.; Supervision - U.Ç.; Data Collection and/or Processing - A.G.E., T.İ.A., A.Ö.; Analysis and/or Interpretation - U.Ç., A.Ö.; Literature Search - A.G.E., T.İ.A.; Writing Manuscript - A.G.E., T.İ.A.; Critical Review - A.G.E., T.İ.A., A.Ö., U.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Renzulli P, Hostettler A, Schoepfer A, et al. Systematic review of atraumatic splenic rupture. Br J Surg 2009;96:1114-21. [CrossRef]
2. Debnath D, Valerio D. Atraumatic rupture of the spleen in adults. J R Coll Surg Edinb 2002;47:437-45.
3. Lai P. Infectious mononucleosis: recognition and management. Hosp Pract 1977;12:47-52. [CrossRef]
4. Elvy A, Harbach L, Bhangu A. Atraumatic splenic rupture: a 6-year case series. Eur J Emerg Med 2011;18:124-6. [CrossRef]
5. Kocael PC, Simsek O, Bilgin IA, et al. Characteristics of patients with spontaneous splenic rupture. Int Surg 2014;99:714-8. [CrossRef]
6. Klotz S, Semik M, Senninger N, et al. Spontaneous splenic rupture after a left-side thoracotomy: report of a case. Surg Today 2003;33:636-8. [CrossRef]

Turk Thorac J 2017; 18: 54-6 DOI: 10.5152/TurkThoracJ.2017.16039

CASE REPORT

Primary Pulmonary Malignant Fibrous Histiocytoma

Tuğba Coşgun[1], Yelda Tezel[2], Mustafa Akyıl[3], İlker Kolbaş[3], Ayçım Şen[4], Çağatay Tezel[3]

[1]Department of Thoracic Surgery, Acıbadem University Atakent Hospital, İstanbul, Turkey
[2]Clinic of Chest Diseases, Haydarpaşa Training Hospital, İstanbul, Turkey
[3]Department of Thoracic Surgery, Süreyyapaşa Chest Diseases and Thoracic Surgery Training Hospital, İstanbul, Turkey
[4]Clinic of Pathology, Süreyyapaşa Chest Diseases and Thoracic Surgery Training Hospital, İstanbul, Turkey

Abstract

Malignant fibrous histiocytoma (MFH) cases are classified within the group of nonclassified sarcomas. The etiopathogenesis is unclear; however, MFH commonly develops in scar tissue and in areas exposed to radiation. MFH is the most common soft tissue sarcoma in adults and may be borne in the lungs, chest wall, mediastinum, or other tissues. Primary MFH of the lung constitutes less than 0.2% of all pulmonary neoplasms; thus, an optimal treatment strategy has not yet been elucidated. We aimed to report a case of MFH of the lung with subsequent treatment administration.

KEYWORDS: Malignant fibrous histiocytoma, pulmonary neoplasm, lung

Received: *27.09.2016* ***Accepted:*** *03.02.2017* ***Available Online Date:*** *01.03.2017*

INTRODUCTION

Primary malignant fibrous histiocytoma (MFH) of lung is a rare kind of tumor; so that an optimal management of cases with primary malignant fibrous histiocytoma (MFH) has not yet been decribed. We aimed to share our experience on primary MFH of the lung.

CASE PRESENTATION

A 50-years-old man was admitted to our clinic with dyspnea and chronic cough. He had a history of smoking approximately 30 packs of cigarettes per year. A clinical examination including auscultation revealed decreased sounds of the left hemithorax. A full blood count showed a normal hemoglobin level, and renal and liver function test results were also normal. Chest X-ray showed opacity in the left lung, and a chest computed tomography (CT) scan revealed a 75×68×96 mm mass in the left lung (Figure 1). Additionally, there were a suspicion of chest wall invasion, particularly at the second rib. A preoperative bronchoscopic examination did not yield a definitive diagnosis, and transthoracic, fine-needle aspiration biopsy of the lesion was nonrepresentative (necrotic tissue). Positron emission tomography (PET) scanning showed high-intensity fludeoxyglucose (FDG) uptake in the 79×75×100 mm mass in the upper left lobe (SUVmax (maximum standard uptake value) of 9.7), but there was no suspicious uptake of metastatisis, in other areas (Figure 2). The patient's skeletal system and intracranial structures showed no FDG uptake. The patient's respiration function test results were unremarkable.

We decided to perform mediastinoscopy due to a high suspicion of a malignancy because of the high FDG uptake in the tumor. Mediastinal 4R, 4L, and 7 levels of lymph nodes were sampled, which revealed anthracosis on frozen section analysis. In the same operation, the left hemiclamshell approach was used due to its ability to provide a wide exposure that allowed the safe and complete removal of the lung cancer involving the mediastinum and apical thoracic dome. We prefer the hemiclamshell incision to provide optimal exposure of the hilar and mediastinal vascular structures. Upon exploration, an 8×10 cm lesion in the upper left lobe was detected. No chest wall invasion was found. Wedge resection from the preoperative, undiagnosed mass was performed, and frozen section analysis revealed a malignant tumor. We subsequently performed lobectomy of the upper left lung lobe. Levels 5, 6, and 11 were dissected after lobectomy. The patient's postoperative course was uneventful. Drains were taken out on postoperative day four, and the patient was discharged on the fifth postoperative day.

Cellular neoplasms that consist of malignant fusiform tumor cells that create short bundlers and storiform pattern are detected on histopathological analysis. Bizarre malignant cells and necrosis attend to these cells. Tumor cells showed vimentin (+), CD 68 focal (+), S100 (-), SMA (-), PanCK (-), and Ki67 80% (+) immunoreactivity on immunohistochemical evaluation, which strongly sug-

Address for Correspondence: Tuğba Coşgun, Acıbadem Üniversitesi Atakent Hastanesi, Göğüs Cerrahisi Bölümü, İstanbul, Türkiye
E-mail: tugba_cosgun@hotmail.com

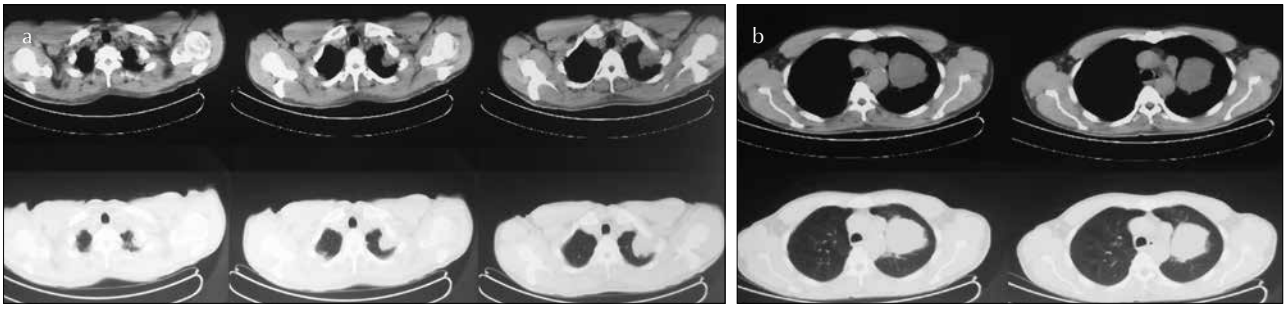

Figure 1. a, b. A chest computed tomography (CT) scan revealed a 75×68×96 mm mass in the left lung. (a) Suspicion of tumor invasion to the first rib. (b) Adjacency of the tumor to mediastinal vascular structures

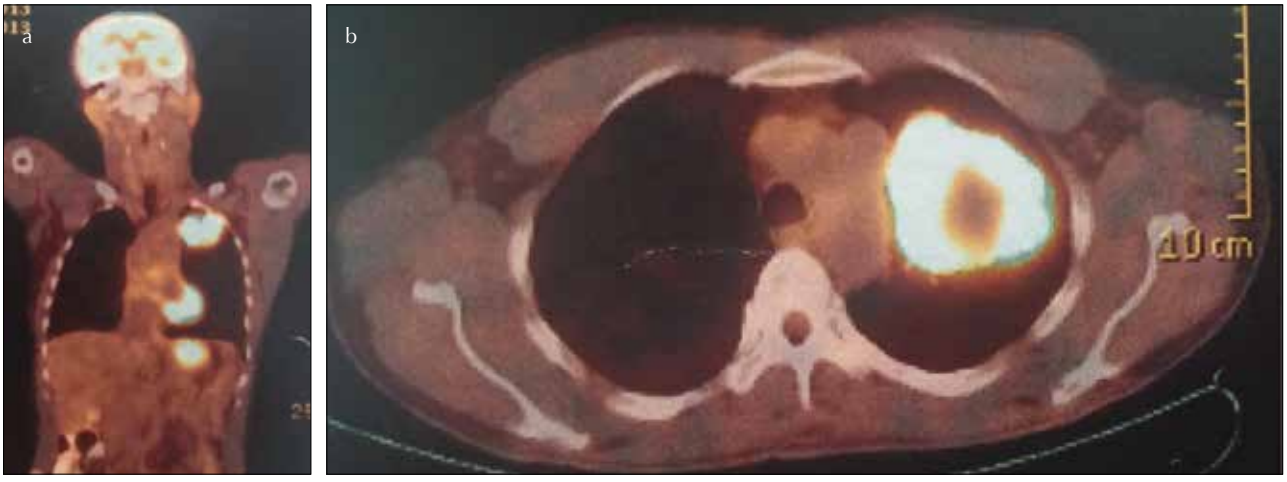

Figure 2. a, b. Positron emission tomography (PET) scanning showed high-intensity fludeoxyglucose (FDG) uptake in the mass in the upper left lobe (SUVmax of 9.7)

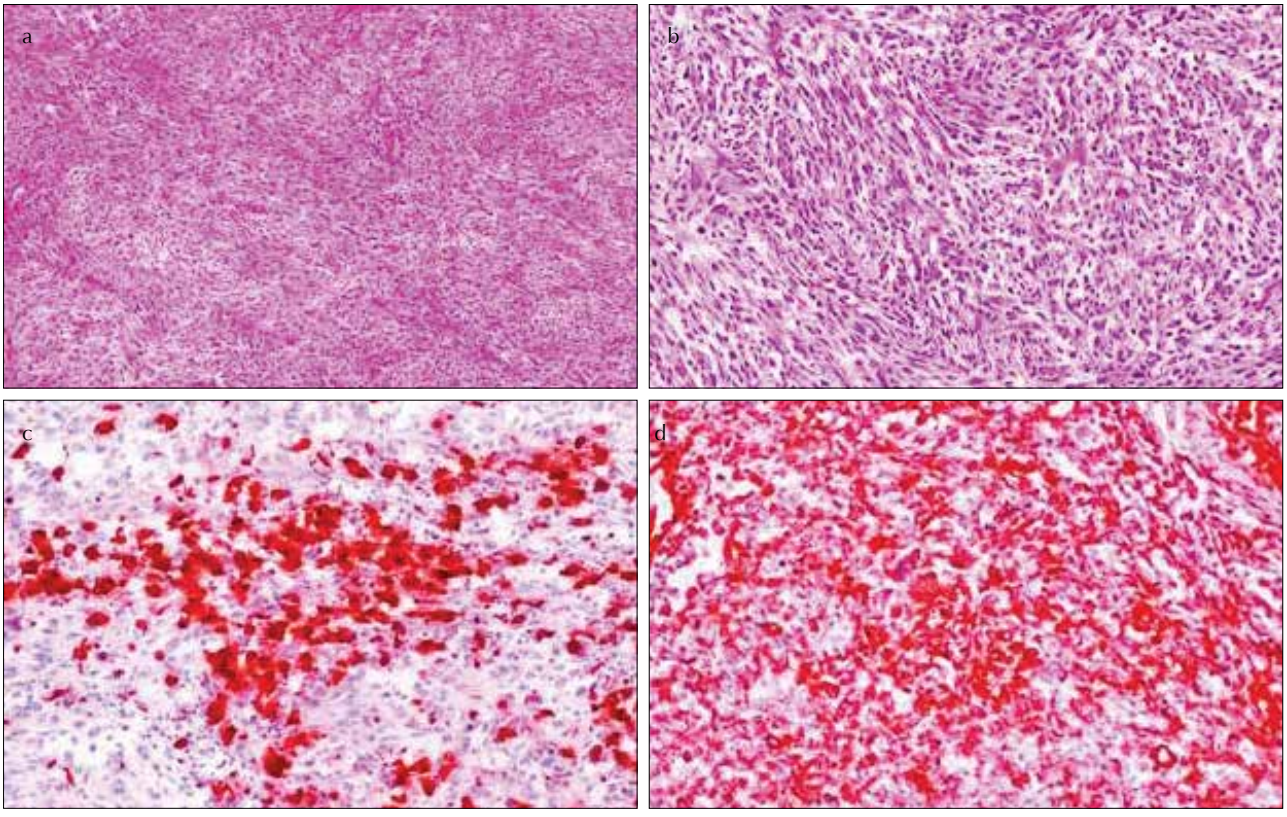

Figure 3. a-d. (a) Representative hematoxylin and eosin (HE) sections at original 4× magnification. Lesion created short bundles and consist of fusiform cells that show a storiform pattern (HE, 4×). (b) Bundles of malignant fusiform cells (HE,10×). (c) Tumor showed CD68 (+) immunoreactivity (HE,10×). (d) Tumor showed vimentin (+) immunoreactivity (HE, 10×)

gested malignant fibrous histiocytoma (MFH) (Figure 3). Resection margins were negative. Dissected lymph nodes were negative.

We took permission from patient to publish this case report at this stage. Recurrence was not detected in the three-year follow-up.

DISCUSSION

Reports on MFH were first described by Weiss and Enzinger [1]. MFH is one of the most common soft tissue tumors in adults. It can occur anywhere in the body, but it most commonly originates in the lower extremities and retroperitoneal region. MFH of the lung constitutes less than 0.2% of all pulmonary neoplasms. However, an optimal treatment strategy has not yet been elucidated [2].

Most MFH cases are asymptomatic (32%); however, the most common clinical symptoms are chest pain, dyspnea, cough, weight loss, fatigue, and hemoptysis [2-4]. Our patient's symptoms were cough and dyspnea. MFH can be seen between the ages of 10 and 80 year (average age, 55 years) [4]. There are different opinions on its frequency depending on gender [2].

Although most lesions are seen as solitary pulmonary masses or nodules, bilateral masses can also be seen. The frequency of occurrence in the right or left lobes is almost equal. Punctate calcifications on CT in pediatric patients have been reported [5]. Ipsilateral pleural effusion can occur in 20% of the patients [5], and endobronchial lesions have also been reported [6]. Without intending to make a generalized statement about FDG uptake in primary pulmonary MFH because it is a type of tumor that is rarely seen in the lungs, in our case, the SUVmax was 9.7. It is believed that PET-CT is useful to exclude other regions of tumors possibility [2].

Malignant fibrous histiocytoma histologically consists of varied spindle-shaped fibroblasts and histiocytes with atypical pleomorphic giant cells. Five distinct histologic subtypes (storiform-pleomorphic, myxoid, giant cell, inflammatory, and angiomatoid) have been described. The most common histologic subtype noted in primary pulmonary MFH is storiform-pleomorphic. Tumors are usually stained with desmin, actin, vimentin, keratin, and neurogenic tumors are often obtained with these stains [2]. In our case, a definitive pathology showed storiform patterns, bizarre cells, and vimetin- and CD68-positive cells. The cytological findings strongly suggested MFH.

Metastatic MFH lesions are more frequently reported in the lungs than primary pulmonary MFH lesions. Patients with MFH detected in the lungs should undergo an exhaustive diagnostic examination (including PET-CT and histopathological verification) to specify that the tumor is primary pulmonary MFH or a metastasis of extrapulmonary primary origin [7].

Because cases diagnosed with primary pulmonary MFH are quite rare, it is difficult to define a management protocol for these patients. In addition, patients with MFH usually have poor survival rates; it has been reported that the five-year survival rate for patients without lymph node metastasis is better than those with lymph node metastasis [8].

According to a review that analyzed previous case reports, surgical resections are preferred if the tumor seems resectable. These malignancies show a tendency for both local recurrence and distant metastasis, but despite their aggressive nature, there are several reports of patients with long-term survival. Better survival rates are mostly related to complete surgical resections with clear margins. In the same vein, survival rates are poor for patients with advanced-stage disease, incomplete resection, or tumor invasion to the mediastinum or chest wall, and the chances of recurrence and metastasis are higher [7]. Our patient had a three-year survival without recurrence.

In addition, adjuvant therapy can be performed; hence, radiotherapy is not preferred [9]. Although doxorubicin, dacarbazine, cyclophosphamide, and cisplatin might be used during chemotherapy, there are, in fact, no large-scale studies that report a favorable response to chemotherapy [7]. Close follow-up is advised due to the relatively high recurrence rates of MFH.

In conclusion, we presented a case of primary pulmonary MFH that is a very rare lung tumor. We also showed that although MFH is an aggressive tumor, long-term survival can be possible with surgical resection in early-stage tumors.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – T.C.; Design – T.C., Ç.T.; Supervision – Ç.T., Y.T.; Resources – Ç.T., M.A.; Materials – Ç.T.; Data Collection and/or Processing – İ.K.; Analysis and/or Interpretation – A.Ş., Y.T., İ.K., M.A.; Literature Search - T.C., Y.T., Ç.T.; Writing Manuscript – T.C.; Critical Review – Ç.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Jeon YH, Park KS. Successful management of a recurrent primary malignant fibrous histiocytoma of the lung: Report of a case. Korean J Thorac Cardiovasc Surg 2012;45:345-7. [CrossRef]
2. Weiss SW, Enzinger FM. Malignant fibrous histiocytoma: an analysis of 200 cases. Cancer 1978;41:2250-66.
3. Noh HW, Park KJ, Sun JS, et al. Primary pulmonary malignant fibrous histiocytoma mimics pulmonary artery aneurysm with partial thrombosis:various radiologic evaluations. Eur Radiol 2008;18:1653-7. [CrossRef]
4. Halyard MY, Camorino JK, Culligan JA, et al. Malignant fibrous histiocytoma of the lung. Report of four cases and review of the literature. Cancer 1996;78:2492-7.
5. Reifsnyder AC, Smith HJ, Mullholan TJ, Lee El. Malignant fibrous histiocytoma of the lung in a patient with a history of asbestos exposure. AJR Am J Roentgenol 1990;154:65-6. [CrossRef]
6. Kim JH, Cho SH, Kim EK, et al. Endobronchial malignant fibrous histiocytoma: Case report of an unusual presentation and palliative flexible bronchoscopic resection. Respir Care 2013;58:92-4. [CrossRef]
7. Patel DP, Gandhi YS, Sommers KE, et al. Primary pulmonary malignant fibrous histiocytoma. Case Rep Pulmonol 2015;2015:381276. [CrossRef]
8. Maeda J, Ohta M, Inoue M, et al. Surgical intervention for malignant fibrous histiocytoma of the lung: report of a case. Surg Today 2007;37:316-9. [CrossRef]
9. Regnard JF, Icard P, Guibert L, et al. Prognostic factors and results after surgical treatment of primary sarcomas of the lung. Ann Thorac Surg 1999;68:227-31. [CrossRef]

Turk Thorac J 2017; 18: 57-64 DOI: 10.5152/TurkThoracJ.2017.060417

CONSENSUS REPORT

The View of the Turkish Thoracic Society on the Report of the GOLD 2017 Global Strategy for the Diagnosis, Management, and Prevention of COPD

Nurdan Köktürk[1], Alev Gürgün[2], Elif Şen[3], Ali Kocabaş[4], Mehmet Polatlı[5], Sibel Atış Naycı[6], Lütfi Çöplü[7], Emel Tellioğlu[8], Funda Elmas[2], Ertürk Erdinç[2]

[1]Department of Pulmonary Medicine, Gazi University School of Medicine, Ankara, Turkey
[2]Department of Pulmonary Medicine, Ege University School of Medicine, İzmir, Turkey
[3]Department of Pulmonary Medicine, Ankara University School of Medicine, Ankara, Turkey
[4]Department of Pulmonary Medicine, Çukurova University School of Medicine, Adana, Turkey
[5]Department of Pulmonary Medicine, Adnan Menderes University School of Medicine, Aydın, Turkey
[6]Department of Pulmonary Medicine, Mersin University School of Medicine, Mersin, Turkey
[7]Department of Pulmonary Medicine, Hacettepe University School of Medicine, Ankara, Turkey
[8]Department of Pulmonary Medicine, Health Sciences University, İzmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, İzmir, Turkey

Abstract

Since the Global Initiative for Obstructive Lung Disease (GOLD) published its first guidelines on chronic obstructive pulmonary disease (COPD) in 2001, much has changed till 2017. Previous versions of GOLD guidelines mentioned the forced expiratory volume in one second (FEV_1)-based approach for staging and treatment modalities. Since 2011, a composite multi-dimensional approach has been introduced to cover various aspects of the disease. Unfortunately, this approach was not found to be correlated with mortality as well as the FEV_1-based approach, despite the fact that it was better for estimating exacerbation rates. Although this assessment tool has been considered as a big step in personalized medicine, the system was rather complex to use in daily practice. In 2017, GOLD introduced a major revision in many aspects of the disease. This mainly includes a revised assessment tool and treatment algorithm. This new ABCD algorithm has excluded spirometry for guiding pharmacological therapy. Treatment recommendations are mainly based on symptoms and exacerbation rates. Escalation and de-escalation strategies have been proposed for the first time. The spirometric measurement has only been retained to confirm the diagnosis and lead to nonpharmacological therapies. In this report, the Turkish Thoracic Society COPD assembly aimed to summarize and give an insight to the Turkish interpretation of GOLD 2017.

KEYWORDS: Chronic obstructive pulmonary disease, diagnosis, management, prevention, Global Initiative for Obstructive Lung Disease guidelines

Received: *15.03.2017* ***Accepted:*** *25.03.2017*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the leading cause of morbidity and mortality worldwide. It causes a considerable burden on the quality of life, public health, and the health economy [1].

Global Initiative for Obstructive Lung Disease (GOLD) has been established to increase awareness of COPD and form guidelines for its prevention, diagnosis, and treatment. Between 2001 and 2011, the committee released guidelines mainly based on spirometric grading. Since 2011, a multi-dimensional assessment tool was proposed as a step forward in personalized medicine. However, treatment recommendations were not based on high-quality evidence; therefore, since then, the guidelines were named as "strategy documents." The current GOLD document was released on November 16, 2016. It has a major revision in evaluation and treatment recommendations. However, in general, the document has been heavily criticized.

The Turkish Thoracic Society (TTS) COPD assembly published a consensus report on the prevention, diagnosis, and treatment of COPD in 2014. After the publication of the new 2017 GOLD document, the TTS COPD assembly decided to publish a Turkish consensus report with the interpretation, criticism, and adaptation of the GOLD 2017 COPD report in regards with the Turkish Health System in March 2017. This current report comprised an executive summary of the Turkish view of the GOLD 2017 COPD report.

Address for Correspondence: Nurdan Köktürk,
E-mail: kokturk.nurdan@gmail.com

Definition of COPD

COPD had been defined in 2016 GOLD document as "a common preventable and treatable disease which is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients" [2].

In GOLD 2017, the definition has been revised to "a common preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases" [1].

In GOLD 2017, there has been an emphasis on the importance of recognizing chronic respiratory symptoms that can precede the development of airflow obstruction and may be associated with the development of acute respiratory events. A considerable number of smokers can have structural abnormalities of emphysema and airway wall thickening without airflow limitations [1].

A major revision in the definition of COPD is the replacement of the term "inflammation" and putting additional emphasis on "respiratory symptoms." The committee did not provide an explanation for this change. Although COPD is still considered a chronic inflammatory disorder, an effective anti-inflammatory strategy has not yet been discovered. It appears that systemic inflammation only exists in a small percentage of COPD patients and that there is no information about the existence of inflammation in patients having insufficient lung development. This would be a rational explanation behind the removal of word "inflammation" from the definition. However, in general medicine, there is a tendency to define diseases with underlying mechanisms. Therefore, "both inflammation and severe airway abnormalities with emphysema" can be mentioned in the definition.

In the new definition, respiratory symptoms were included for the first time in the GOLD guidelines. In this definition, symptoms with airflow limitation are considered mandatory. However, in the chapters on "diagnosis and assessment," the same document mentions airflow limitation with or without symptoms for making a diagnosis. There are people with risk factors and airflow limitation but no symptoms and there are people with symptoms but no airflow limitation. Although the definition requires both symptoms and airflow limitation, making a diagnosis requires airflow limitation on the background of either symptoms or risk factors. This discrepancy should be justified by the GOLD committee. The reason of why symptoms were included in the definition would be a justification for symptom-based treatment strategy, which will be discussed later.

A symptom-based definition and assessment can result in several limitations. Symptoms can be perceived and expressed differently in different populations depending on sex, ethnicity, and the social, cultural, and economic status. Patients can underestimate their symptoms and exacerbations. In contrast, in some groups such as women, patients having a low socioeconomic status, minority groups, and immigrants, the symptoms may be overexpressed. Approximately 25% of COPD patients are asymptomatic, and around 50% of smokers have symptoms without having airflow limitations. Hence, symptoms may be related to comorbid conditions [3-6]. For example, in a patient with a forced expiratory volume in one second (FEV_1) of <30%, severe dyspnea is expected. However, patients may slow-down their walking pace and therefore they may deny that they have dyspnea. In contrast, in a patient with a preserved FEV_1, disproportionate symptoms may occur due to comorbid conditions.

Burden of COPD

Based on epidemiological studies, the estimated number of COPD patients was 384 million in 2010, with a global prevalence of 11.7%. Globally, there are 3 million deaths due to COPD annually, and by 2030, this number is expected to increase to 4.5 million. COPD-related mortality is mainly driven by smoking, reduced mortality from other common causes of death, aging of the world's population, and the scarcity of effective disease-modifying therapies [1].

The Global Burden of Disease study revealed that COPD is the fifth leading cause of disability-adjusted life years lost in 2013 [7].

Factors Influencing Disease Development and Progression

Cigarette smoking is the most well-studied risk factor; however, nonsmokers can also develop COPD. Epidemiological studies have shown that never-smokers had milder disease, fewer symptoms and lower systemic inflammation. They did not have increased risk of lung cancer or cardiovascular disease [8]. There are no data that monitor the entire course of the disease including the pre- and perinatal periods. The perinatal period may be very important in developing COPD.

Cigarette smoking is the leading risk factor for COPD. However, fewer than 50% of smokers develop COPD [9]. The socioeconomic status may be linked to a child's birth weight. Although controversial, some studies have suggested that women are susceptible to tobacco smoke [10-12].

Any factor that affects lung growth during gestation and childhood, which is termed "childhood disadvantage factors," has the potential for increasing the risk of COPD. A recent study showed that 50% of patients developed COPD due to abnormal lung growth with a normal decline in the FEV_1 [13].

Occupational exposure to organic and inorganic dusts and fumes are underestimated risk factors for COPD. The proportion of COPD cases attributable to workplace exposure is 19.2%. The risk from occupational exposure in less regulated areas is likely to be much higher than reported [1].

Worldwide, 3 billion people use biomass and coal as their main source of energy. Indoor air pollution is a very important risk factor for COPD. The role of outdoor air pollution as a risk factor for COPD is unclear; however, this has an impact on impaired lung growth [14,15].

A lower socioeconomic status is associated with an increased risk of developing COPD. Asthma, bronchial hyper-reactivity, chronic bronchitis, HIV, and tuberculosis increase the risk of developing COPD [1].

GOLD 2017 has gathered epidemiological findings from mostly developed countries. However, over 90% of COPD patients live in low- and middle-income countries [16]. The Burden of Obstructive Lung Disease study revealed that airway obstruction was correlated with smoking rate but not mortality. However, restrictive spirometric impairment, as a consequence of poverty and poor lung development, was well correlated with mortality. This restrictive impairment was more common in low–middle-income countries. One of the best predictors of mortality in COPD is the gross national income (GNI) per capita [17]. The mortality rate increases particularly in countries that have a GNI per capita of below US$ 20000 [18]. People in the low socioeconomic status have 14-times more respiratory system disorders [17]. The social determinants of health (income, housing, lifestyle and working conditions, and access to qualified education and health services) are the best predictors of the risk of COPD [19]. It appears that the GOLD 2017 report did not evaluate the social determinants of health and thoroughly assessed the underlying mechanisms of childhood disadvantage factors, indoor and outdoor air pollution.

Pathogenesis and Pathophysiology

The inhalation of cigarette smoke and other noxious particles such as biomass smoke cause lung inflammation. In response to chronic inflammation, repeated injury and repair cause pathological changes in the airways, lung parenchyma, and pulmonary vasculature. Although some patients develop COPD without smoking, the nature of the inflammatory response is still unknown. Lung inflammation persists after smoking cessation. The GOLD 2017 report has mentioned that peribronchiolar and interstitial fibrosis may occur in COPD patients, which may contribute to small airway limitation [1].

Diagnosis and Assessment

Diagnosis

GOLD 2017 reports that COPD should be considered in any patient who has dyspnea, chronic cough, or sputum production and/or a history of exposure to risk factors. Spirometry is required for making a diagnosis. Comorbidities should be actively sought and appropriately treated.

In the previous version of GOLD, symptoms with risk factors were considered as main factors for suspecting the diagnosis of COPD. However in GOLD 2017 report, symptoms or risk factors are sufficient to make a diagnosis. This approach has advantages and disadvantages. As discussed in the "Definition" chapter, the expression of symptoms can depend on several factors. In addition, symptoms can occur due to other comorbid conditions or asthma. Therefore, in the absence of predisposing risk factors, clinicians should be careful in the interpretation of symptoms. In contrast, some patients who have risk factors but no symptoms may be found out with the spirometry screening. These patients should be followed up carefully to check whether they will develop symptoms and require treatment along with the natural course of the disease. They should be encouraged to stop smoking and avoid other risk factors and be physically active. Public spirometric screening cannot be recommended until a precise advantage of screening is shown [1,20]. Additionally, it is well known that some patients can have symptoms without airflow limitation; they were referred to as GOLD 0 in the past. Later on, GOLD 0 was removed from GOLD staging based on evidence that such patients did not necessarily develop airflow limitation. However, chronic bronchitis symptoms may precede the development of airflow obstruction [21].

Spirometry is the most reproducible and objective measurement of airflow limitation. Good-quality spirometry is possible in health care settings, and all healthcare workers who care for COPD patients should have access to spirometry. A post-bronchodilator $FEV_1/FVC<70\%$ is required for making a diagnosis of COPD. It is simple and independent of reference values and has been used in numerous clinical trials. This criterion may lead an over- and underestimation of airflow obstruction depending on age compared with the lower limit of normal (LLN) values [22,23]. In concordance with GOLD, the TTS has encouraged clinicians to perform spirometry. All doctors should be able to assess the spirometry results for diagnosing COPD. Spirometry should be performed according to standardized criteria [24,25]. Recently, normal spirometry has been defined using a new approach from the Global Lung Initiative (GLI) using GLI equations. The GLI requires a single parameter called z-score. A z-score below -1.64 denotes an LLN at the fifth percentile of normal distribution [26,27]. GLI criteria need more supportive data before any recommendation can be made.

Assessment

Since 2011, GOLD has recommended a multi-dimensional approach for evaluating patients. It comprises three components: spirometry, symptom level, and number and severity of exacerbations. The high risked patients were decided on by either FEV_1 or the number of exacerbations. This approach was considered rather complex by busy clinicians.

In the new assessment tool, FEV_1 is not a part of the staging evaluation, although this is not underestimated for the diagnosis and evaluation for the nonpharmacological approach. Although St George's Respiratory Questionnaire score 25 is well correlated with COPD Assessment Test 10 and modified Medical Research Council (mMRC) 1, the recommended cut-off point of the mMRC is still 2. In the definition of exacerbation, exacerbation that requires emergency department admission is considered as a severe exacerbation. Pharmacological therapy is tailored by ABCD assessment tool (Figure 1).

The new assessment system to lead pharmacological therapy is quite simple and comprises two modifiable components of the disease: symptoms and the number of exacerbations in the previous year. FEV_1 is not a component of this assessment. [1]. However, spirometry is already underused in practice. In addition, making a differential diagnosis still requires spirometry, and it is still beneficial during follow-up. Therefore, we recommend spirometry in each follow-up visit to monitor disease activity and for making a differential diagnosis when needed. The definition of exacerbation that requires health care utilities is not an optimal approach for the evaluation of exacerbation severity. In Turkey, sometimes, emergency room (ER) admissions and even hospitalizations can occur with a wide range of indications. Sometimes, patients may be admitted to the ER to be treated with only short-acting agents.

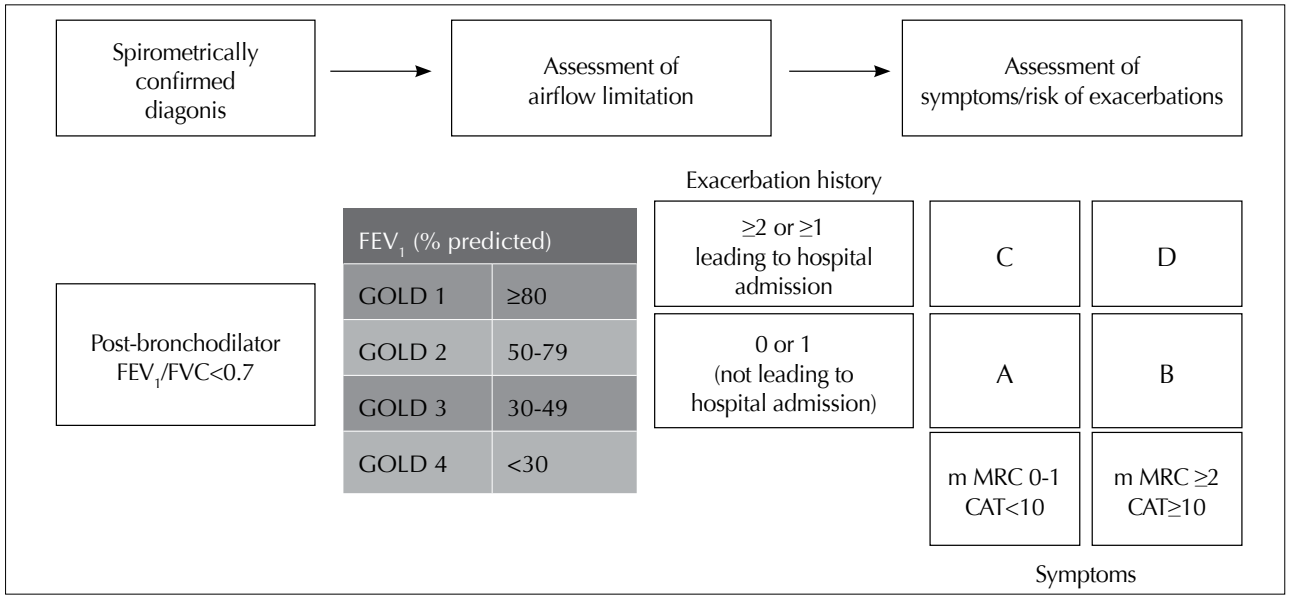

Figure 1. The new ABCD assessment tool for staging COPD [1]

Therefore, symptom severity and physical findings should be taken into consideration for the evaluation of exacerbation severity, and ER admission itself can be considered in the moderate exacerbation.

Evidence supporting prevention and maintenance therapy

Smoking cessation has the greatest capacity to influence the natural history of COPD [1]. Every clinician should assess the smoking status and refer smokers to smoking cessation clinics. E-cigarettes are being increasingly used as a form of nicotine replacement therapy. Their efficacy is controversial, and the overall safety profile has not been defined. Vaccination is recommended for both influenza and pneumococcal disease [1]. Influenza vaccinations are recommended to all COPD patients, and pneumococcal vaccinations are recommended to patients over 65 years [1]. An adult vaccination schedule has just been published in Turkey. Accordingly, there is no age restriction regarding to pneumococcal vaccination in COPD patients in Turkey [28].

After disease establishment, prevention strategies would not be a certain solution. Besides smoking, dusts and noxious particles from workplace exposure, biomass smoke fumes, and outdoor pollution should be avoided in population settings. Public policies, local and national resources, cultural changes, effective ventilation, and nonpolluting cooking stoves are feasible measures worldwide [1]. Healthy intrauterine growth, easy access to health care facilities, and healthy housing and workplace are the most powerful prevention tools for COPD [29-32]. GOLD 2017 did not emphasize on the social determinants of health for primary prevention. The GOLD 2017 report may have prioritized pharmacological treatment strategies rather than disease prevention, which is actually considered to be the main treatment strategy.

Pharmacological therapy for stable COPD

Pharmacological therapy is used to reduce symptoms, improve the health status, and reduce the frequency and severity of exacerbations. There is no conclusive evidence to show that pharmacological therapy modifies the long-term decline in lung function. The report mentions that each treatment regimen needs to be individualized for symptoms, airflow limitation, and severity of exacerbations [1].

In the new document, pharmacological therapies have been placed according to the new ABCD assessment tool. For the first time in history of GOLD, the committee recommended preferential therapy and escalation and de-escalation management (Figure 2) [1]. In each visit, patients should be questioned about risk factors, healthy life style, physical activity, and vaccination. Inhaler techniques should be checked particularly using the teach-back method. Adverse drug events, comorbidities, and the exacerbation of history should be checked (1). The committee has declared that escalation therapy has not been systematically tested and that trials of de-escalation are limited [1]. Evidence for therapeutic recommendations for patients in groups C and D are not strong enough for frequent exacerbations; therefore, recommendations will be re-evaluated as additional data become available [1].

Group A: GOLD 2017 recommends either short- or long-acting bronchodilators according to the persistence of symptoms. A change in different groups is possible. Treatment should be continued if the benefit is persistence [1].

Group B: GOLD 2017 recommends either long-acting beta-2 agonists (LABA) or long-acting antimuscarinics (LAMA) for initial therapy. For patients with persistent symptoms, a combination (dual bronchodilation) is recommended. For severely symptomatic patients, an initial combination is recommended [1].

Group C: Initial therapy should consist of LAMA. Patients with further exacerbations a LABA could be added to LAMA (GOLD recommendation) or therapy could be switched to inhaled corticosteroids (ICS)+LABA. ICS+LABA is not the first choice due to the risk of excessive pneumonia [1].

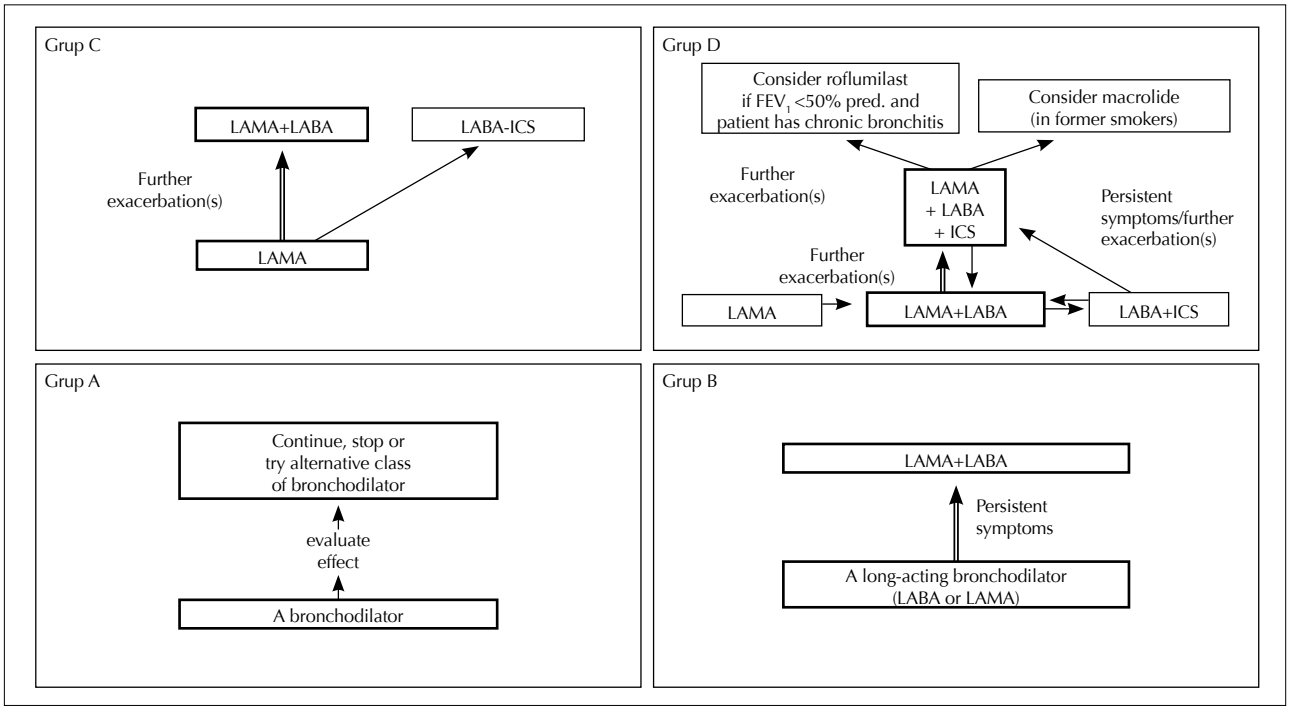

Figure 2. In patients with a major discrepancy between the perceived level of symptoms and severity of airflow limitation, further evaluation is warrented [1]
Preferred treatment: ⟹

Group D: Initial therapy should consist of LABA+LAMA. If patients continue to have exacerbations, escalation to LAMA+LABA+ICS can be offered (studies are underway). Switching to ICS+LABA can be done, although there is no evidence that switching results in better exacerbation prevention. A combination of LABA+ICS is recommended for asthma–COPD overlap patients as the first choice. If a monobronchodilator is chosen by clinicians, LAMA should be preferred. Patients with persistent symptoms with triple therapy (LAMA+LABA+ICS), roflumilast or macrolide could be added. Step-down is possible from LABA+LAMA+ICS to LABA+LAMA if there is no exacerbation [1].

The GOLD 2017 treatment recommendation has several limitations, particularly in groups C and D. There is no study that is fully designed prospectively on the definition of groups C or D. Most studies on exacerbation had recruited patients with one or more exacerbations. Only 19% of the population had two or more exacerbations in the FLAME study. In patients with severe exacerbations, both treatment arms (LABA+LAMA vs ICS+LABA) provided comparable results. Most exacerbations during the follow-up were mild in the FLAME study [33]. Considering these findings, the evidence on patients with two or more exacerbations were not strong enough to refer certain treatment strategy. On the other hand ICS are overused in Turkey [34]. Therefore, the TTS recommends starting pharmacological therapy with one bronchodilator (LABA or LAMA), and during follow-up, if the symptoms are persistent, the other group bronchodilator can be added. If the patient still has exacerbations (two moderate or one severe exacerbation), ICS can be added. This approach requires the close follow-up of patients. Withdrawal from ICS may be recommended when the patient is an infrequent exacerbator [1].

In the GOLD 2017 document, the blood eosinophil count has been discussed as a predictor of response to using ICS [1]. However, a prospective analysis is needed to raise clear conclusions and has not yet been considered for tailoring treatment.

Nonpharmacological therapy in COPD

A detailed chapter regarding nonpharmacological therapy such as rehabilitation, self-management, and behavioral changes in the management of COPD was mentioned in the GOLD 2017 report.

Pulmonary Rehabilitation

GOLD 2017 declares that pulmonary rehabilitation (PR) is the most effective therapeutic strategy for reducing symptoms and improving the health status and exercise intolerance [1]. It is appropriate for all COPD patients who are symptomatic. It can reduce readmission and mortality rates if it commenced early after hospital discharge. It is also one of the most cost-effective strategies [1]. Accessing and/or completing PR programs in Turkey are limited. The major barrier is the lack of awareness of its benefit. Limitations to access program, lack of finance, and transportation are the other barriers [1]. In Turkey, there are 35 rehabilitation centers. Home-based programs and having family practitioners incorporated into the program would be a solution for transportation problems and problems related to treatment adherence.

Physical Activity

Physical inactivity is related to poor outcomes in COPD. It should be encouraged. However, information is lacking on required details for its optimization in standard care [1].

Education, Self-Management, and Integrative Care

Didactic sessions are insufficient for promoting self-management skills. Education is considered to be the first step for changing the behavior. Topics such as smoking cessation, correct use of inhalers, early recognition of exacerbation, decision-making and taking actions, and when to seek help and surgical interventions will be better dealt with using self-management interventions [1].

Self-management interventions improve the health status, but not overall mortality, in COPD patients. However, the issue possesses many unstandardized aspects. Heterogeneity among interventions, patient populations, follow-up times, and outcome measures make generalization difficult in real life [1]. In a limited experience of a Turkish institute without a case manager, self-management is considered to be ineffective in preventing exacerbation but is considered to improve treatment adherence (s study is in progress).

For the first time, GOLD 2017 has introduced a structured nonpharmacological approach in each category of ABCD staging. Dealing with risk factors, increasing physical activity and ensuring adequate sleep and a healthy diet are recommended for all COPD patients, and managing strategies for breathlessness and stress management are recommended for group B and D patients [1].

Although there has been a major interest to implement behavior-targeted interventions to improve physical activity, there is still no information on optimal quality assurance methods [1]. There is a continuous fear among patients to be physically active. However, every patient should be encouraged to be physically active. Patients should be encouraged to undergo a comprehensive rehabilitation program, and a maintenance home-based exercise program should be recommended after the completion of the rehabilitation program. Endurance, strength training, upper extremity exercise, and inspiratory muscle training (when needed) are the components of exercise training [1]. Motivational interventions that aiming to meet patient expectations, for gaining self-management skills, and end-of-life issues are the components of behavioral interventions [1]. Patient education alone does not change the behavior or motivate patients and has no impact on improving exercise performance or lung function; however, it can play a role for improving skills and being able to cope with illness and the health status [1].

Supportive, Palliative, End-of-Life Care

Palliative care is a term used for controlling symptoms as well as managing terminal patients close to death [1]. Nutritional support, palliative treatment for dyspnea, treatment for anxiety and depression, and end-of-life care and hospice services are needed in certain conditions. Turkey has a lack of structured supportive and end-of-life care services, hospice services, and related regularities. In Turkey, doctors managing COPD are neglected to give information to patients about their future risks. In particular, information on prognosis is not often discussed. Therefore, a majority of patients in Turkey are not aware of and provided the end-of-life care in practically.

Although malnutrition is a common problem and a prognostic factor, nutritional supplementation and dietary consultation are often neglected in COPD patients in Turkey. Doctors should be encouraged to support patients in this regard.

Oxygen Therapy and Ventilatory Support

Long-term oxygen therapy has been shown to increase the survival rate in patients with severe resting hypoxemia but not in those with moderate resting or exercise-induced hypoxemia [1]. Moderate-to-severe hypoxemic patients at sea level may be supplemented with 3 l/min of supplementary oxygen to provide 50 mmHg PaO_2 during air travel [1]. Noninvasive positive pressure ventilation (NPPV) is the standard care during acute respiratory failure; however, its benefit when used in chronic patients remains undetermined [1]. Poor adherence to NPPV is a major issue to solve. In COPD and obstructive sleep apnea patients, NPPV has a clear benefit in terms of both survival rates and risk of hospital admission [1].

Interventional Therapy

Lung volume reduction surgery (LVRS) increases elastic recoil, improves expiratory flow rates, and reduces exacerbations. It improves survival in patients with low post-rehabilitation exercise capacity. It has been shown to result in a higher mortality rate in patients with a FEV_1 of ≤20% and DLCO of ≤20% [1]. Bullectomy is required if the bullae cause compression and complications and if there is relatively preserved lung tissue. Hypercapnia, severe emphysema, and pulmonary hypertension are not absolute contraindications [1]. In appropriately selected patients, lung transplantation has been shown to improve the health status and functional capacity but not prolong survival. The median survival rate has increased to 5.5 years [1].

Bronchoscopic interventions

Endobronchial valve replacement and nitinol coil implantation are the main bronchoscopic interventions in emphysema treatment. In selected cases, treatment improves the 6-min walk distance, lung function, and health status. Major complications of coil therapy include pneumonia, pneumothorax, hemoptysis, and COPD exacerbations [1]. Endobronchial one-way valves may be considered if interlobar collateral ventilation is absent in computed tomography scans [1].

Patients with heterogeneous upper lobe predominant emphysema can be candidates for either LVRS or bronchoscopic volume reduction. However, homogenous emphysema patients are not routinely considered candidates for undergoing LVRS, but bronchoscopic therapy may be considered [1].

Endobronchial therapy has become popular in Turkey. However, treatment is very expensive and is not lack of complications; therefore, appropriate patient selection and close follow-up are required to see the long-term results.

Management of COPD exacerbations

In previous guidelines, COPD exacerbation was defined as "the worsening of respiratory symptoms that is beyond the normal day to day variation and leads to change in medication." However, in the new version, it has been defined as "acute worsening of respiratory symptoms that needs addi-

tional therapies." Exacerbations were classified as mild [treated with short-acting bronchodilators (SABDs) only], moderate (SABDs+antibiotics and or oral corticosteroids), or severe (patients require hospitalization or visits to the ER). A considerable amount of exacerbations are not reported to health care professionals and could be significantly important [1].

The GOLD 2017 definition of COPD exacerbation can lead to different limitations. Although the definition is adopted in clinical trials, in real life, it could lead to standardization problems according to the attending doctor or hospital policy. For example, in Turkey, ER admissions can take place for patients with less symptoms and could result in only SABD administration. ER admission can be considered moderate exacerbation in Turkey if it is not resulted in hospitalization.

GOLD 2017 also underlined the importance of the differential diagnosis of respiratory symptoms, respiratory virus-triggered exacerbations, and eosinophilia during exacerbations [1]. The strongest predictor of a patient's future exacerbation frequency is the number of exacerbations they had in the prior year. COPD patients showed a moderately stable phenotype, but a significant proportion has changed with the worsening of FEV_1 [1].

Corticosteroid administration is recommended to be via the oral route and with a dose of 40 mg daily for 5 days. The more expensive nebulized budesonide may be an alternative to oral corticosteroids in some patients [1]. Antibiotics are recommended according to Anthonisen criteria and patients on invasive or noninvasive ventilation. The optimal duration is 5–7 days. On the basis of the COPD Audit study, the GOLD 2017 report has underlined the importance of oxygen therapy, has described the detail of ventilator support, and has defined the criteria of hospital discharge and the care-bundle [1]. Early follow-up (within one month) following discharge should be performed when possible and is associated with less exacerbation-related readmissions [1].

Comorbidities of COPD

Comorbidities have a significant impact in over course of COPD. In general, comorbidities should be actively sought out and treated according their guidelines. The presence of comorbidities should not alter COPD treatment. Lung cancer and cardiovascular diseases are important prognostic comorbidities. Osteoporosis, anxiety and depression, and gastroesophageal reflux are commonly underdiagnosed and are associated with a poor health status and prognosis. Comorbidities may occur in any grade of COPD and influence mortality and hospitalization rates [1,35]. In an investigation in Turkey, Charlson's Comorbidity index has been found to be related with the long-term mortality of COPD patients [36]. Another study has shown that comorbidities are related to hospital readmission [37].

GOLD 2017 has taken a comprehensive section for comorbidities. The aging population is under the risk of multimorbidity mainly composed of obesity, cardiovascular disorders, metabolic syndrome, airway disease, and sleep disorders. When COPD is a part of it, it may be overlooked or underdiagnosed under the mask of restrictive conditions. Such patients are becoming a major burden in daily practice in Turkey, which might be the case in other countries.

REFERENCES

1. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org
2. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016. Available from: http://goldcopd.org
3. Menezes AMB, Perez-Padilla R, Jardim JR, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. Lancet 2005;366:1875-81. [CrossRef]
4. Woodruff PG, Barr RG, Bleecker E, et al. Clinical significance of symptoms in smokers with preserved pulmonary function. N Eng J Med 2016;374:1811-21. [CrossRef]
5. Agusti A, Calverley PM, Decramer M, et al. Prevention of exacerbations in chronic obstructive pulmonary dişese: Knowns and unknows. J COPD 2014;1:166-84. [CrossRef]
6. Kokturk N, Kilic H, Baha A, et al. Sex Difference in Chronic Obstructive Lung Disease. Does it Matter? A Concise Review. J COPD 2016;13:799-806. [CrossRef]
7. DALYs GBD, Collaborators H, Murray CJ, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990- 2013: quantifying the epidemiological transition. Lancet 2015; 386:2145-91. [CrossRef]
8. Thomsen M, Nordestgaard BG, Vestbo J, Lange P. Characteristics and outcomes of chronic obstructive pulmonary disease in never smokers in Denmark: a prospective population study. Lancet Respir Med 2013;1:543-50. [CrossRef]
9. Rennard SI, Vestbo J. COPD: the dangerous underestimate of 15%. Lancet 2006;367:1216-9. [CrossRef]
10. Foreman MG, Zhang L, Murphy J, et al. Early-onset chronic obstructive pulmonary disease is associated with female sex, maternal factors, and African American race in the COPDGene Study. Am J Respir Crit Care Med 2011;184:414-20. [CrossRef]
11. Lopez Varela MV, Montes de Oca M, Halbert RJ, et al. Sex-related differences in COPD in five Latin American cities: the PLATINO study. Eur Respir J 2010;36:1034-41. [CrossRef]
12. Silverman EK, Weiss ST, Drazen JM, et al. Gender-related differences in severe, early-onset chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;162:2152-8. [CrossRef]
13. Lange P, Celli B, Agusti A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. N Eng J Med 2015;373:111-22. [CrossRef]
14. Gauderman WJ, Avol E, Gilliland F, et al. The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med 2004;351:1057-67. [CrossRef]
15. Gauderman WJ, Urman R, Avol E, et al. Association of improved air quality with lung development in children. N Engl J Med 2015;372:905-13. [CrossRef]
16. Assad NA, Kapoor V, Sood A. Biomass smoke exposure and chronic lung disease. Curr Opin Pulm Med 2016;22:150-7. [CrossRef]
17. Schraufnaget DE, Slasi F, Kraft M, et al. An official American Thoracic Society and European Respiratory Society policy statement: disparities in respiratory health. Eur Respir J 2013;42:906-15. [CrossRef]
18. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1459-544. [CrossRef]
19. Kılıç B. Sağlıkta eşitsizlikler. In: Kocabaş A (Edit): Göğüs Hastalıklarında Son Gelişmeler. Akademisyen Tıp Kitapevi, Ankara 2014: 511-6.
20. U. S. Preventive Services Task Force, Siu AL, Bibbins-Domingo K, et al. Screening for Chronic Obstructive Pulmonary Disease:

US Preventive Services Task Force Recommendation Statement. JAMA 2016;315:1372-7. [CrossRef]
21. Allinson JP, Hardy R, Donaldson GC, et al. The Presence of Chronic Mucus Hypersecretion across Adult Life in Relation to Chronic Obstructive Pulmonary Disease Development. Am J Respir Crit Care Med 2016;193:662-72. [CrossRef]
22. van Dijk W, Tan W, Li P, et al. Clinical relevance of fixed ratio vs lower limit of normal of FEV1/FVC in COPD: patient-reported outcomes from the CanCOLD cohort. Ann Fam Med 2015;13:41-8. [CrossRef]
23. Guder G, Brenner S, Angermann CE, et al. "GOLD or lower limit of normal definition? A comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study". Respir Res 2012;13:13. [CrossRef]
24. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38. [CrossRef]
25. Türk Toraks Derneği Ulusal Spirometri ve Laboratuvar Standartları. Tüberküloz Toraks Dergisi. Baskıda. (Makale no: 2017007).
26. Vaz Fragoso CA, McAvay G, Van Ness PH, et al. Phenotype of normal spirometry in an aging population. Am J Respir Crit Care Med 2015;192:817-25. [CrossRef]
27. Vaz Fragoso CA, McAvay G, Van Ness PH, et al. Phenotype of Spirometric Impairment in an Aging Population. Am J Respir Crit Care Med 2016;193:727-35. [CrossRef]
28. Türkiye Enfeksiyon Hastalıkları ve Klinik Mikrobilyoloji Uzmanlık Derneği. Erişkin Bağışıklama rehberi, 2. Güncelleme 2016. http://ekmud.org.tr/wp-content/uploads/Eriskin-BagisiklamaRehberi-web.
29. Wouters M, Wouters B, Augustin I, Franssen F. Personalized medicine and chronic obstructive pulmonary disease. Cur Opin Pulm Med 2017;23:241-6. [CrossRef]
30. Ferko T, Schraufnagel D. The global burden of respiratory disease. AnnalsATS 2014;11:404-6.
31. McGinnis JM, Williams-Russo P, Knickman JR. The case for more active policy attention to health promotion. Health Affairs 2012;21:78-93. [CrossRef]
32. Gershon AS, Dolmage TE, Stephenson A, Jackson B. Chronic obstructive pulmonary disease and socioeconomic status: a systemic review. COPD 2012;9:216-26. [CrossRef]
33. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. N Engl J Med 2016;374:2222-34. [CrossRef]
34. Gunen H, Yilmaz M, Aktas O, et al. Categorization of COPD patients in Turkey via GOLD 2013 strategy document: ALPHABET study. Int J Chron Obstruct Pulmon Dis 2015;10:2485-94. [CrossRef]
35. Dursunoğlu N, Köktürk N, Baha A, et al. Turkish Thoracic Society-COPD Comorbidity Group. Comorbities and their impact on chronic obstructive pulmonary disease. Tuberk Toraks 2016;64:292-301.
36. Kokturk N, Teksut G, Bakir H, Ozkan S. What Affects Mortality In Patients With Chronic Obstructive Pulmonary Disease: Ado Indices And Charlson Comorbidity Score C47. Asthma and COPD. ATS Annual Congress, SanDiego, 2014, pp. A4617.
37. Ozyilmaz E, Kokturk N, Teksut G, Tatlicioglu T. Unsuspected-risk factors of frequent exacerbations requiring hospital admission in chronic obstructive pulmonary disease. Int J Clin Pract 2013;67:691-7.[CrossRef]