IMPORTANT ISSUES IN HEALTH SCIENCES

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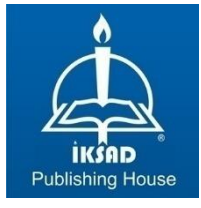

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AN ALTERNATIVE APPROACH TO COVID-19: GINGER

PREFACE

I am pleased to present the edition of book ‘‘Important Issues in Health Sciences’’ which deals with different important medical and clinical subjects including up to date COVID 19. The book is divided into 10 chapters including basic, medical and clinical subjects.

I would like to thank all authors for their efforts in the writing and submission of chapters of this book. I would also like to express my thanks and appreciation to those contributed remotely or closely in the preparation of this book. I wish them continued success. I hope that the book will be beneficial for the medical and educational work.

Editor

Prof. Dr. Mehmet BAYRAKTAR [1]

16th May 2021

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CHAPTER 1

ASSESMENT OF UPPER RESPIRATORY DISEASES AT A GLOBAL AND LOCAL LEVELS

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INTRODUCTION

Upper respiratory tract is an area located on the larynx and it is frequently exposed to infectious agents. All kinds of infections occurring in the nose, paranasal sinus, ear, pharynx, nasopharynx region as a result of this exposure are called upper respiratory infections (İnci, 2008; s:49-66).

Infections can be viral or bacterial, acute or chronic. Viruses are in the first place in upper respiratory tract infections. Upper Respiratory Infections can be classified as sinusitis, influenza, cold, otitis media, tonsillitis, pharyngitis, rhinitis.

Sinusitis is an inflammation of of the paranasal sinuses. The majority of patients with nasal and sinus symptoms are self-limiting viral infections or allergic conditions. Many cases are due to bacterial complications of viral Upper respiratory infections or allergic conditions (Parri, 1995, p:317-92).

The common cold is a self-limiting cold-related illness caused by a variety of respiratory viruses. Influenza (flu) causes epidemics and pandemics. It is a highly contagious viral infection. It is caused by a number of influenza viruses. As a result of influenza infection, a limited immunity is formed for several years until the virus undergoes a genetic change. Influenza infection has high fever, myalgia, headache, malaise, muscle and joint pain. There is no sore throat. The most effective way of prevention is to vaccinate those at risk for complications (Dikici, 2011, s:36-52).

Acute otitis media is a common complication of upper respiratory tract and was not included in upper respiratory infections in this study.

Evidence-based management and rational drug use stand out as an important issue because upper respiratory infections are mostly caused from viruses and there is no specific treatment for these infections, and the treatment is aimed at controlling the symptoms of the infection.

Viruses that cause respiratory infections are an important cause of morbidity and mortality in adult individuals, as well as they can have serious effects on public health because they can lead to epidemics and even pandemics (Liberman, 1998; Mandell et al., 2007; Wu et al., 2015).

Millions of people of all ages suffer from upper respiratory diseases[2] in all countries around the world. Upper respiratory diseases avarage account for above the ten thousands deaths annually.

In 1990, while the share of deaths caused by upper respiratory infections in total globally deaths was 0.0757%; its share in 2019 was dropped by 0.0167%.

Measured in DALYs, in 1990 the burden of upper respiratory diseases was account for 0.2506 % of the global burden and rised up even if a little with 0.2516 % in 2019.

[2] Upper Respiratory Diseases: Diseases caused from upper respiratory infections

Measured in YLDs, in 1990 the burden of upper respiratory diseases was account for 0.80 % of the global burden and decreased up even if a little with 0.68 % in 2019.

Measured in YLLs, in 1990 the burden of upper respiratory diseases was account for 0.11 % of the global burden and decreased even if a little with 0.029 % in 2019.

The burden of upper respiratory diseases has significant adverse effects on the disability and quality of life affected individuals.

The literature has shown that effective management plans reduce morbidity and mortality caused by upper respiratory diseases. So with this study, it was aimed to analysis the current situation of the upper respiratory diseases according to globally then the current status of influenza in Turkey was try to revealed.

This study was a descriptive-resrospective study and designed in two sections. First section upper respiratory diseases were analyzed according to income groups and level of globally. From this perspective 30-year data of upper respiratory diseases for the years 1990-2019 were analyzed retrospectively. In the first stage analysis, we evaluated the prevelance rate, incidence rate, deaths numbers, The Disability-Adjusted Life Year (DALY), Years Of Life Lost (YLL) and Years Lost Due To Disability (YLD) from upper respiratory diseases. The data (upper respiratory diseases) were taken from Global Burden Of Diseases Database.

The second stage it was evaluated that the current situation of the number of cases for influenza in Turkey over the years in total and age group. The data (influenza in Turkey) were created by examining the data published under the title of Epidemiology Surveillance Information in "FluId (www.who.int/fluid)"for 10-years between 2010-2019 were analyzed retrospectively. The total number of cases was detailed by years, weeks and age.

1.1. Basic Concepts of The Analysis

Prevelance is obtained by dividing the number of all (old and new) cases detected in a population in a given time period by the number of people at risk at the same time. It refers to the prevalence of a disease in the community at that time. Prevalence helps to measure the number of diseases in a population and determine healthcare needs.

Incidence is the number of new infections (cases) or the subsequent cases for each health outcome in the population, stratified by age and sex. Incidance is the rate obtained by dividing the number of new cases of a disease by the population at risk within a certain period of time (day, week, month, year). Incidence indicates the determination of etiological factors and in the probability of developing a specific diseases. Prevalence and incidence are important criteria determining the disease level.

The disability-adjusted life year (DALY) is a health gap metric, measuring the healthy life years lost due to diseases, injuries or risk factors (Murray, 1994). According to WHO (2013); DALYs are

calculated by adding the number of years of life lost due to premature mortality (YLL) and the number of years lost due to disability (YLD):

$$DALY = YLL + YLD$$

YLL is the product of the number of deaths (M) and the average remaining life expectancy (RLE) at the time of death:

$$YLL = M \text{ x } RLE$$

YLD, calculated from an incidence perspective, is defined as the product of the number of incident cases (N), the average duration until recovery or death (D), and the disability weight (DW), which reflects the reduction in health- on a scale from 0 (no impact on full health) to 1 (death):

$$YLDinc = N \text{ x } D \text{ x } DW$$

Diseases caused by an infectious agent may consist of one or more health outcomes, which can be acute or chronic, and with varied durations varying from a day or less to life-long. Thus, an incidence based approach is considered the most suitable approach for estimating the burden of infectious diseases. In this approach, all health outcomes and the resulting burden, including those in future years, are assigned to the initial event, i.e. the infection with the agent.

1.2. Evaluation Of The Burden Of Upper Respiratory Diseases

In this section, the prevalence rate, incidence rate, number of deaths and disease burden of upper respiratory diseases were examined under subheadings. The analysis was made in six stages. The first stage;

information was given about the basic concepts subject to analysis than the other each stage; the prevalence, incidence, number of death, DALYs, YLDs, YLLs values that belonged the upper respiratory enfections were examined.

1.2.1. Prevelance Rates

The world average of upper respiratory diseases prevalence was 3121.265 ± 60.81 (min: 3043.320; max: 3232.460). While the prevelance rate of upper respiratory diseases in LMIC, LOWIC, UMIC countries was below the world average; high-income countries and Turkey have a value above the average rate at thirty years (Table 1).

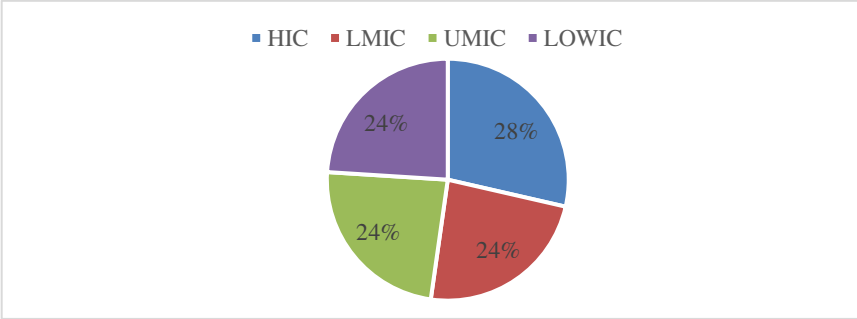
Table 1: The Descriptive Analysis of Prevelance Rate of Upper Respiratory Diseases

	HIC	LMIC	LOWIC	UMIC	TR	GLOBAL
Mean	3614.459	3020.158	3022.586	3037.353	4141.542	3128.056
Median	3626.345	3003.720	3014.260	3044.860	4210.345	3121.265
Maximum	3755.180	3102.160	3078.230	3128.810	4333.450	3232.460
Minimum	3469.310	2966.890	2965.680	2941.110	3907.880	3043.320
Std. Dev.	88.00649	46.80634	43.44704	57.33076	148.3525	60.81252
Skewness	-0.094312	0.650036	0.079895	-0.066977	-0.375880	0.350717
Kurtosis	1.999920	1.905386	1.336789	1.920029	1.547764	1.795849
Jarque-Bera	1.294674	3.610456	3.489754	1.480350	3.342665	2.427485
Probability	0.523438	0.164437	0.174666	0.477030	0.187996	0.297083

Source: The values in the table were calculated by the author using the data from http://ghdx.healthdata.org.

The Prevalence Rate of Upper Respiratory Diseases by Income Groups was showed a balanced distribution (24%-28%) over the World.

Chart 1: Distribution Of The Prevelance Rate Of Upper Respiratory Diseases By Income Groups, 1990-2019



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

Prevelance rate of upper respiratory diseases has been decreased about -5.2 % globally in 30 years. While this decrease was around 4.89 % in middle and high income countries; in the low income group countries this decrease was calculated as 1.69 % in 30 years.

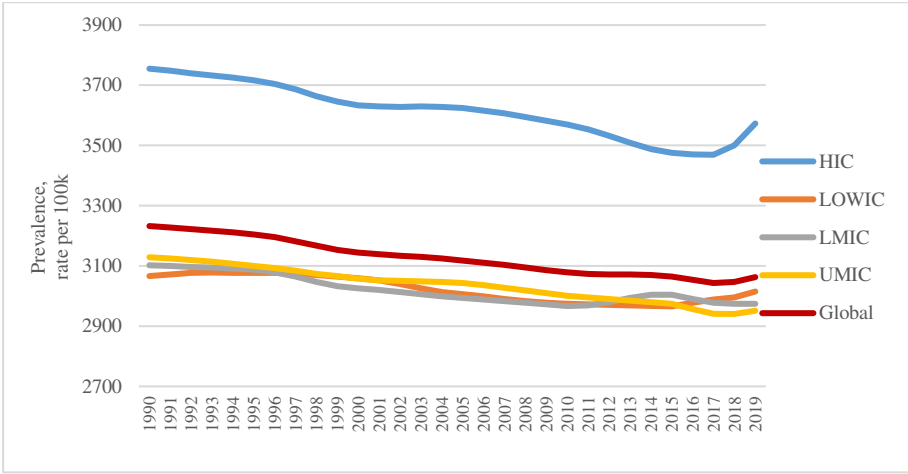
Table 2: Prevelance Rate Of Upper Respiratory Diseases According To Income Groups, % Change

	HIC	LMIC	LOWIC	UMIC	TR	GLOBAL
1990	3755,18	3066,54	3102,16	3128,81	4253,65	3232,46
2019	3572,75	3014,86	2973,86	2951,65	3907,88	3062,98
%	**-0,0486**	**-0,0169**	**-0,0414**	**-0,0566**	**-0,0813**	**-0,0524**

Source: The values in the table were calculated by the author using the data from http://ghdx.healthdata.org.

While the upper respiratory diseases prevalence rate in LOWIC, LMIC and UMIC countries was -3.23% under the the world average; in HIC countries, this rate was above the world average with 15.54% in along with 30 years.

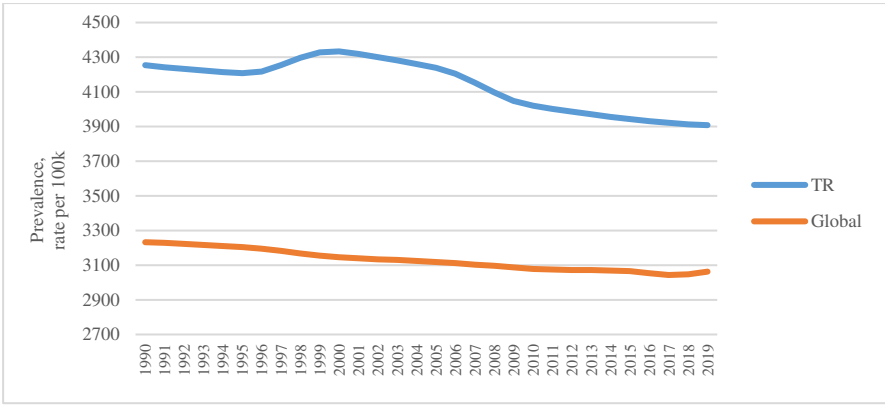
Chart 2: Prevelance Rate Of Upper Respiratory Diseases According To Income Groups



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

If in Turkey, the upper respiratory diseases prevalence rate was quite high from the world average rate with 32.37 %.

Chart 3: Prevelance Rate Of Upper Respiratory Diseases In Turkey



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

1.2.2. Incidence Rate

The world average of upper respiratory diseases incidence was 226947.5 ± 4390.685 (min: 221241.8; max: 234955.8) at thirty years. While the incidence rate of upper respiratory diseases in LMIC, LOWIC, UMIC countries was below the world average; high-income countries and Turkey have a high value above the average rate at thirty years (Table).

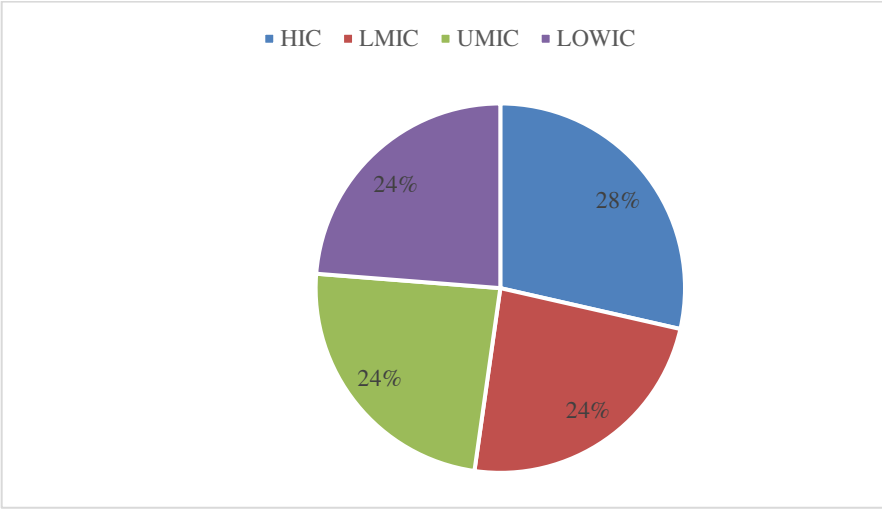
Table 3: The Descriptive Analysis of Incidence Rate of Upper Respiratory Diseases

	HIC	LMIC	UMIC	LOWIC	TR	GLOBAL
Mean	262474.8	219706.7	220792.9	219657.3	300803.5	227401.9
Median	263318.7	218399.4	221341.6	219072.5	305933.4	226947.5
Maximum	272749.1	225506.3	227526.7	223507.3	314536.6	234955.8
Minimum	251883.0	215991.9	213814.4	215695.3	283990.4	221241.8
Std. Dev.	6419.170	3313.736	4172.626	3009.706	10667.47	4390.685
Skewness	-0.093960	0.631282	-0.057229	0.081787	-0.379231	0.335118
Kurtosis	2.002552	1.879456	1.923393	1.332552	1.543148	1.796442
Jarque-Bera	1.287770	3.562109	1.465230	3.508925	3.372104	2.372211
Probability	0.525248	0.168460	0.480650	0.173000	0.185249	0.305408

Source: The values in the table were calculated by the author using the data from http://ghdx.healthdata.org.

The incidence rate of upper respiratory diseases by income groups was showed a balanced distribution (24%-28%) over the World.

Chart 4: Distribution Of The Incidence Rate Of Upper Respiratory Diseases By Income Groups, 1990-2019



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

Incidence rate of upper respiratory diseases has been decreased about -5.2 % globally in 30 years. While this decrease was around 4.88 % in middle and high income countries; in the low income group countries it was calculated as 1.62 % in 30 years.

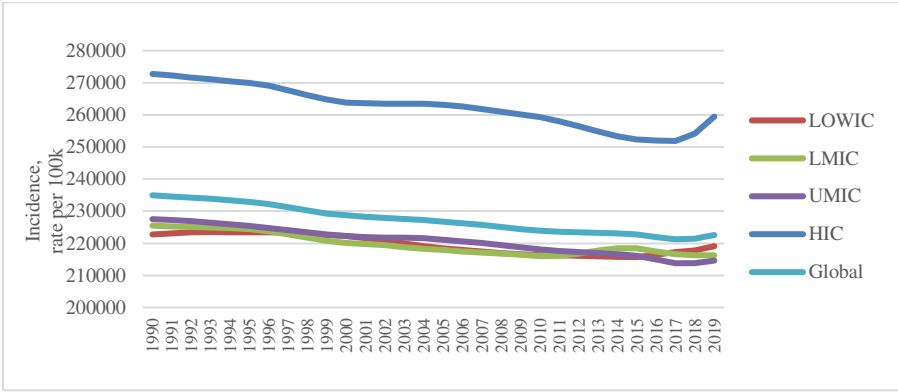
Table 4: Incidence Rate Of Upper Respiratory Diseases According To Income Groups, % Change

	HIC	LOWIC	LMIC	UMIC	TR	Global
1990	272749,11	222714,16	225506,25	227526,67	309058,78	234955,84
2019	259459,63	219106,89	216310,81	214567,88	283990,44	222668,36
%	**-0,0487**	**-0,0162**	**-0,0408**	**-0,0570**	**-0,0811**	**-0,0523**

Source: The values in the table were calculated by the author using the data from http://ghdx.healthdata.org.

While the upper respiratory diseases incidence rate in LOWIC, LMIC and UMIC countries was - 3.22% under the the world average; in HIC countries, this rate was quite high in the world average with 15.41% in along with 30 years.

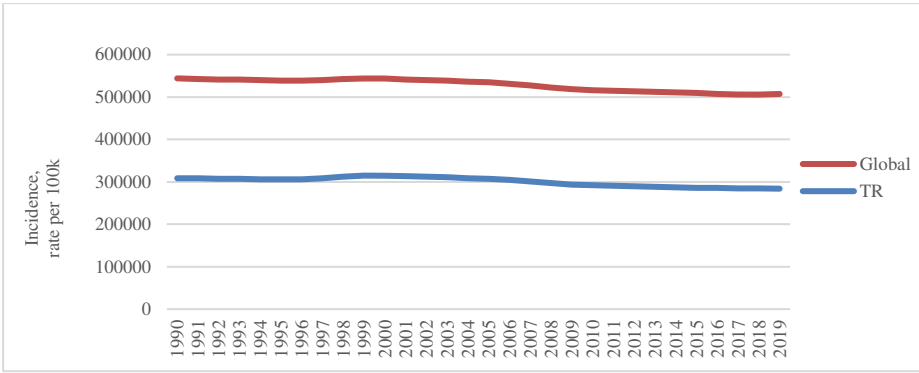
Chart 5: Incidence Rate Of Upper Respiratory Diseases According To Income Groups



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

If in Turkey, the upper respiratory diseases incidence rate was quite high from the world average rate with 32.25 % (as same the prevelance rate so) in along with 30 years.

Chart 6: Incidence Rate Of Upper Respiratory Diseases In Turkey



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

1.2.3. Death Numbers

The world average of upper respiratory diseases death was 17870.84 ± 8499.383 (min: 9464.120; max: 34403.53) at thirty years.

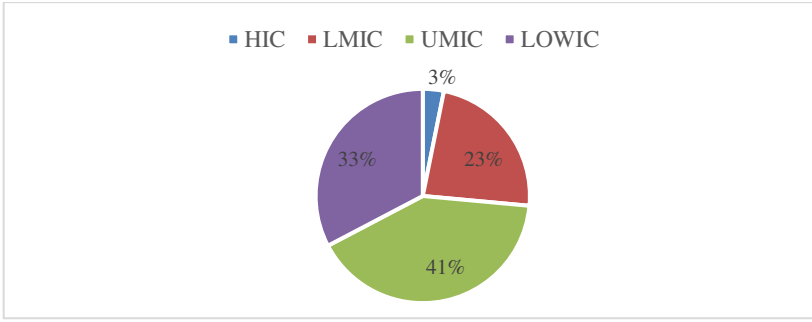
Table 5: The Descriptive Analysis of Upper Respiratory Diseases Deaths, 1990-2019

	HIC	LMIC	UMIC	LOWIC	TR	GLOBAL
Mean	680.0950	4364.100	8919.712	5737.713	17.50400	19708.36
Median	567.9000	4159.820	7298.645	5838.260	13.96000	17870.84
Maximum	1400.980	7188.440	17820.61	7984.440	41.94000	34403.53
Minimum	387.2100	2167.910	3450.630	3334.610	6.390000	9464.120
Std. Dev.	317.4191	1573.948	5309.406	1378.837	10.50043	8499.383
Skewness	0.886262	0.325380	0.422829	-0.120524	0.767954	0.371586
Kurtosis	2.527028	1.912648	1.588942	1.976600	2.442091	1.694256
Jarque-Bera	4.206926	2.007279	3.382774	1.381814	3.337846	2.821589
Probability	0.122033	0.366543	0.184264	0.501121	0.188450	0.243949

Source: The values in the table were calculated by the author using the data from http://ghdx.healthdata.org.

In the distribution of avarage deaths due to upper respiratory diseases by income groups between 1990-2019; the highest share was determined in UMIC (41%); the second highest share was seen in LOWIC (33%) and the lowest share was seen in HIC countries (3%).

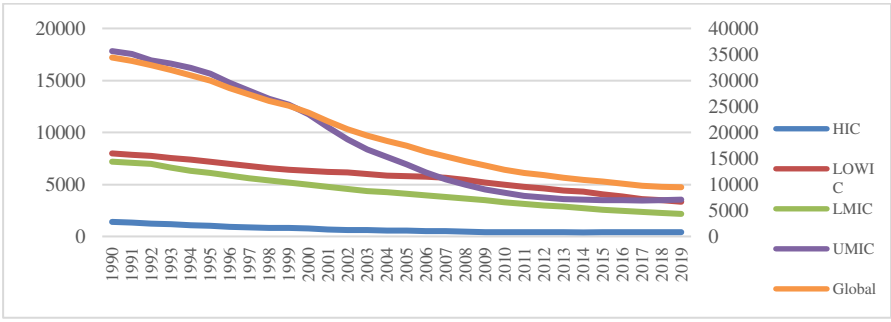
Chart 7: Distribution Of The Death Number Of Upper Respiratory Diseases By Income Groups, 1990-2019



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

Globally the number of death 9,464 had been realized from upper respiratory diseases in 2019. The distribution of upper respiratory diseases related deaths according to income groups was evaluated in that respectively; HIC (4%), LOWIC (35%), LMIC (23%), UMIC (38%) in 2019.

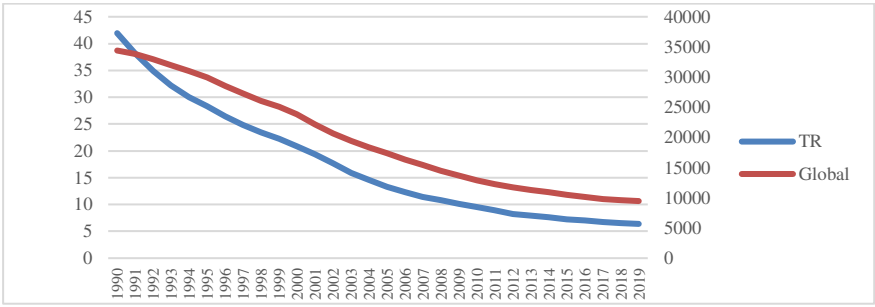
Chart 8: Number Of Death From Upper Respiratory Diseases According To Income Groups



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

The number of death 6.39 had been realized from upper respiratory diseases in Turkey at 2019. Upper respiratory diseases related deaths in Turkey, its share of in the global upper respiratory infections was 0.0675 %.

Chart 9: Number Of Death From Upper Respiratory Diseases In Turkey



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

In 2019 number of death from upper respiratory diseases has been decreased about - 72.49 % globally according to 1990. While this decrease was around -73.55 % in middle and high income countries; in the low income group countries it was calculated as -58.24 %. The number of death from upper respiratory diseases in Turkey has been decreased – 84.76 % in 30 years.

Table 6: Number Of Death From Upper Respiratory Diseases According To Income Groups, % Change

	HIC	LOWIC	LMIC	UMIC	TR	Global
1990	1400,98	7984,44	7188,44	17820,61	41,94	34403,53
2019	410,51	3334,61	2167,91	3547,08	6,39	9464,12
%	**-0,7070**	**-0,5824**	**-0,6984**	**-0,8010**	**-0,8476**	**-0,7249**

Source: The values in the table were calculated by the author using the data from http://ghdx.healthdata.org.

1.2.4.The Disability-Adjusted Life Year

The world average of upper respiratory diseases DALY was 6222415 ± 129881.8 (min: 6111984; max: 6501578) at thirty years.

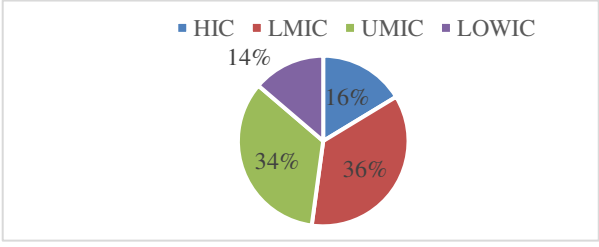
Table 7: The Descriptive Analysis of Upper Respiratory Diseases DALY

	HIC	LMIC	UMIC	LOW_IC	TR	GLOBAL
Mean	1001263.	2227888.	2180571.	838347.7	74999.81	6251664
Median	998283.0	2190811.	2084566.	840767.4	76323.16	6222415
Maximum	1066744.	2491659.	2561200.	911880.8	79272.24	6501578
Minimum	973184.7	2050263.	2002748.	779721.8	66826.91	6111984
Std. Dev.	25093.63	138506.3	196722.7	38857.73	3697.951	129881.8
Skewness	0.587147	0.524833	0.764382	0.289050	-0.971200	0.687578
Kurtosis	2.528668	1.882777	2.036679	2.201725	2.629958	2.162300
Jarque-Bera	2.001400	2.937485	4.081380	1.214303	4.887307	3.240994
Probability	0.367622	0.230215	0.129939	0.544901	0.086843	0.197800

Source: The values in the table were calculated by the author using the data from http://ghdx.healthdata.org.

In the distribution of avarage DALY due to upper respiratory diseases by income groups between 1990-2019; the highest share was determined in LMIC (36%); the second highest share was seen in UMIC (34%) and the lowest share was seen in HIC and LOWIC respectively (16%, 14%).

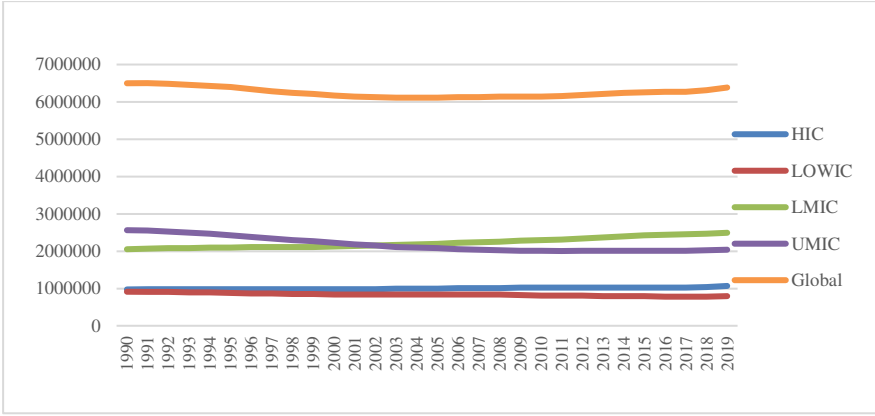
Chart 10: Distribution Of The Disability-Adjusted Life Year Of Upper Respiratory Diseases By Income Groups, 1990-2019



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

Globally DALY of upper respiratory diseases was 6385504.06 had been realized from upper respiratory diseases in 2019. The distribution of upper respiratory diseases related DALYs according to income groups was evaluated respectively; HIC (17 %), LOWIC (12 %), LMIC (39 %), UMIC (32 %) in 2019.

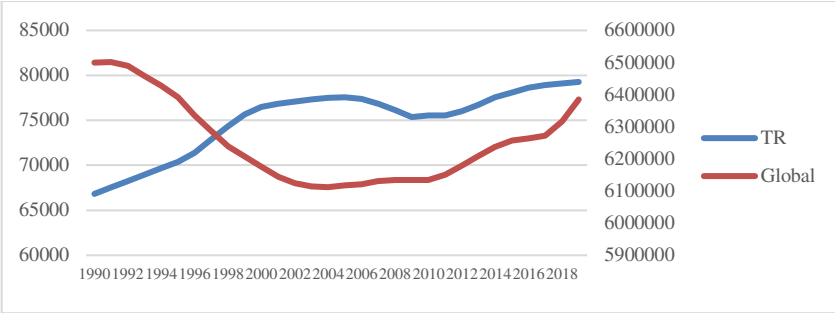
Chart 11: DALY From Upper Respiratory Diseases According To Income Groups



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

DALY of upper respiratory diseases 79272.24 had been realized in Turkey at 2019. In Turkey, the DALY caused from upper respiratory diseases share of global upper respiratory diseases' DALY was calculated 1.241 %.

Chart 12: DALY From Upper Respiratory Diseases In Turkey



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

In 2019 DALY caused from upper respiratory diseases has been decreased about - 1.76 % globally according to 1990. But this situation was differed according to income groups; in thirty years while DALY caused from upper respiratory diseases in upper middle income and low income countries decreased -17 %; in the low middle income and high income countries it was increased by 15 %. In Turkey DALY caused from upper respiratory diseases has been increased 18 % in 30 years.

Table 8: DALY Caused From Upper Respiratory Diseases According To Income Groups, % Change

	HIC	LOWIC	LMIC	UMIC	TR	Global
1990	973184,66	911880,79	2050263,08	2561199,98	66826,91	6499742,76
2019	1066743,9	787204,92	2491659,13	2035967,56	79272,24	6385504,06
%	**0,0961**	**-0,1367**	**0,2153**	**-0,2051**	**0,1862**	**-0,0176**

Source: The values in the table were calculated by the author using the data from http://ghdx.healthdata.org.

1.2.5. Years Lost Due To Disability

The world average the Years Lost Due To Disability from upper respiratory diseases were 5066396 ± 466202.2 (min: 4307984.; max: 5886954) at thirty years.

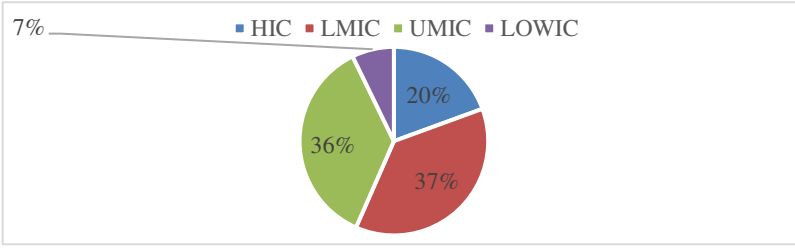
Table 9: The Descriptive Analysis of Upper Respiratory Diseases YLD

	HIC	LMIC	UMIC	LOWIC	TR	GLOBAL
Mean	982562.5	1901565.	1815263.	374682.8	73768.72	5077181.
Median	983872.3	1881100.	1833099.	365155.4	75494.58	5066396.
Maximum	1056635.	2352991.	1941578.	532104.9	78798.46	5886954.
Minimum	929787.8	1482690.	1640699.	252305.8	63585.52	4307984.
Std. Dev.	33303.78	267666.3	85778.69	81658.97	4480.763	466202.2
Skewness	0.165851	0.142354	-0.428766	0.288623	-1.012424	0.059811
Kurtosis	2.001185	1.784781	2.075747	1.977776	2.704619	1.827430
Jarque-Bera	1.384573	1.947270	1.987007	1.722693	5.234078	1.736537
Probability	0.500430	0.377708	0.370277	0.422593	0.073019	0.419678

Source: The values in the table were calculated by the author using the data from http://ghdx.healthdata.org.

In the distribution of avarage YLD due to upper respiratory diseases by income groups between 1990-2019; the highest share was determined in LMIC (37%); the second highest share was seen in UMIC (36%) and the lowest share was seen in HIC and LOWIC respectively (20%, 7%).

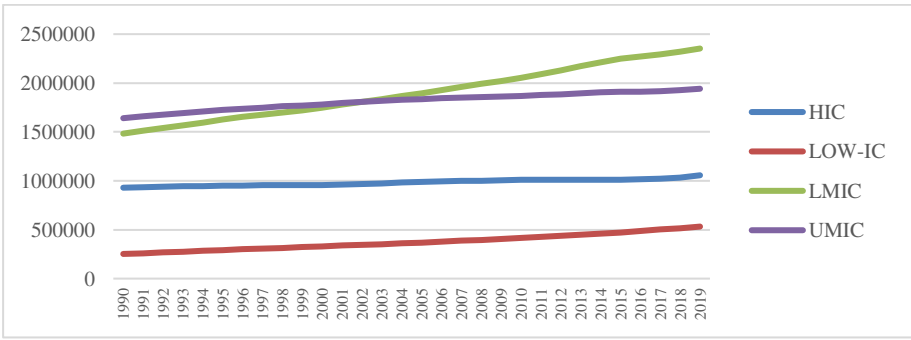
Chart 13: Distribution Of The Years Lost Due To Disability Of Upper Respiratory Diseases By Income Groups, 1990-2019



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

Globally YLD of upper respiratory diseases was 5886953.52 had been realized from upper respiratory diseases in 2019. The distribution of upper respiratory diseases related YLD according to income groups was evaluated respectively; HIC (18 %), LOWIC (9 %), LMIC (40 %), UMIC (33 %) in 2019.

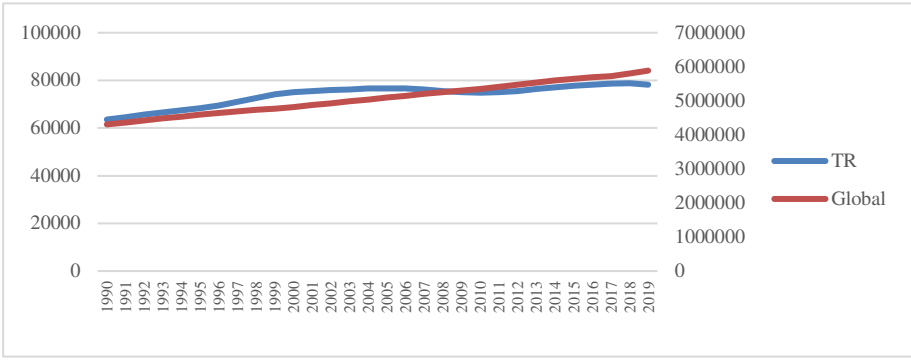
Chart 14: YLD From Upper Respiratory Diseases According To Income Groups



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

YLD caused from upper respiratory diseases 78088.02 had been realized in Turkey at 2019. In Turkey, the YLD caused from upper respiratory diseases share of global upper respiratory diseases' YLD was calculated 1.3 %.

Chart 15: YLD From Upper Respiratory Diseases In Turkey



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

In 2019 YLD caused from upper respiratory diseases has been increased about 36 % globally according to 1990. In thirty years while the high increased YLD caused from upper respiratory diseases was calculated in low income countries by 110% and followed by low middle income countries with 58%. In high and upper middle income countries this burden was increased avarage about 15.9% in thirty years. In Turkey YLD caused from upper respiratory diseases has been increased about 23 % in 30 years.

Table 10: YLD From Upper Respiratory Diseases According To Income Groups, % Change

YLD	HIC	LOWIC	LMIC	UMIC	TR	Global
1990	929787,79	252305,83	1482690,01	1640698,81	63585,52	4307983,85
2019	1056634,69	532104,87	2352991,21	1941578,11	78088,02	5886953,52
%	**0,1364**	**1,1089**	**0,5869**	**0,1833**	**0,2280**	**0,3665**

Source: The values in the table were calculated by the author using the data from http://ghdx.healthdata.org.

1.2.6. Years Of Life Lost

The world average the Years Of Life Lost from upper respiratory diseases are 1048137 ± 536527.3 (min: 498550.5; max:2191759) at thirty years.

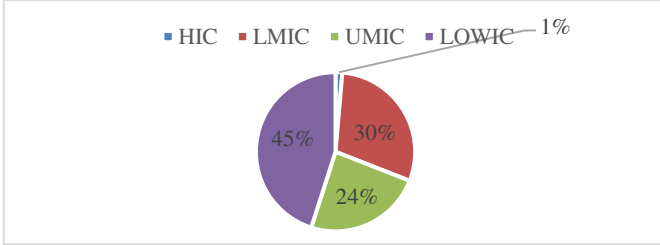
Table 11: The Descriptive Analysis of Upper Respiratory Diseases YLL

	HIC	LMIC	UMIC	LOW_IC	TR	GLOBAL
Mean	18700.37	326322.5	365308.2	463665.0	1201.089	1174482
Median	14410.70	309710.8	251466.5	472078.5	905.1400	1048137
Maximum	43396.88	567573.1	920501.2	659575.0	3241.380	2191759
Minimum	10109.17	138667.9	94389.46	255100.1	284.2200	498550.5
Std. Dev.	9995.974	133375.9	280292.1	119588.1	872.8798	536527.3
Skewness	1.166308	0.326979	0.705462	-0.114474	0.777498	0.493584
Kurtosis	3.138345	1.929057	2.031157	1.982603	2.458139	1.955040
Jarque-Bera	6.825291	1.968226	3.661702	1.359392	3.389532	2.583055
Probability	0.032954	0.373771	0.160277	0.506771	0.183642	0.274851

Source: The values in the table were calculated by the author using the data from http://ghdx.healthdata.org.

In the distribution of avarage YLL due to upper respiratory diseases by income groups between 1990-2019; the highest share was determined in LOWIC (45%); the second highest share was seen in LMIC (30%), UMIC (24%) and the lowest share was seen in HIC (1%).

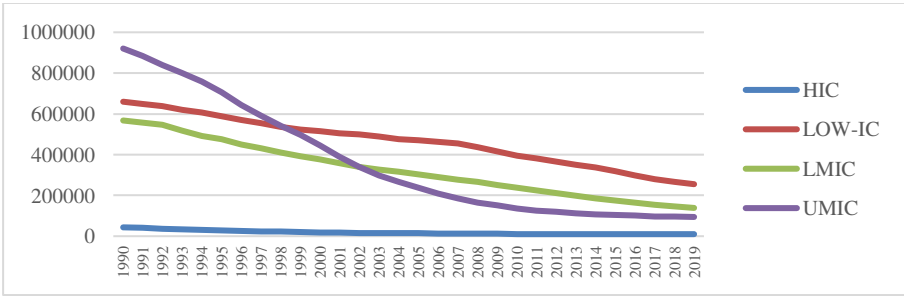
Chart 16: Distribution Of The Years Of Life Lost Of Upper Respiratory Diseases By Income Groups, 1990-2019



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

Globally YLL caused from upper respiratory diseases was 498550.54 had been realized from upper respiratory diseases in 2019. The distribution of upper respiratory diseases related YLL according to income groups was evaluated respectively; HIC (2 %), LOWIC (51 %), LMIC (28 %), UMIC (19 %) in 2019.

Chart 17: YLL From Upper Respiratory Diseases According To Income Groups

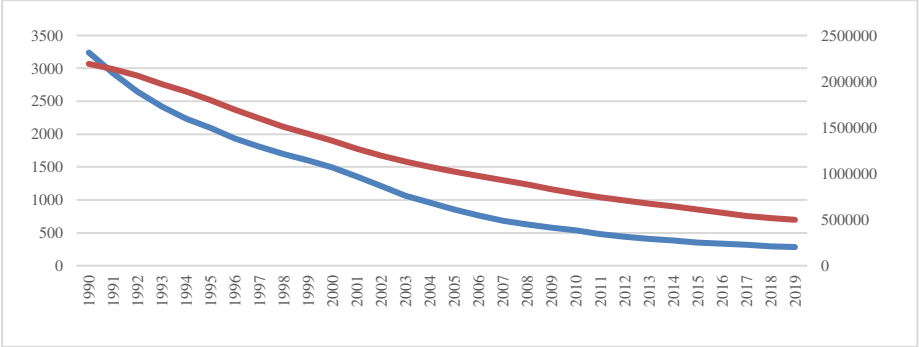


Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

YLL caused from upper respiratory diseases 284.22 had been realized in Turkey at 2019. In Turkey, the YLL caused from upper respiratory

diseases share of global upper respiratory diseases' YLL was calculated 0.057 %.

Chart 18: YLL From Upper Respiratory Diseases In Turkey



Source: The chart were prepared by the author using the data from http://ghdx.healthdata.org.

In 2019 YLL caused from upper respiratory diseases has been decreased about 77 % globally according to 1990. While this decrease was around -90 % high income countries; in the low income, low middle income, upper middle income group countries it was calculated about -71 %. In Turkey YLL caused from upper respiratory diseases has been decreased about - 91 % in 30 years.

Table 12: YLL From Upper Respiratory Diseases According To Income Groups, % Change

YLL	HIC	LOW-IC	LMIC	UMIC	TR	Global
1990	43396,88	659574,96	567573,07	920501,18	3241,38	2191758,92
2019	10109,17	255100,05	138667,91	94389,46	284,22	498550,54
%	**-0,7671**	**-0,6132**	**-0,7557**	**-0,8975**	**-0,9123**	**-0,7725**

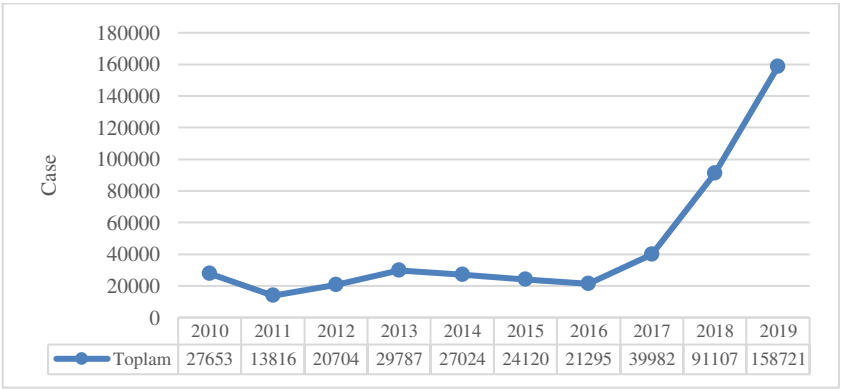
Source: The values in the table were calculated by the author using the data from http://ghdx.healthdata.org.

1.3. Influenza In Turkey

The number of influenza cases in Turkey over the years has increased by 473% in ten years.

Especially in the last three years, the increase has been around 731%.

Chart 19: Total Number of Influenza Cases by Years, Turkey

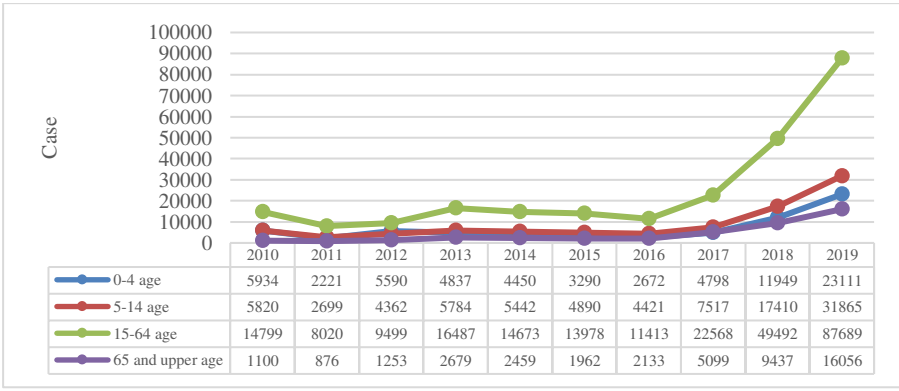


Source: The values in the chart were prepared by the author using the data from http://apps.who.int/flumart

In the distribution of influenza cases by age, it was found that the age groups were generally close to each other in the first seven (7) years. However, in the last three (3) years, influenza affected the age group between the ages of 15-64 more than other age groups. When we look at the age distribution of flu-related data in Turkey, in ten years;

- The number of 0-4 years old was 289%,
- The number of 5-14 years old was 447%
- The number of 14-64 years old was 492%
- The number of over 65 and upper age cases increased by 136%.

Chart 20 : Influenza by Age Groups and Years, Turkey



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
0-4 age	5934	2221	5590	4837	4450	3290	2672	4798	11949	23111
5-14 age	5820	2699	4362	5784	5442	4890	4421	7517	17410	31865
15-64 age	14799	8020	9499	16487	14673	13978	11413	22568	49492	87689
65 and upper age	1100	876	1253	2679	2459	1962	2133	5099	9437	16056

Source: The values in the chart were prepared by the author using the data from http://apps.who.int/flumart

The number of influenza cases increased by age groups in Turkey according to ten years. However, there have been changes in the distribution of the total number of influenza cases by age groups in ten years.

That was to say;

- 29% decrease in the number of 0-4 years old
- 0.48 % decrease in the number of 5 -14 years old
- 0.19% increased in the number of 15-64 years old
- 150% increased in the number of 65 age and upper old was evaluated

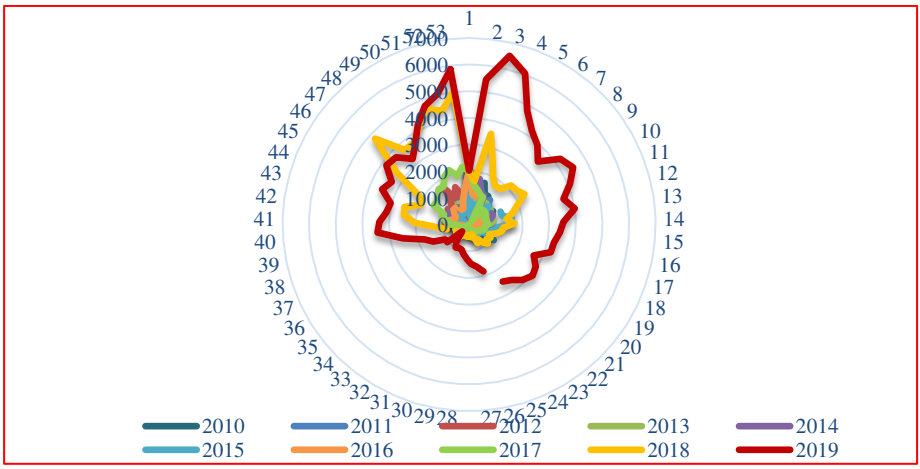
Table 13: The Distrubution Of Influenza Cases Share In Age Groups, Turkey

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Değişim %
0-4 year	21	16	27	16	17	14	13	12	13	15	**-0,29**
5-14 year	21	20	21	20	20	20	22	19	20	20	**-0,048**
15-64 year	54	58	46	55	54	58	55	56	56	55	**0,019**
65 and upper age	4	6	6	9	9	8	10	13	11	10	**1,5**
Total	100	100	100	100	100	100	100	100	100	100	

Source: The values in the table were calculated by the author using the data from http://apps.who.int/flumart

When we evaluate the number of influenza cases according to weeks; the maximum number of cases were seen in the week of 2-23 and 40-52 of the year. This situation is consistent with the general fact that the influenza virus is more effective in the winter months.

Chart 21: Influenza by weeks, 2010-2019, Turkey



Source: The values in the chart were prepared by the author using the data from http://apps.who.int/flumart

1.4. CONCLUSION

- The prevalence and incidence rate of the upper respiratory diseases has decreased over the years globally.
- The prevalence and incidence rate of the upper respiratory diseases according to income groups was showed the balanced distribution.
- The number of deaths caused from the upper respiratory diseases has decreased over the years in globally.
- In the distribution of avarage deaths due to upper respiratory diseases by income groups; the lowest share was determined in HIC countries.
- DALY caused from upper respiratory diseases has been decreased for thirty years generally. But this situation was differed according to income groups; in thirty years while DALY caused from upper respiratory diseases in upper middle income and low income countries decreased; in the low middle income and high income countries it was increased.
- While the YLD caused from the upper respiratory diseases share was determined at a low level in LOWIC according to other countries; the values of YLD have increased over the years in LOWIC countries.
- The YLL of the upper respiratory diseases has decreased over the years globally for thirty years and in the distribution of

avarage YLL due to upper respiratory diseases by income groups; the lowest share was determined in HIC countries.

- The death of the upper respiratory diseases has decreased over the years in Turkey for thirty years. 78% of deaths due to upper respiratory diseases occurred in the 0-15 age range. While the number of deaths due to the upper respiratory diseases decreased by around 85% in thirty years; and the number of deaths in the 0-14 age range dropped to 33% at the same time.
- In Turkey DALY caused from upper respiratory diseases has been increased 18 % in 30 years.
- The prevalence and incidence rate of the upper respiratory diseases has decreased over the years in Turkey.
- While the DALYcaused from the upper respiratory diseases has decreased in globally, it was increased over the years in Turkey.
- The YLD and YLL of the upper respiratory diseases has decreased over the years in Turkey.
- There has been a serious increase in the course of influenza in Turkey in the last 3 years. This situation has been evaluated as the limited immunity, which appears for a few years until the influenza virus undergoes a genetic change, is impaired and the immunity against the altered viruses (like coronavirus) is highly limited significantly.

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CHAPTER 2

HYPEROXIA DURING CARDIOPULMONARY BYPASS

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INTRODUCTION

Oxygen (O2) plays an important role during adenosintriphosphate synthesis, which is vital for all cells, and also causes oxidation that can damage cells. This reveals the oxygen toxicity paradox (1). Besides the direct toxic effect of high fractions of inhaled oxygen on lung tissue, animal and human studies show that hyperoxia

can induce vasoconstriction and reduce cardiac output and organ perfusion (2, 3). Therefore, it is important to keep perioperative oxygenation within normal limits. Perioperatively recommended inspiratory oxygen concentration (FiO2) is below 60%, while partial pressure of oxygen (PO2) is 80-140 mm / Hg (4)

Critical event is defined as an undesirable and preventable accident associated with general or regional anesthesia application that may lead to an undesirable outcome in the patient. While the most common human and equipment related events are observed, the system-related ones constitute approximately 10% of the critical events (5).

The aim of this chapter is to present a critical event that causes perioperative system-induced hyperoxia in cardiac surgery and to express the possible effects that have or may be experienced.

CASE

The patient was operated for mitral valve replacement due to mitral cord rupture and mitral insufficiency after myocardial infarction. PO2 levels were monitored at normal levels in blood gases before and after induction. At the beginning of cardiopulmonary bypass, the first blood

gas obtained with 40% FiO2 was PO2: 250 mm/Hg, and PO2: 716 mm/Hg was detected one hour later. The main oxygen system was controlled by the hospital technical service, since the control in different blood gas measuring devices was similar (PO2: 720-680 mm/Hg). In addition, it was observed that the device worked properly when the mixer part of the cardiopulmonary bypass system (CPBS), which adjusts the air/O2 ratio to be delivered to the blood and sends it to the oxygenator, was controlled (Figure 1). However, it was understood that there was an air leak from the device because oxygen came to the device with high pressure. During these controls, the oxygen level of CPBS was reduced to the lowest level (FiO2: 21) so that the patient would not be exposed to oxygen toxicity. Despite the very low oxygen level, PO2: 250 mm / Hg was still detected in the blood gas taken. Meanwhile, the technical team reviewed the O2 manometer settings again. The problem was solved by reducing the pressure levels after a total of one hour. In blood gas taken, while FiO2: 40, normal levels of PO2 (PO2: 138 mm/Hg) were obtained.

DISCUSSION

European Resuscitation Council guidelines recommend that supplemental O2 administration be given only to patients with hypoxaemia, shortness of breath or pulmonary disease rather than routine use (6). Although there are studies showing that supplemental oxygen therapy prevents wound infections, the damages of hyperoxia are more severe (7, 8). The use of high oxygen as part of the treatment is very common in cardiac patients, especially in acute dysfunctions.

The reason for this is probably to prevent deterioration in tissue oxygenation caused by a decrease in cardiac output. However, oxygen is a vasoactive element (9). Therefore, attention should be paid to the vasoconstrictor effects of oxygen during coronary stent placement. In particular, narrowing of coronary arteries is a common cause of stent thrombosis and sudden cardiac death (10). Hyperoxia may cause a decrease in cardiac output due to both a decrease in heart rate by activating the parasympathetic system and an increase in systemic vascular resistance. (11). In our case, hyperoxia occurred during CPB. During this period, it is difficult to understand the body's response to hyperoxia, as the patient's hemodynamics are under the control of the perfusionist and mediated by the CPBS.

Figure 1: Mixer Section of Cardiopulmonary Bypass System

Reactive oxygen species (ROS) are known as free radicals derived from oxygen. High ROS levels cause cellular damage and myocyte contractile dysfunction, necrosis, increased apoptosis, vascular dysfunction. Due to the increase in ROS formation, "oxygen toxicity" may cause serious side effects, especially in ischemia / reperfusion situations such as cardiovascular surgery (9, 12). Although these effects are particularly pronounced after prolonged exposure (12-24 hours), some retrospective studies indicate that even shorter duration hyperoxia is associated with increased mortality and morbidity. (4, 13). In our case, exposure to hyperoxia lasted a total of 1 hour. Although this is not a very long exposure time, the very high PO2 level is disturbing. However, in our case, no complications that we would associate with oxygen toxicity were observed.

The pressure elevation in the central oxygen system in our case is within the scope of the system-related critical event. Understanding the relationships between errors, events and accidents is important in terms of taking precautions for harm that may be caused to patients and evaluating risk management. Critical incident reporting is important in terms of not experiencing the situation again, taking precautions and setting an example in assistant doctor training (14). However, critical incident reporting is very low in our country and in the world. Also, delay of notification is quite common. Establishing a multidisciplinary information system without wasting time after a critical incident ensures the correct transfer of the event and a more understandable (15).

CONCLUSION

Hyperoxia is a situation that we encounter frequently in operating rooms, intensive care and emergency rooms where oxygen is used, but we do not know much about the results. However, when the harmful effects up to mortality are considered, prevention of hyperoxia is very important. System-related technical accidents that may cause hyperoxia, as in our case, should be resolved as soon as possible and the patient should be minimally affected.

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CHAPTER 3

INVESTIGATION OF THE RELATIONSHIP BETWEEN PSORIASIS AND NUTRITION

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ABBREVIATIONS

TNF-α: Tumor necrosis factor-α

IL-23: Interleukin-23

NAFLD: Non-alcoholic fatty liver disease

ROS: Reactive oxygen species

DC: Dendritic paper

IBD: Inflammatory bowel disease

UC: Ulcerative colitis

CH: Crohn's disease

PsA: Psoriatic artist

IMQ: Imiquimod

SFA: Saturated fatty acid

n-3: Omega-3

n-6: Omega-6

AA: Arachidonic Acid

PGE2: Prostaglandin E 2

COX-2: Cyclooxygenase-2

GLUT: Glucose transporter

PPAR: Peroxisome proliferator activated receptors

EPA: Eicosapentaenoic acid

DHA: Docosahexaenoic acid

B9: Folic acid

B12: Cobalamin

UV: Ultraviolet

Tregs: T cells

GPx: Glutathione peroxidase

TrxR: Thioredoxin reductase

MD: Mediterranean Diet

EVOO: Extra virgin olive oil

PASI: Psoriasis Area and Severity Index

AGA: Atigliadin IgA antibody

GFD: Gluten-free-diet

INTRODUCTION

Psoriasis is an ancient and universal disease that was first defined by Hippocrates (460-377 BC). He used the word 'psora' which means itching (Nickoloff & Nestle, 2004). Psoriasis, an immune-mediated chronic inflammatory skin disease, accelerated tumor necrosis factor-α (TNF-α), interleukin-23 (IL-23)/interleukin-17 (IL-17) axis, T-cell-mediated hyperproliferation of keratinocytes, angiogenesis. It is characterized by inflammatory cell infiltration (Kormeili et al., 2004; Nickoloff & Nestle, 2004; Takeshita et al., 2017). Psoriasis is a non-contagious but painful skin disease that affects men and women equally (Zuccotti et al., 2018). Although it is not life-threatening disease including seriously affects quality of life (Kormeili et al., 2004). Patients with psoriasis suffer from the poor quality of life inclusive social stigma and discrimination. This skin disease involves the interaction of environmental factors and genetic components which induce the lesions on the skin, scalp, knees, elbows, nails, lower back as well as anywhere on the body (Mahil et al., 2016). Lesions in psoriasis are usually sharply demarcated, thick, and dry erythematous plaques covered with white psoriasis-colored papulosquamous (Madden et al., 2020). Patients with psoriasis are more likely to develop comorbid diseases such as psoriatic arthritis, obesity, metabolic syndrome, gastrointestinal diseases, non-alcoholic fatty liver disease (NAFLD), inflammatory bowel disease (IBD), and psychiatric disorders (Kanda et al., 2020). In addition to having many treatment options, the skin disease is generally resistant to treatment,

and frequently recurs after discontinuation of the drug after acceptable improvement (Kormeili et al., 2004). In psoriasis disease, it can be seen in any age, including childhood, two peak periods, 20-30 and over 50 years old (Xhaja et al., 2014). On the other hand, the disease is a genetically complex and multifactorial autoimmune disease due to chronic skin disease affecting approximately 2% of the general population (Wolters, 2005). However, diet, obesity, infections, drugs, stress, alcohol and smoking can also trigger this disease (Xhaja et al., 2014). Nutrition is an environmental factor affecting malnutrition, high body mass index, and metabolic diseases which increase the severity of clinical symptoms in patients (Zuccotti et al., 2018). Since the effect of nutrition on psoriasis has not been taken into consideration, the importance of diet in psoriasis treatment has been interesting for the scientific world with the comorbidities coming up and the effects of functional foods on diseases, and studies have emerged in this direction (Kaçar et al., 2014). What is known because of the literature review on the relationship between the nutrition and psoriasis disease (Ricketts et al., 2010; Festugato, 2011; Kanda et al., 2020; Madden et al., 2020):

- Restriction of alcohol consumption in some patients
- Gluten-free diet in patients with positive anti-gliadin antibodies
- Low-calorie diet in patients with metabolic syndrome for reducing disease severity.

A pilot study involving 43 psoriasis patients with an unbalanced diet and consuming unhealthy foods, 88.37% of the patients showed

improvement in their clinical findings and erythematous tissues after receiving healthy nutrition training (Festugato, 2011). In addition, it was found that improving the quality of life, exacerbations were milder, and their intervals were longer. However, most patients, doctors, and nutritionists are not aware of how effective medical nutrition therapy is, because of being very few literatures summarizing the importance of diet in psoriasis. In addition, there is a lack of evidence synthesis regarding of the relationship between psoriasis and diet (Ford et al., 2018). This shortcoming demonstrates the need for accessible evidence-based dietary recommendations for clinicians and patients. However, as a result of the literature review, it was found that psoriasis patients are highly motivated to make changes in their eating habits, perceive these changes as safe and natural, and believe that diet will have a positive effect (Barrea et al., 2020). Therefore, this study was aimed to review dietary interventions in psoriasis, create an evidence-based synthesis and demonstrate the effect of nutrition on psoriasis comorbidities by compiling current findings.

1. EPIDEMIOLOGY

Although the prevalence of psoriasis disease varies due to geography and ethnic origin, its incidence increases worldwide (Zuccotti et al., 2018). It was observed that the incidence increases towards the poles, while a low incidence was observed in the Equator region (Kormeili et al., 2004; Wolters, 2005; Zuccotti et al., 2018). It is more common among European Caucasians and less common among Asian and African populations (Kormeili et al., 2004). The prevalence rate is

approximately 1-5% in Europe, whereas approximately 4-6% is in the USA (Wolters, 2005). It constitutes 1.3% of all dermatological diseases in Turkey (Kundakçi et al., 2002).

2. ETIOLOGY AND PATHOGENESIS OF PSORIASIS

In the skin of a healthy individual, the epidermis cells divide continuously moving towards the skin surface (Brown et al., 2004). After that, they peel off, and dead cells are shed. It normally takes about 28 days for new cells which can grow deep within the skin to reach the skin surface. However, this process accelerates in psoriasis patients and new epidermal cells rise to the surface within a few days with a 30-fold increase. For this reason, their skin is thicker, and the cells become overgrown and less mature, causing red, scaly and crusted spots covered with silvery lesions. Environmental, genetic and immunological factors have been considered in the etiology of psoriasis (Lai et al., 2018). This disease caused by the disruption of skin immune homeostasis in genetically susceptible individuals includes the dynamic interactions between many cell types and cytokines in response to triggering in the skin (Mahil et al., 2016). It is accepted that the immunological effects are caused by keratinocyte hyperproliferation in the epidermis, and the transport of T lymphocytes activated in the dermis to lesional skin (Kormeili et al., 2004). Studies have been shown that oxidative stress, increased free radical formation and immune inflammation, play an important role in the pathogenesis of psoriasis (Wolters, 2005). The oxidative stress caused by endogenous and exogenous factors resulting an increase in

reactive oxygen species (ROS) and inducing the T cell activation and inflammatory reactions (Lai et al., 2018). Afterwards, the formation of keratinocyte proliferation, angiogenesis, and the release of inflammatory cytokines take places. ROS-mediated transcription factors and their proliferation; T cell activation mediates the immunopathological process of psoriasis by causing keratinocyte proliferation and differentiation. Thickening of the epidermis (acanthosis) is observed due to the increase in keratinocyte turnover (Mahil et al., 2016). The presence of abnormal differentiation leads to the retention of keratinocyte nuclei in the stratum corneum (parakeratosis), which further emphasizes the importance of keratinocyte skin cells in the development of psoriasis. Besides, psoriatic surfaces are heavily infiltrated by T cells and dendritic cells (DC).

Psoriasis plays an active role in hereditary susceptibility alleles, especially TNF-α gene polymorphism (Lai et al., 2018). Considered the primary pro-inflammatory cytokine, TNF-α is the main gene in the pathogenesis of psoriasis that can accelerate the infiltration of lymphocytes, neutrophils, and monocytes. It especially stimulates and activates Th1 and Th17 immune responses. Studies are increasing about that activated T cells are at the center of the pathogenesis of psoriasis (Kormeili et al., 2004). They also support by the detection of increased active T lymphocyte levels, especially Th1 and Th17, in the psoriatic skin plaques and blood of patients. Inflammation is central to the production of many pro-inflammatory cytokines such as

interleukins (IL-1, IL-6, IL-17, IL-18, IL-22, IL-23, and IL-33), tumor necrosis factor-alpha (TNF-a) It is formed by abnormal activation of T lymphocytes (Th-1 and Th-17) (Zuccotti et al., 2018). Inflammation, which is an important clinical finding of psoriasis, is seen as an important point in the pathogenesis of psoriasis as a trigger factor of hyperproliferation and angiogenesis that stimulate the development of psoriatic lesions (Barrea et al., 2020).

3. PSORIASIS AND COMORBIDITIES

Patients with psoriasis suffer from many diseases that are triggered by the highly inflammatory condition (Kanda et al., 2020). At the same time, psoriasis can be triggered because some diseases cause inflammation. While psoriatic arthritis affects the most common patients, cardiometabolic diseases characterized by chronic inflammation, obesity, metabolic syndrome, gastrointestinal diseases, non-alcoholic fatty liver disease (NAFLD), inflammatory bowel disease are comorbid diseases. In addition, psychiatric disorders are strongly associated with the impact of psoriasis which decrease the quality of life in psoriasis patients (Barrea et al., 2016; Kanda et al., 2020).

3.1. Obesity

Obesity seen as an important risk factor for psoriasis, is a chronic, low-grade inflammatory condition that is generally defined as an excessive increase in the ratio of body fat to lean mass (Barrea et al., 2016). An increase in body mass index above 30 is accepted as

obesity (Kunz et al., 2019). The incidence of psoriasis has doubled between the 1970s and 2000s and considering that the genetic basis of psoriasis should not change significantly in this process, it has been concluded that the environmental factors included in the western lifestyle play a role in this increase. Obesity occurs as a result of excess calorie intake and high-fat, high-sugar, and high-salt diet, which are seen in Western eating habits. However, it is very difficult to say whether psoriasis triggers obesity or obesity triggers psoriasis (Barrea et al., 2016). Because conditions such as significant social isolation, bad eating habits, depression, increased alcohol consumption, and decreased physical activity in psoriasis patients show how psoriasis may indirectly cause obesity (Kunz et al., 2019). Increasing adipose tissue with obesity worsens psoriasis. On the other hand, the adipose tissue is an important endocrine organ that provides factors that play a role in inflammation and immunity and has a key role in lipid and glucose metabolism and insulin-mediated processes (Barrea et al., 2016; Kunz et al., 2019). A study included 78,626 women, 892 of whom had psoriasis (Setty et al., 2007). It was found that weight gain and excessive fat accumulation were important risk factors in the development of psoriasis. Patients with body mass indexes of 35 and above had a higher risk of developing psoriasis in comparison to thin patients. Inflammatory macrophages in adipose tissue increase the production of cytokines produced from adipose such as TNF-alpha, IL-6, and leptin, which play an active role in the pathogenesis of psoriasis (Ni, & Chiu, 2014). Leptin regulates appetite and body weight, and causes disruption of insulin signal in the insulin

receptor substrate (Barrea et al., 2016). It plays an important role in pro-inflammatory conditions associated with complications such as visceral obesity. Increasing leptin levels can induce the proliferation and apoptosis inhibition in T cells, and can be effective in increasing the production of other pro-inflammatory cytokines such as IL-6 and TNF-alpha (Ni, & Chiu, 2014). In a recent meta-analysis of 38 studies, higher leptin levels were found in patients with psoriasis compared to those without it (Kyriakou et al., 2017). It was observed that psoriasis patients with morbid obesity had a valid improvement in the severity of psoriasis, and associated with the degree of postoperative weight loss after bariatric surgery (Barrea et al., 2016). In another meta-analysis study, 7 prospective studies were resulted in psoriasis increased with higher body mass index, waist circumference, waist-hip ratio, and weight gain (Aune et al., 2018). With this study, it has been observed that every 5-unit increase in body mass index leads to a 19% increase in psoriasis risk, an 11% increase in psoriasis risk to 5 kg weight increase, a 10 cm increase in waist circumference to a 24% increase in psoriasis risk, a 0.1 unit increase in the waist-hip ratio to a 37% increase in the risk of psoriasis. These studies have been shown that maintaining ideal body weight and reducing body mass in overweight or obese individuals can decrease the incidence of psoriasis and have positive effects on the severity of psoriasis (Kunz et al., 2019). For this reason, weight loss is recommended in obese and morbidly obese psoriasis patients.

3.2. Celiac Disease

Celiac disease is triggered by exposure to gluten, which consists of two main proteins, gluten, and gliadin, in genetically susceptible individuals, and is characterized by mucosal inflammation and villous atrophy, and is first defined as a disease affecting the small intestine (Bhatia et al., 2014; Acharya & Mathur, 2020). One of the diagnostic tests for celiac disease is the anti-gliadin antibody test (Kolchak et al., 2017). A meta-analysis study was conducted to show that anti-gliadin antibody (AGA) levels were higher in psoriasis patients compared to the control group (Bhatia et al., 2014). In general, about 14% of the psoriasis patients in the study were IgA AGA positive. Although, IgA AGA antibodies were high in psoriasis patients in the study, a diagnosis of celiac disease could not be made as a result of the biopsy strangely. This suggests that gluten sensitivity, which is not related to IgE-mediated allergy, and celiac disease. It can be screened with the anti-gliadin test and that psoriasis patients may have gluten sensitivity, but gluten enteropathy may also be (Bhatia et al., 2014; Kolchak et al., 2017). On the other hand, celiac disease produces an autoantibody specific to the Th2 axis, Th1 and Th17 cells play an active role in the pathogenesis of psoriasis and the celiac disease (Bhatia et al., 2014). In addition, gluten intake in celiac patients can cause psoriatic lesions by activating T cells (Wolters, 2005). There are some hypotheses linking celiac disease to psoriasis (Abenavoli et al., 2007):

- Th1 and Th17 lymphocytes are important factors in the pathogenesis of both diseases

- Intestinal permeability present in both cases may have a stimulating role between these two diseases
- Vitamin D deficiency found in celiac disease and psoriasis may have an effect on the formation of psoriatic lesions in individuals with these two diseases.

In a meta-analysis study in which researchers included 12,912 psoriasis cases, an approximately 3-fold increased risk of celiac disease was found in psoriasis patients (Ungprasert et al., 2017). As a result of the literature study, it was found that there is a relationship between celiac disease and psoriasis (Abenavoli et al., 2007; Bhatia et al., 2014; Kolchak et al., 2017; Ungprasert et al., 2017; Acharya & Mathur, 2020).

3.3. Inflammatory Bowel Disease (IBD)

Ulcerative colitis (UC) and Crohn's disease (CD) are mostly seen as IBD, and systemic inflammation plays an important role among genetically predisposed IBD patients and psoriasis patients (Ni, & Chiu, 2014). As a result of the researches, there are three hypotheses that show an epidemiological link between IBD and psoriasis: (a) IBD patients have a higher risk of secondary psoriasis; (b) A predisposition to ulcerative colitis and Crohn's disease in psoriasis patients; (c) It is the unintended side effect of psoriatic lesions in inflammatory bowel patients treated with anti-TNF agents. (Pietrzak et al., 2017). Additionally, both psoriasis and IBD share common inflammatory pathways, and Th17 and IFN-gamma are important factors in the

pathogenesis of both diseases. Th17 lymphocytes in psoriatic lesions produce IL-23 cytokine, which causes intestinal inflammation (Ni, & Chiu, 2014). In a study, secondary psoriasis developed in a very small proportion of patients who received anti-TNF treatment, suggesting that secondary psoriasis occurs with a genetic predisposition (Pietrzak et al., 2017). As a result of the literature research, it has been found that patients with psoriasis and psoriatic arthritis have a high risk of inflammatory bowel disease (Ni, & Chiu, 2014; Pietrzak et al., 2017).

3.4. Non-alcoholic fatty liver disease (NAFLD)

NAFLD is the presence of high triglyceride levels in the hepatocytes of patients without excessive alcohol consumption, in severe cases, it can cause the formation of fibrosis, cirrhosis, and hepatocarcinoma (Ni, & Chiu, 2014). The findings obtained because of the studies explain that the risk of NAFLD in psoriasis patients is approximately two times higher than in the current population (Miele et al., 2009; Ni, & Chiu, 2014; Pietrzak et al., 2017). One of the important effects leading to this relationship is that anti-psoriatic drugs, agents such as methotrexate and anti-TNF are hepatotoxic (Pietrzak et al., 2017). In a cross-sectional study in which researchers included 142 Italian patients, a serious relationship was found between psoriasis and NAFLD (Miele et al., 2009). Of the patients in this study, 59% were clinically diagnosed with NAFLD, and 21% had NAFLD-related factors (viral hepatitis, significant ethanol, and methotrexate use). Many studies show that these two diseases trigger each other and cause the disease to continue (Pietrzak et al., 2017). The findings

show that the presence of NAFLD causes a more severe risk of psoriasis and that psoriasis patients with NAFLD have a higher risk of liver fibrosis than those without psoriasis.

3.5. Metabolic Syndrome

Metabolic syndrome is caused by the combination of systemic disorders such as obesity, hypertension, insulin resistance, and dyslipidemia, which increase the risk of cardiovascular disease (Ni, & Chiu, 2014). Psoriasis and metabolic syndrome have common pathogenesis including low-level inflammation involving pro-inflammatory cytokines such as IFN-gamma, IL-17, IL-23, and TNF-alpha (Singh et al., 2017; Madden et al., 2020). In a meta-analysis study, the data of 35 studies including 1 450 188 participants and 46 714 psoriasis patients were analysed (Singh et al., 2017). The findings showed that the risk of metabolic syndrome is significantly higher in psoriasis patients compared to the control group without psoriasis. In addition, it was determined that the patient group with severe psoriatic findings had a higher risk for metabolic syndrome than the patient group with mild symptoms.

3.6. Psoriatic Arthritis (PsA)

PsA is the most common comorbidity of psoriasis, which occurs with symptoms of stiffness, pain, swelling, and tenderness of adjacent tendons, ligaments as well as joints (Takeshita et al., 2017). PsA is chronic inflammatory arthritis seen in 6-42% of the psoriatic population. The incidence of PsA increases according to the severity of psoriasis. PsA is a devastating, erosive, progressive disease, and

damage and loss of function can be seen even in the first years of the disease, so rapid intervention and early diagnosis are essential (Villani et al., 2015). Undiagnosed PsA is common among psoriasis patients. In fact, most psoriatic patients have been found to have psoriasis skin disease 7-12 years ago.

3.7. Psychiatric Disorders

The skin is the organ in which a person introduces herself/himself to the outside world (Russo et al., 2004). This organ affects that person's self-esteem, body image, and the thoughts of others about that person. Any deformation in this organ can lead to many psychiatric problems. Psychological problems are important comorbidity for psoriasis (Ni, & Chiu, 2014). It is estimated that pro-inflammatory cytokines such as IL-1, TNF-alpha, and IFN-gamma. Their high levels effects as neuromodulators and lead to depressive disorders. Psoriasis and stress affect each other in a vicious circle. It has been reported that stress has an effect on the onset and exacerbation of psoriasis, and psoriasis also causes psychological problems. Mood disorders such as increased depression, anxiety, and suicidal tendency are common among psoriasis patients (Takeshita et al., 2017). In a meta-analysis examining the relationship between psoriasis and depression, psoriasis patients have more symptoms of depression. Psoriasis patients say that they are exposed to social stigma, high levels of stress, and many negative conditions in their quality of life (Ni, & Chiu, 2014). The prominence of the lesions in these patients can lead to embarrassment, withdrawal from social life, and a decrease in self-esteem. Studies

have found that psoriasis patients think that people try not to touch them and often try to hide their illness.

4. PSORIASIS DISEASE AND MICROBIOTA

As a result of recent studies, it has been proven that microbiota plays an effective role in the pathogenesis of chronic inflammatory diseases (Zuccotti et al., 2018). Commensal skin microbiota acts as an important barrier and plays a key role in maintaining skin integrity (Benhadou et al., 2018). It has been found that the microbial diversity in psoriatic lesions is higher than in healthy skin, but it has not been known whether this condition is the cause or the result of the disease. Changes in the composition of the intestinal microbiota lead to impairment in the immune system and may lead to the formation of inflammatory diseases (Madden et al., 2020). It has been found that intestinal microbiota is reduced in psoriasis patients compared to healthy individuals, and *Akkermansia muciniphilia* bacteria, which decreases in cases of low inflammation, are found less than controls (Benhadou et al., 2018). The results obtained show that the gut-skin axis is in interaction with each other.

5. EFFECT OF ALCOHOL AND SMOKING IN PSORIASIS DISEASE

It is known that alcohol consumption in psoriasis patients exacerbates symptoms and unfortunately psoriasis patients consume alcohol at high rates (Kanda et al., 2020). It has been observed that alcohol consumption stimulates inflammation and activates T lymphocytes by increasing the release of CD80 and CD86 genes (Madden et al., 2020).

It is thought that ethanol discharged by exocrine glands may cause keratinocyte hyperproliferation by deforming the skin barrier. A systematic study revealed a relationship between alcohol consumption and the incidence of psoriasis (Brenaut et al., 2013). However, there is not enough evidence to say that alcohol is a definite risk factor because it has been explained that alcohol consumption was not evaluated before the onset of psoriasis in the studies examined. Despite this, in a survey study, it was found that the most effective nutritional behaviour change in psoriasis patients was to quit alcohol consumption (Madden et al., 2020). It should be noted that psoriasis will cause an increase in visceral fat through increased energy and this will aggravate psoriasis. Ethanol stimulates TNF-α synthesis in monocytes/macrophages and increases lymphocyte proliferation and histamine release from mast cells (Kanda et al., 2020). In addition, alcohol-induced liver damage causes skin barrier deformation via TNF-α. It was reported that this deformation was treated with anti-TNF-α and positive results were obtained. In order to investigate the effects of chronic alcohol consumption in mice, drinking water containing 5% ethanol was administered for 10 weeks (Farkas et al., 2003). As a result, it has been noted that epidermal thickness increased and psoriasiform dermatitis caused by IMQ (imiquimod) was exacerbated by Th17-mediated cytokine expression. In summary, this result showed that alcohol has a significant effect on psoriasis mediated by Th17. In addition, psoriasis patients are more likely to die from alcohol-related causes than the risk of suicide due to alcoholic liver disease and alcohol-related anxiety (Kanda et al., 2020). It is

difficult to establish a link between psoriasis and smoking due to the paucity of clinical studies (Madden et al., 2020). However, a meta-analysis study explained that smokers have a higher prevalence and risk of psoriasis compared to non-smokers. A case-control study reported that smoking was associated with an increased risk of psoriasis by 70%, but this was not associated with the severity of the disease (Wolk et al., 2009). However, it is suggested that smoking exacerbates or initiates psoriatic pathogenesis by producing free radicals (Madden et al., 2020). In addition, it is said to directly damage the skin by stimulating the formation of ROS and reducing the release of protective antioxidant genes. Cigarette consumption causes functional changes in some leukocytes, resulting in the higher release of interleukin 1B and TNF-alpha, which have an effect on the severity of psoriasis (Festugato, 2011). As a result of the literature review, it was found that there was a relationship between the severity of the disease and daily smoking, and patients should be advised to quit smoking in order not to aggravate clinical symptoms (Wolk et al., 2009; Festugato, 2011; Madden et al., 2020). This situation should be applied in smoked foods (Festugato, 2011).

6. RELATION OF NUTRITIONAL COMPONENTS AND PSORIASIS DISEASE

Considering the relationship between psoriasis and cardiovascular diseases, obesity, and metabolic syndrome, it is seen that the nutritional disorder underlying the occurrence of these diseases, especially nutrition as a Western diet, plays a central role in the

severity of psoriasis (Festugato, 2011; Debbaneh et al., 2014; Ford et al., 2018). For this reason, it is very important to organize a diet that has an effect on reducing psoriatic violence and to create a personalized nutrition program. Researchers conducted a cross-sectional survey study in order to establish a relationship between nutrition and psoriasis, to determine the nutritional habits of psoriasis patients and foods that increase and decrease psoriasis severity (Kaçar et al., 2014). In this study, psoriasis patients regularly intake gluten-containing food as 94%, sugar-rich 77%, fat-rich 55%, and fresh fruits-vegetables 43%. It was observed that processed food-based diet consumption was 32%, spicy and hot food consumption was 26%. As a result of this research, the severity of psoriatic inflammation was found to be associated with sugar-rich nutrition and gluten consumption.

6.1. Carbohydrates

Simple candies are consisting of glucose, fructose, galactose, maltose, sucrose, and lactose (Kanda et al., 2020). Especially Western-type diet contains high levels of simple sugar. As a result of the researches, it has been concluded that consuming too many simple sugars aggravates psoriatic symptoms. IL-17F levels were elevated in rats fed high amounts of fructose; In another study, it was found that mice fed high amounts of glucose caused Th17 differentiation in T lymphocytes due to the effect of mitochondrial reactive oxygen species (ROS). In mouse studies, it has been proven that a Western diet with high fat and simple sugar levels triggers imiquimod (IMQ)

mediated psoriasiform dermatitis (Yu et al., 2019). In this study, they fed a group of mice with a western diet with high levels of fat and sugar for 12 to 16 weeks and fed the control group a high-fat but low-sugar diet. It was found that IMQ exacerbated psoriasiform dermatitis in mice fed the Western diet, while the control group fed high-fat low-simple sugar had a greater mass gain, but less inflammation was observed in response to the IMQ than the mice fed the Western diet. This result explains that the sugar content in the Western diet, where obesity alone is not sufficient, has a significant effect on the increase of psoriatic severity. Complex carbohydrates are composed of fruits, vegetables, whole grains and legumes with high fiber and nutrient content (Kanda et al., 2020). The high fiber content of foods containing glucose-based resistant starch creates an anti-inflammatory effect in the intestine (Rasmussen et al., 2019). Low fiber intake leads to a decrease in intestinal microbiota richness and metabolism. The effect of fibers in dietary supplements; loss of body weight, improvement in inflammatory bowel diseases and a decrease in inflammatory cytokines (Kanda et al., 2020). One study demonstrated that mice fed dietary fiber-rich seaweed improved psoriatic symptoms and altered the composition of the gut microbiota.

6.2. Red Meat

Red meat, which contains high amounts of saturated fatty acids (SFA), causes inflammation by stimulating the IL-23 / IL-17 pathway (Kanda et al., 2020). In one study, mice were fed a diet containing heme iron molecules produced from red and processed meat (Rasmussen et al.,

2019). As a result of this diet, the intestinal microbiota has been deformed in the form of an increase in *Enterobacteriaceae* and *E.coli* and a decrease in *Firmicutes* and *Lactobacillus.* In addition, butyrate synthesis, which stimulates T cells, led to a decrease in colitis. Therefore, it is thought that excessive consumption of red meat may aggravate the clinical manifestations of psoriasis due to the effect of saturated fatty acids and hem protein. Taurine, a beneficial amino acid for the human body, is found in cow's milk, meat products, fish and eggs (Ricketts et al., 2010). Research show that taurine has an effect on psoriasis, but the literature data do not provide conclusive information that excessive taurine intake can exacerbate the disease or that reducing taurine intake alleviates the disease. Clinical improvement was observed in 12 chronic psoriasis patients who were given cholestyramine, which is a bile acid binder, and it was found that there was an increase in the amount of taurine in the faeces considering that cholestyramine binds and excretes it (Roe, 1962). This result suggests that the reduction of taurine in the body may be associated with the reduction and disappearance of psoriatic lesions. In another study, the administration of high doses of taurine caused erythema and increased itching in psoriatic lesions (Ricketts et al., 2010). In addition, studies have examined whether the amount of taurine in a regular diet influences the severity of psoriasis (Roe, 1965; Ricketts et al., 2010). In another study, 15 patients were studied and it was concluded that psoriasis was completely cured in 9 patients with low taurine in the diet and partial improvement was observed in 6 patients (Roe, 1965). However, patients who are fed a low protein-low

taurine diet showed greater improvement compared to patients fed a high protein diet.

6.3. Fatty Acids

Saturated fatty acids (SFA) are abundant in foods such as butter, red meat, and dairy products and are a major risk factor that causes obesity, dyslipidemia, and cardiovascular disease when consumed (Kanda et al., 2020). It has been proven that a high-fat diet with SFA content exacerbates psoriasiform dermatitis in mice. SFAs cause a series of inflammatory reactions such as insulin resistance, oxidative stress, endoplasmic reticulum stress and lipotoxicity (Kunz et al., 2019). In a study, it was concluded that SFAs play an active role in the severity of psoriasis. The high degree of stimulation of SFAs to myeloid cells leads to disruption and differentiation of keratinocyte proliferation, which leads to an increase in psoriatic inflammation. Fatty acids, which play an active role in intracellular signals, provide the formation of skin structure and protection of homeostasis (Madden et al., 2020). Omega-6 fatty acids, one of the polyunsaturated fatty acids, are essential fatty acids that cannot be produced in the human body. Linoleic acid (18: 2, n-6) and arachidonic acid (20: 4, n-6) are n-6 fatty acids thought to play a role in the pathogenesis of psoriasis (Kanda et al., 2020). Linoleic acid is found only in vegetable oils and seeds, such as grape seeds, poppy seeds, sunflower, hemp, corn, cottonseed, and soybeans (Wolters, 2005). Arachidonic acid (AA) is found in foods of animal origin such as meat, egg yolk and shrimp. Linoleic acid is transformed into arachidonic acid in the cell

membrane with metabolic effects (Kanda et al., 2020). Although the effect of linoleic acid on psoriasis is controversial, the connection of arachidonic acid with psoriasis is an important issue due to its inflammatory effects. It has been found that psoriasis is more common in individuals who take a diet rich in omega-6, which is found in vegetable and animal oils (Barrea et al., 2016). With the effect of various stimulants such as arachidonic acid that is released from membranes and transforms into lipid mediators through metabolic reactions (Kanda et al., 2020). The main lipid mediators derived from AA influencing psoriasis, prostanoids and leukotrienes. Prostaglandin E2 (PGE2), a prostanoid, mediates the development of IMQ-induced psoriasiform dermatitis. PGE2 stimulates IL-23 production which induces cyclooxygenase-2 (COX-2) in Th17 cells. They provide PGE2 production, which increases interleukin release. Arachidonic acid, which is abundant in the Western diet, has been shown to increase the severity of inflammation (Duarte et al., 2012). In a study, it was observed that there was hyperproliferation and differentiation in the epidermal surface of the patient group given a diet rich in corn oil. Membrane protein encoded as CD36 gene, which is located on the surface of cells and responsible for fatty acid uptake into the cell, deforms lipid metabolism as a result of feeding with a high-fat diet (Madden et al., 2020). In fact, CD36 and glucose transporter (GLUT) 4 are used to increase fatty acid in the body by metabolic reactions with increased insulin release. In psoriasis, CD36 expression is increased and glucose uptake is regulated together with peroxisome proliferator-activated receptors (PPARs). It has been observed that the

concentrations of arachidonic acid and leukotrienes increase in psoriatic lesions (Wolters, 2005). The most abundant derivatives of omega-3 in foods are α-linolenic acid (C18: 3n-3), eicosapentaenoic acid (EPA; C20: 5n-3) and docosahexaenoic (DHA; C22: 6n-3) acids (Wolters, 2005). While A-Linolenic acid is found in linseed and walnut oil; EPA and DHA are found in oily fish called cold sea fish such as mackerel, sardines, salmon, geranium. The prevalence of psoriasis is lower in Japan, Norway and Eskimo countries due to the high consumption of cold-water fish rich in omega-3s (Duarte et al., 2012). Studies show that n-3 intake reduces the area and severity of psoriatic lesions, but it has been proven that psoriasis patients are fed a diet with a low n-3 content (Kanda et al., 2020). The omega-3 fatty acid EPA, which acts as an inhibitor by competing with AA in the phase of conversion of AA to PGE2 and LTB4 in the phospholipids in the membranes, aims to prevent arachidonic acids from causing prostaglandin-induced inflammation (Duarte et al., 2012). Although this mechanism is fully known, studies on n-3 are criticized for being both incomplete and inconsistent (Wolters, 2005). In an uncontrolled study, some of the psoriasis patients were told to consume 170 grams of white fish and some of them oily fish. As a result of 6 weeks from the beginning, no improvement was observed in those who consumed white fish and a significant improvement was observed in those who consumed oily fish. Benefits have been reported in only one of 4 studies in which oral omega-3 supplements were given. Nevertheless, it is generally emphasized that omega-3 fatty acids have an anti-psoriatic effect (Kanda et al., 2020). In another study, it was observed

that the secretion of IL-12, IL-23, IL-6 was decreased and the stimulation enabling Th1/Th17 differentiation was decreased in dendritic cells treated with DHA. The study, where mice were given a diet rich in DHA, concluded that the inflammation caused by the Th17 lymphocyte had improved.

6.4. Vitamins and Minerals

Vitamin and mineral deficiencies can be seen in psoriasis patients because of malnutrition due to the presence of an inflammatory condition as well as malnutrition (Duarte et al., 2012; Ford et al., 2018; Kanda et al., 2020). In addition, supplements of some vitamins and minerals can alleviate the symptoms of psoriasis. All information has been obtained by searching the current literature.

Folic Acid (Vitamin B9)

The connection of folic acid supplements with psoriasis patients is not fully known due to the lack of literature (Duarte et al., 2012). Increased homocysteine level is a risk factor for cardiovascular disease. In addition, this molecule is thought to trigger endothelial damaged by the accumulation of asymmetric dimethylarginine, a natural nitric oxide synthase inhibitor. The reduction of nitric oxide, which is protective against thrombosis and atherosclerosis, may increase aortic stiffness and other endothelial dysfunction. In a meta-analysis study, it was found that hyperhomocysteinemia and folate deficiency was observed in psoriasis patients (Tsai et al., 2019). This study was conducted with patients not using methotrexate medication because methotrexate has been reported to be effective on

homocysteine and folate levels. Homocysteine is an amino acid that is recycled to methionine through methylation in the presence of vitamins B9 and B12 (Spector et al., 1980). High homocysteine levels cause cardiovascular diseases such as stroke and peripheral vascular diseases (Tsai et al., 2019). Psoriasis is also linked to metabolic syndrome and cardiovascular disease. Psoriasis and cardiovascular diseases both have common pathogenesis involving various inflammatory cells and mediators such as C-reactive protein, tumor necrosis factor-α, Th17 cells, and interleukin-17A. In a recent meta-analysis of randomized, placebo-controlled studies, it was not found that the incidence of myocardial infarction was reduced in patients given homocysteine levels and vitamin B6, B9 or B12 supplements alone or in combination, but it was observed that it prevented stroke (Martí-Carvajal et al., 2017). Inflammation in the intestinal mucosa seen in psoriasis patients may cause folic acid malabsorption (Tsai et al., 2019). Since the literature on this subject is insufficient, no definitive conclusions can be reached regarding what causes hyperhomocysteinemia in psoriasis and the effect of folic acid and cobalamin supplementation in reducing the risk of cardiovascular disease in psoriasis patients. Therefore, more clinical studies are needed.

Vitamin B12

Cobalamin (Vitamin B12) is synthesized only by bacteria and is abundant in foods such as animal organ meats (especially liver and kidney), fish, milk and eggs (Kanda et al., 2020,9). Cobalamin is an

important vitamin that participates in biochemical reactions taking place in the human body as a coenzyme (Wolters, 2005). Adenosylcobalamin plays an active role in this biochemical reaction as the coenzyme of the methylmalonyl-CoA mutase, which enables the transformation of methylmalonyl-CoA into succinyl-CoA formed as a result of the citric acid cycle. This biochemical reaction is very important in the deformation of single-chain fatty acids and branched-chain amino acids. This vitamin may have an effect on psoriasis due to its role in nucleic acid synthesis. In addition, other studies have shown that vitamin B12 has an immunomodulatory effect on T cells and cytokines. Vitamin B12 suppresses the production of IL-6, IL-10, IL-1β n, and TNF-α, and protects many cells from inflammatory oxidative stress by reducing nitric oxides and ROS (Kanda et al., 2020). Vitamin B12 was found to be low in psoriatic lesions, this situation attracted the attention of researchers and led to the emphasis on the use of cobalamin in psoriasis (Ricketts et al., 2010). In a randomized, prospective clinical study, a group of 13 patients with chronic psoriasis to be administered twice daily for 12 weeks received a vitamin B12 cream containing avocado oil and calcipotriol cream was used in other patients (Stücker et al., 2001). A significant improvement has been observed with the use of both creams. However, recovery was slower in the group using vitamin B12 cream. In another study, one group was treated with high-dose vitamin B12 supplements and the other with a placebo (Ford et al., 2018). As a result of this study, it has been proven that high doses of vitamin B12 are ineffective. However, it is thought that vitamin B12 may be

effective in combined micronutrient treatment in plaque psoriasis. Another study compared a group of psoriasis patients treated with low-dose methotrexate and psoriasis patients who received a combination of vitamin and mineral supplements in addition to low-dose methotrexate for 3 months (folic acid, magnesium, iron, zinc, copper, manganese, selenium, chromium, iodine, A, D E, K, C, B1, B2, B3, B6, and B12). Combined micronutrient supplements have been noted to reduce the severity of psoriasis. However, this result is based on only a small study.

Vitamin D

Vitamin D is a vitamin produced from 7-dehydrocholesterol by skin that is moderately affected by solar ultraviolet (UV) B rays (Wolters, 2005). 1,25-dihydroxyvitamin D3, the active form of vitamin D, affects many tissues via the receptor (Madden et al., 2020). As keratinocytes, the skin is the most important tissue affected by calcitriol. *In vitro* studies report that calcitriol inhibits the proliferation of human keratinocytes and has anti-proliferative and pro-differentiating effects (Duarte et al., 2012). The vitamin D requirement in humans is met in two ways; Consumption of foods that are sources of vitamin D, such as cod liver oil, swordfish, salmon, tuna, sardines, beef liver, eggs, or cheese, and skin exposure to UVB radiation for 15-20 minutes (Kanda et al., 2020). A relationship has been established between the worsening of psoriasis in winter and the decrease in seasonal UVB radiation exposure (Madden et al., 2020). In addition, since there is a high risk of non-melanoma skin cancer in

psoriasis patients, it is recommended to pay attention to sun exposure and not exceed the recommended time. It is claimed that 1,25-dihydroxyvitamin D3 inhibits keratinocyte proliferation and reduces T cell proliferation by triggering dendritic cell activity and activating regulatory T lymphocytes (Tregs). In addition, vitamin D may regulate intracellular calcium levels, in which case it is discussed on the possibility that vitamin D may have an effect on epidermal development. Vitamin D is an important modulator that plays a central role in inflammation (Kanda et al., 2020). Vitamin D reduces the differentiation and maturation of dendritic cells, the production of IL-17A, IL-22, and the synthesis of TNF-α, IL-1β, IL-6, IL-8 cytokines. In a placebo-controlled study conducted in Norway, psoriasis patients were given oral vitamin D supplements (Madden et al., 2020). It was thought that there was a negative relationship between low vitamin D levels and high CRP levels. In a randomized placebo-controlled study of 41 patients with moderate to severe psoriasis, 1 μg of 1-α-hydroxyl vitamin D3 supplement was administered for 12 weeks (Siddiqui & Al-Khawajah, 1990). There was no difference in PASI scores between the placebo group and the two groups that received D3 supplements. Although it is known that oral 1,25-(OH)2-D3 treatment has curative effects in psoriasis, it should be kept in mind that it has potential side effects in hypercalcemia, hypercalciuria and kidney stones. Low serum vitamin D levels seen in psoriasis patients are associated with the severity of psoriatic lesions (Ford et al., 2018). However, the insufficiency of studies on this subject causes uncertainties in the use of vitamin D supplements.

Vitamin A

Food sources of vitamin A (retinol) in abundance are liver, fish, eggs, and butter (Kanda et al., 2020). Beta-carotene is a pro-vitamin A that converts to vitamin A after intestinal absorption. It is found in yellow-green vegetables such as carrots, spinach, tomatoes, sweet potatoes, peppers, broccoli, melons, oranges, and pumpkins. There are two retinoid receptor families, retinoic acid receptors and retinoid X receptors (Ricketts et al., 2010). And each family has subtypes a, and γ. Through these receptors, retinoids normalize hyperproliferative keratinocytes and hyperproliferation and stimulate terminal differentiation. Studies show that retinoids have a significant effect on psoriasis (Kanda et al., 2020). Retinoic acids have been shown to reduce T cell formation and TNF-α synthesis. Reports on serum vitamin A levels in psoriasis patients contradict each other (Ricketts et al., 2010). Some studies report that serum vitamin A levels are low in psoriasis patients, while some studies indicate that there is no difference in serum vitamin A levels in psoriasis patients and non-patients.

Selenium

It has been found that the level of selenium is generally low in patients with psoriasis (Ricketts et al., 2010). Selenium is a trace element with UVA and UVB protective, antioxidative and immunoregulatory effects (Kanda et al., 2020; Ricketts et al., 2010). It is found in abundance in foods such as eggs, fish and shellfish, pumpkin and poultry (Kanda et al., 2020). Selenium has a direct effect on the

immune system (Ford et al., 2018). It is known that high and low doses of selenium have an inducing effect on DNA synthesis inhibition and cell proliferation (Ricketts et al., 2010). Such as selenium, glutathione peroxidases (GPxs), or thioredoxin reductases (TrxRs) selenium-containing proteins are involved in many biological reactions through selenoproteins (Kanda et al., 2020). Gpx is the enzyme that reduces reactive oxidative stress. Selenium and selenoproteins play a role in inflammation by affecting eicosanoid production (Kanda et al., 2020). In a study, 69 patients were given 600 µg selenium supplement to one group every day for 12 weeks and 600 IU vitamin E supplement in addition to 600 µg selenium to the other group (Fairris et al., 1989). As a result of the study, it was observed that there was no change in the severity of psoriasis and no side effects in both groups. Combination antioxidant supplementation is thought to be effective in patients with severe erythrodermic or arthropathic psoriasis (Ricketts et al., 2010). In another study, a double-blind and placebo-controlled study of 58 patients was conducted to observe the effect of the combined supplementation of selenium aspartate, coenzyme Q10, and Vitamin E for the treatment of severe erythrodermic and arthropathic forms of psoriasis (Kharaeva et al., 2009). A statistically significant improvement was noted in the results of the PASI and Severity Score with this combination of antioxidants. Additionally, a decrease in oxidative stress was found as a result of this study.

7. NUTRITION INTERVENTION IN PSORIASIS DISEASE

Considering the comorbidities seen in psoriasis, nutritional disorders underlie the development of these diseases (Ricketts et al., 2010; Festugato, 2011; Debbaneh et al., 2014; Kaçar et al., 2014; Ford et al., 2018). Especially in the form of the Western diet, a diet consisting of high calories, high fat and sugar seems to be effective in psoriasis severity. However, adaptation of patients to changes in their diet and finding these changes as safe and natural will increase the positive effect of medical nutrition therapy (Barrea et al., 2020). In the light of the researches, the positive effects of the Mediterranean diet, Gluten-free diet, Low-calorie diet and Ketogenic diet have been determined.

7.1. Mediterranean Diet

Findings obtained from the literature research show that adherence to a healthy diet reduces the risk of inflammation in the long term (Barrea et al., 2016; Zuccotti et al., 2018; Madden et al., 2020). It is observed that healthy eating programs with a high content of fruits and vegetables, in particular, provide low inflammation with biomarkers such as low CRP levels (Barrea et al., 2016). The opposite of this healthy diet, which includes high-energy, low-nutritional, processed foods, triggers inflammation and increases CRP levels. The traditional Mediterranean diet (MD) is a healthy diet with lots of green and yellow vegetables, salads, legumes, vegetable dishes such as bread, pasta, fruits and nuts, and grains that are very high in antioxidants and polyphenols (Zuccotti et al., 2018). The consumption of dairy products, fish and poultry is moderate, and consumption of

wine, red meat and eggs is limited (Barrea et al., 2016). Extra virgin olive oil (EVOO) is the most used oil source. The Mediterranean diet includes a number of anti-inflammatory mediators such as antioxidants, polyphenols and the monounsaturated fatty acid contained in extra virgin olive oil, and is a very tasty and healthy diet that is suitable for this diet in the long term (Madden et al., 2020). Animal fats such as butter, cream, and lard are not included in this diet (Barrea et al., 2016). High MUFA intake is associated with low consumption of animal fats, reduced risk of coronary heart disease, prevention of various types of cancer, modification of immune and inflammatory responses, and reduced risk of osteoporosis. Many studies support this thesis (Barrea et al., 2016; Martí-Carvajal et al., 2017). There is evidence that the Mediterranean diet will be beneficial for psoriasis patients (Martí-Carvajal et al., 2017). In the foods that make up MD, the presence of nutritional components such as-carotene, zinc, selenium, vitamin C and vitamin E and flavonoid compounds with important antioxidant effects affect CRP levels and clinical severity in psoriasis patients. Flavours such as garlic, onion, and herbs, which are widely used in the Mediterranean diet to increase flavour, contain large amounts of flavonoids or allicin, are effective in inflammation and have positive contributions in cardiovascular and neurocognitive diseases (Barrea et al., 2016). In a study conducted by researchers, 49 male and 13 female patients participated and the relationship between adherence to the Mediterranean diet and psoriasis severity was investigated using the PREDIMED questionnaire, which measures Mediterranean eating habits (Barrea et

al., 2015). Psoriasis Area and Severity Index (PASI) score shows that there is a significant correlation between these two variables. It has been found that psoriasis patients have low compliance with the Mediterranean diet. It was observed that they consumed more red meat compared to the control group. This study examining the relationship between adherence to the Mediterranean diet and the severity of psoriasis reported a strong relationship between higher EVOO consumption and lower psoriasis severity. In summary, the rich food variety of the Mediterranean diet has a protective effect against psoriasis and other chronic inflammatory diseases (Barrea et al., 2016). It is thought that encouraging the Mediterranean diet in patients who are willing to change their eating habits because their quality of life decreases will provide improvement in disease symptoms (Barrea et al., 2015).

7.2. Gluten-free diet

Many studies show that the gluten-free diet alleviates the clinical symptoms of psoriasis, that there is gluten sensitivity in psoriasis patients and is associated with celiac (Michaëlsson et al., 2000; Addolorato et al., 2003; Duarte et al., 2012). However, studies are insufficient and contradictory (Addolorato et al., 2003). The relationship between celiac disease and psoriasis has been tried to be explained by the similar cytokines they produce (Duarte et al., 2012). Th1 is very important in the pathogenesis of both diseases (Ricketts et al., 2010). Th1 cells, which play a key role in psoriasis pathogenesis, produce IFN-c and IL-2 (Wolters, 2005). It was observed that they

produced similar cytokines as a result of *in vitro* administration of gluten to T cells from celiac patients (Duarte et al., 2012). Increased cytokines in serum can induce celiac disease or increase susceptibility to psoriasis. The case report describing improvement in psoriatic lesions after starting a gluten-free diet proves a link between celiac disease and psoriasis (Michaëlsson et al., 2000). Higher levels of anti-gliadin IgA antibody (AGA) are observed more frequently in psoriasis patients without celiac disease compared to healthy individuals (Kolchak et al., 2017). One study included 97 patients, 13 of them patients had high AGA levels. These patients underwent a dietitian counselling GFD and a significant decrease in PASI scores was observed. In another case, he was diagnosed with celiac disease as a result of the findings he showed one year after the diagnosis of psoriasis (Addolorato et al., 2003). Gluten-free diet therapy was recommended, but the patient did not fully implement it. Subsequently, in addition to the persistence of psoriatic lesions, low serum vitamin and mineral levels were observed. As a result of the examinations, it was determined that malabsorption was present and gluten-free diet therapy was initiated. This time, with the patient's full compliance with GFD, an increase in serum vitamin D levels was observed as well as improvement of gastrointestinal symptoms. It was observed that psoriatic lesions disappeared after 1 month of gluten-free diet therapy. In another study, 30 psoriasis patients with high Ig A levels were administered gluten-free diet therapy for 3 months in addition to therapeutic treatment (Michaëlsson et al., 2000). A positive difference was observed in the PASI scores of all patients after 3

months of gluten-free diet therapy. It was noted that psoriatic severity increased in 18 of 30 patients with the cessation of gluten-free diet in the 6th month.

7.3. Low calorie diet

There is a bidirectional link between psoriasis and obesity, which affects each other (Zuccotti et al., 2018). Increased body mass causes increase in the incidence of psoriasis and the severity of clinical symptoms in psoriasis, and decreases the response to treatment (Zuccotti et al., 2018; Barrea et al., 2020). All of these can be caused by the pro-inflammatory effects of body fat (Ford et al., 2018). The National Psoriasis Foundation Medical Board has published a systematic review of dietary recommendations for adults with psoriasis or psoriatic arthritis, reporting that it is very important to reduce body weight with a hypocaloric diet in psoriatic patients who are overweight and obese. It provides significant improvement in psoriatic lesion severity in overweight or obese psoriasis patients through weight loss, reduced fat mass and visceral tissue as a result of a personalized hypocaloric diet (Zuccotti et al., 2018). Weight loss with diet refers to losing weight with the effect of diet change, not through exercise or surgery (Ford et al., 2018). In dietary weight reduction interventions, weight reduction with a hypocaloric diet, that is, a diet that gives less energy than an individual's daily expenditure, provides positive effects in psoriasis patients. The effect of calorie restriction in psoriasis patients has been examined in many studies; however, none of them provided evidence that calorie restriction is

beneficial for a long time (Ricketts et al., 2010). The energy content of hypocaloric diets ranges from 800 to 1400 kcal per day, and the duration of the diet should be in the range of 16 weeks to 6 months to observe a reduction in the severity of lesions (Ford et al., 2018). In addition, dermatological quality of life can be maintained for up to 1 year after this intervention. In order to examine the effect of the hypocaloric diet on disease symptoms, the researchers gave a low-calorie diet (1000 kcal/day) for 24 weeks on 262 overweight/obese psoriasis patients receiving anti-TNF-a treatment, and a normal diet to the control group (Al-Mutairi,& Nour, 2014). Patients in the hypocaloric diet group showed improvement in clinical manifestations of psoriasis and greater reduction in weight loss compared to controls fed a normal diet. Another study included 303 overweight/obese patients with psoriasis was conducted to examine the effects of physical exercise combined with diet therapy on weight loss (Naldi et al., 2014). The patients were divided into two groups: one group was given simple information about the positive effects of weight loss in psoriasis, the other group was given a diet plan with 20 weeks of exercise. As a result of the study, more improvement was observed in psoriatic findings compared to the PASI scores of the group exercising with diet. Prescription of targeted individual dietary interventions along with medical treatments in psoriasis patients is currently recommended (Ford et al., 2018).

7.4. Ketogenic diet

Recently, ketogenic diet has been used as an intervention in various diseases such as obesity, overweight, type 2 diabetes mellitus and cardiovascular diseases (Barrea et al., 2020). The most important step in the ketogenic diet is carbohydrate restriction. It is usually reduced to 30-50 g/day (Muscogiuri et al., 2019). For this reason, in the first 3-4 days of the ketogenic diet, glucose is produced in the body through glycogenolysis and gluconeogenesis. Free fatty acids are released from adipose tissue as a result of biochemical processes that occur due to low glucose and insulin levels. The anti-inflammatory effect and antioxidant activity of ketone bodies that occur during ketogenesis decreases oxidative stress and ROS production (Barrea et al., 2020). When many studies are reviewed, it is recognized that a low-calorie ketogenic diet is a successful method and treatment option for psoriasis (Castaldo et al., 2020). This diet program is safe, feasible and highly adaptable, and the reduction of cardiovascular diseases leads to deterioration of the inflammation state. Literature sources show that ketosis and weight loss develop, adiposity decreases, glycaemic control and insulin sensitivity improve in individuals who receive ketogenic diet therapy (Castaldo et al., 2016; Barrea et al., 2020; Castaldo et al., 2020). In addition, the ketogenic diet is said to have more anti-inflammatory effects compared to other diets (Barrea et al., 2020). In a case report prepared, the efficacy of a very low calorie ketogenic diet (VLCKD) was investigated in regenerating the response to systemic therapy in recurrent plaque psoriasis (Castaldo et al., 2016). In this case, after low calorie ketogenic diet therapy, the

patient lost a significant amount of weight (12% of initial body weight) and decreased visceral adiposity. In addition, a higher rate of improvement in psoriatic findings was observed as a result of the PASI score (Castaldo et al., 2016). The effects of the ketogenic diet were observed by clinical data of 30 psoriasis patients before and after programmed diet (Castaldo et al., 2020). As a result of the treatment, there was a significant improvement in PASI scores. In addition, it was found that the low B12 and folic acid levels before the diet increased. With the ketogenic diet, patients lost approximately 10% of their initial body weight.

8. CONCLUSION AND RECOMMENDATIONS

Psoriasis' prevalence is increasing worldwide, seriously reduces the quality of life of patients. Although it has many risk factors, comorbidities and risks related to nutrition are more prominent than others. Comorbidities such as obesity and metabolic syndrome increase the severity of psoriasis since they are directly linked to inflammation. Inflammation is central to the pathogenesis of psoriasis. Simple sugars and saturated fatty acids cause increased inflammation. Omega 3/Omega 6 fatty acids, selenium, vitamin D, vitamins B12 and B9 can be given as examples of nutrients that reduce the inflammation. Considering the stimulating and regulating effect of foods and diet on psoriasis, nutritionists should examine the current diets of psoriatic patients and, if deemed necessary, personalized diet plans should be arranged and the patient should be encouraged. In addition to the appropriate calorie and balanced nutrition program, it

should be explained which foods should be consumed less or frequently. Low-calorie diets can be recommended for obese patients to lose weight. Supplements may be considered in patients with low serum vitamin D and selenium. A healthy and balanced diet is seen as an important factor for the elimination and progression of psoriasis. In order to alleviate and improve the symptoms that reduce the quality of life, it is necessary to stop or reduce the inflammation with nutrition along with medication. The Mediterranean diet moderately alleviates the clinical findings in many patients due to its high content of antioxidants, polyphenols and anti-inflammatory foods. Moreover, this diet has a very high applicability, at the same time, its taste compatibility is more appreciated than other diets, and so positive results have been obtained. Ketogenic diet can directly reduce the inflammation in the body by providing rapid weight gain in obese or overweight patients. In general, the nutritional status of psoriasis should be examined and an appropriate diet should be applied in addition to the medical treatment. However, most patients, doctors and nutritionists do not have enough information about how medical nutrition therapy should be applied and how important this treatment is. In this point, because of lack in clinical studies on nutrition in psoriasis patients, the evidence-based research is more needed.

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CHAPTER 4

SEPTIC ARTHRITIS OF THE NATIVE JOINT AND SEASONALITY

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INTRODUCTION

Septic arthritis (SA), one of the causes of monoarticular arthritis, is the infective picture of the joint cavity and soft tissues around the joint due to bacterial, viral, or fungal microorganisms.

Bacteria are the most common cause of microorganisms (Cullu, 2012). Staphylococcus aureus is the most common organism isolated from synovial fluid cultures in multiple prior studies worldwide and has been associated with poorer joint outcomes compared with other organisms (Fort, 2020).

Most cases of SA are caused by hematogenous involvement of a joint in the presence of bacteremia. Less commonly, it is caused by the spread of soft tissue infections around the joint adjacent to the joint.

As the factors causing infection in the joint; It was stated that open fractures or dislocations, arthrocentesis or intra-articular injection may be performed (Goldenberg et al. 1976).

1. SYMPTOMS AND SIGNS

In patients with septic arthritis, there is joint involvement in addition to the general clinical picture of infection. Features of joint involvement are clear guides for clinical suspicion. In addition to general symptoms such as increased fever, fatigue, inability to use extremity, swelling in the joint, increased warmth and redness, tenderness with palpation in the joint, and limitation in the range of motion of the joint constitute the basic local findings.

It should be kept in mind that these local findings differ according to the joint involved. For example, in hip joint involvement, the patient tends to keep the hip in mild flexion, abduction, and external rotation while trying to provide relief by expanding the joint volume, while in knee joint involvement, it tends to keep it in slight flexion.

In cases with delayed diagnosis or inadequate treatment, irreversible joint damage can occur within a very short time and may result in the death of the patient (Kane et al. 2014).

2. LABORATORY FINDINGS

Among laboratory findings, increased white blood cell count (WBC) and erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are findings that support septic arthritis.

According to Kocher et al., the presence of infection; Fever above 38.5, unable to step on the extremity, erythrocyte sedimentation rate above 40mm/t, and white blood cell count above 12000 cell/ml.(Kocher et al. 1999).

3. JOINT ASPIRATION AND SINOVIAL LIQUID EXAMINATION

Aspirating of increased synovial fluid is the way to be followed in a diagnostic approach. Microbiological and biochemical examination of the fluid taken is guiding in terms of both diagnosis and treatment.

On macroscopic examination of the aspirate, it is seen that it has a cloudy, yellow-green, and dense appearance. It is observed that the glucose value is less than 50% compared to serum, with values above

50000 cells/ml in cell count and the percentage of neutrophils greater than 80%. The microorganism that grows can be detected by performing an aspirate culture (Kolinsky et al. 2018).

4. RADIOLOGICAL METHODS

Radiological examinations; It can be used to support the diagnosis of septic arthritis or in case of doubt in the diagnosis, as an auxiliary diagnostic method. They have no use as a definitive diagnostic method.

4.1. Direct Radiography:

Although it has no diagnostic specificity, periarticular soft tissue swelling is a noteworthy finding. Subluxation or even luxation may be observed in pediatric cases, especially in the hip joint (Krogstad, 2018).

4.2. Ultrasonography:

It may show the increase of intra-articular synovial fluid. However, it does not provide detailed information about the character of the liquid. Requiring experience is a disadvantage while being a guide while performing aspiration is one of the indications for use (Krogstad, 2018).

4.3. Magnetic resonance imaging (MRI):

It can provide detailed information about the intra-articular synovial fluid increase and surrounding soft tissue (Krogstad, 2018).

4.4. Scintigraphy:

Bone scintigraphy can provide important information in the early period. It has a diagnostic value especially in cases with multiple focused involvements (Krogstad, 2018).

5. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of septic arthritis is broad and may include gout, pseudogout, trauma, hemarthrosis, rheumatic fever, rheumatoid arthritis, spondyloarthropathies, osteomyelitis, viral arthritides, septic bursitis, and Lyme disease (Mathews et al. 2018).

In addition to these diseases, transient synovitis, Juvenile Rheumatoid arthritis, Kawasaki's syndrome, rheumatic fever, avascular necrosis, femoral head epiphysis slippage, tumoral lesions can be counted.

6.TREATMENT

Early diagnosis and subsequent medical and surgical intervention prevent the articular cartilage from deteriorating, so it is of great importance to prevent permanent disability (Mathews et al. 2010).

Components of management include early recognition and treatment, with joint aspiration, antibiotics, and orthopedic surgery consultation for possible operative management (Oztuna, 2010; Patti et al. 1994).

Intra-articular infective fluid should be drained. For this, drainage can be provided by repeated aspiration or surgically (by arthroscopic or arthrotomy). Antibiotherapy can be determined according to gram staining and culture characteristics. In the treatment, together with the cleaning of the joint from microorganisms, the protection of the

anatomical structures and the rehabilitation of the extremity including the relevant joint are linked to the treatment result (Shirtliff et al. 2020).

7. SEASONALİTY OF SEPTİC ARTHRİTİS

Although the risk factors for developing septic arthritis are well known; Our information about seasonal frequency is limited.

Uckay et al. In their study investigating the seasonal frequency of osteoarticular infections; Reported the results of 159 septic arthritis and 91 prosthetic joint infections cases. The authors reported that there is no difference in seasonal frequencies of infection cases in both groups (Uçkay et al. 2015).

In a study about the seasonal frequency of infection after total joint replacement; when compared with winter and spring, it is stated that the frequency of infections is statistically higher in the summer and fall months. (Weston et al. 1999).

Based on the insufficient literature on the subject, it was aimed to retrospectively evaluate the prevalence of septic arthritis cases in our clinic throughout the year according to the seasons and to share the experience of our clinic in order to contribute to the limited literature on this subject.

7.1. Patients And Methods

The design and protocol of this study were approved by the institutional review board (IRB) of Istanbul Education and Research Hospital (IRB number; 2694/ Date;22.01.2021). This retrospective

study was conducted by evaluating the records of 26 patients (17 male, 9 female) treated for septic arthritis at the mentioned hospital between January 2015 and December 2020.

Patients diagnosed with septic arthritis with a minimum of 1-month follow-up (for surviving patients) and available demographics and medical records were included in this study. The overall information and complete health history were obtained from the medical history. The demographic data comprised of age, gender distribution, joint and side with septic arthritis.

7.2. Statistical analyses

IBM SPSS Statistics software, version 20.0 (IBM Corp., Armonk, New York, NY, USA), was used for statistical analysis. A $p < 0.05$ was regarded statistically significant. Descriptive statistical methods (mean, standard deviation, frequency, ratio) were used. In the comparison of the groups, besides the student's t-test, one-way or multi-directional variance analysis (ANOVA) was used when necessary.

7.3. Results

26 patients whose information was obtained after scanning the archives and records were included in the study. The average age of the patients was 52,7 years (range 6-79). 17 (65.4%) of the patients were male, 9 (34.6%) were female.

When joint involvement was examined, knee joint involvement in 22 (84%) patients, hip in 2 (8%) patients, elbow in one (4%), and

shoulder joint involvement in one (4%) patient were detected (Figure 1).

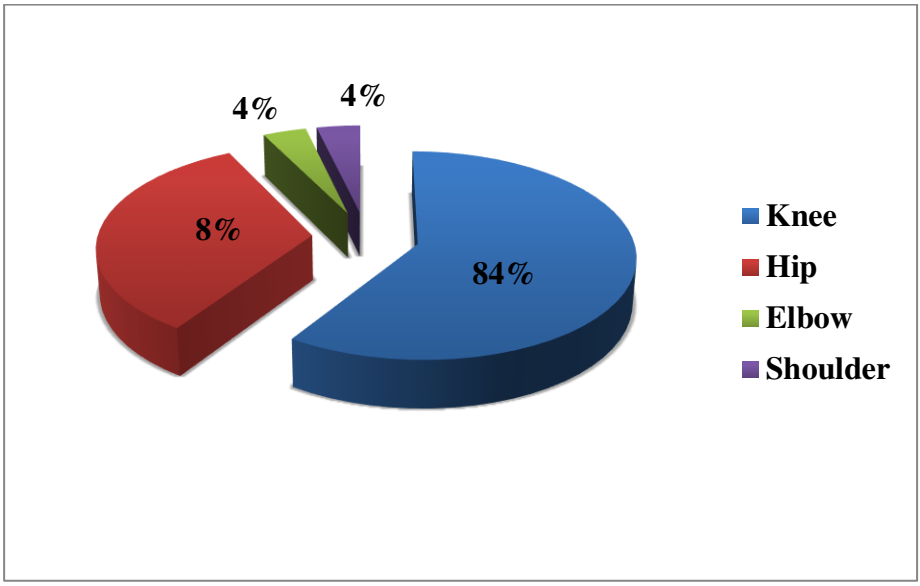

Figure 1. Percentage of joints involved in patients with septic arthritis.

24 of the patients had lower extremity involvement and 2 had upper extremity involvement. In the surgical treatment applied to the patients, 11 patients underwent open arthrotomy and drainage, and 15 patients underwent arthroscopy and drainage. Considering the application seasons of the patients; It was determined that 7 (27%) patients had involvement in winter, 6 (23%) patients in spring, 5 (19%) patients in summer, and 8 (31%) patients in autumn and applied for treatment. (Figure 2 and 3). There was no statistically significant difference between septic arthritis and seasonality ($p > 0.05$).

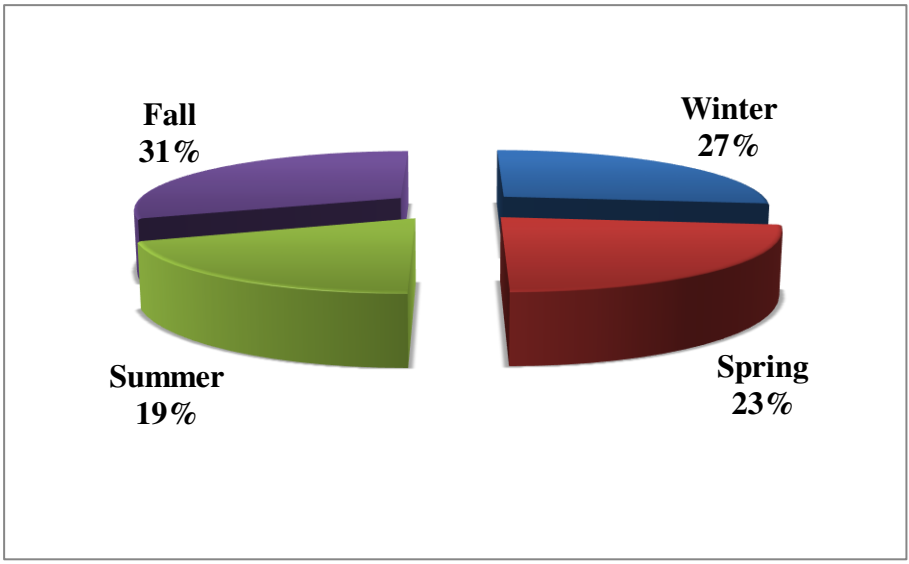

Figure 2. Seasonal percentages of patients diagnosed with septic arthritis.

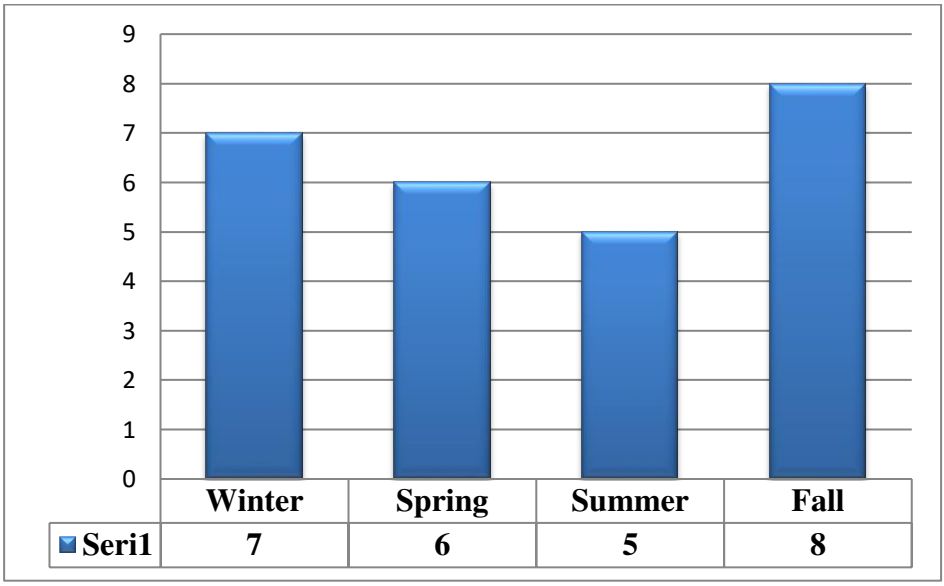

Figure 3. Number of patients by seasonal period.

7.4. Discussion

Although septic arthritis is a well-known disease that requires urgent treatment; Whether it differs according to seasonal periods is not yet clear in the literature. In the present study, although the number of patients was limited, no seasonal frequency was found in septic arthritis. Considering the application seasons of the patients; It was observed that 27% of the patients occurred in the winter season, 23% in the spring, 19% in the summer, and 31% in the autumn. It was observed that it showed an even distribution in all four seasons.

In a recent study on this subject, the authors; It found that the total number of infections per season accumulated over the 8-year study period was 119 in spring, 129 in summer, 95 in autumn, and 112 in winter, which did not reflect any significant seasonal fluctuations. None of the different infection subgroups, namely arthroplasties, hematogenous arthroplasty infections, and arthritis, indicated no seasonal fluctuations. Stated that they concluded that osteoarticular infections, including hematogenous prosthetic joint infections, did not show a significant seasonality (Uçkay et al. 2015). In our study, the case is Uckay et al. similarly, it was found that there was no seasonal relationship in septic arthritis cases.

7.5. Study Limitations

The present study had some limitations. One was its relatively small sample size, which limited the power of the results. Another limitation was that the patients were comorbid, whether there was trauma, or whether there was any other infective focus.

CONCLUSION

Although there is no statistically significant difference between the incidence of septic arthritis cases and seasonality, studies with larger patient groups are needed on this subject.

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CHAPTER 5

PREVALENCE OF DEPRESSION AND ANXIETY DISORDERS AMONG URO-ONCOLOGY CANCER PATIENTS

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INTRODUCTION

Depression and anxiety are the most common psychological illnesses seen among cancer patients (García Montes et al., 2020). Although these disorders are common among cancer patients, there is limited information in the literature for occurrence in urooncology cancer patients. In the studies conducted, important data have been obtained for the relationship of psychosocial supports in the treatment of cancer disease, decreasing the levels of depression and anxiety, and increasing the quality of life (Leite et al., 2015). Cancer is the most serious disease affecting patients' physical and psychological well-being (Wondie et al., 2020). Cancer disease is a difficult event that causes serious psychological suffering in both the treatment process and the acceptance of the disease. High levels of depression and anxiety occur among patients due to fear of death, hopelessness to treatment, long recovery time, and other concerns (Inhestern et al., 2017). As with other cancer diseases, it is possible that severe psychological symptoms may be seen among patients with kidney cancer, prostate cancer, bladder cancer and testicular cancer, which are types of uro-oncology cancer. Due to the limited data and information in the literature regarding this subject, the purpose of this study is to examine the prevalence of anxiety and depression among uro-oncology cancer patients. In this study, uro-oncology cancer patients include the patients diagnosed with kidney, bladder, prostate and testicular cancers.

METHODS AND MATERIALS

A total of 330 patients with diagnosed kidney cancer (79), bladder cancer (57), prostate cancer (138), and testicular cancer (56) were participated in the study. Each participant has completed the socio-demographic questionnaire, the Hospital Depression and Anxiety Scale (HADS). The socio-demographic form included the patients' personal information including age, marital status, education, income, occupation, chronic disease, health-related questions and type of operation that had been done. The Hospital Anxiety and Depression Scale is a commonly use for the participants to measure anxiety and depression levels. Consisting of 14 items, HADS measures both anxiety (HADS-A) and depression (HADS-D) levels with an equal number of questions. Patients rank the question on a Likert scale ranging from 0 to 3 and the subscale from 0 to 21. A total score of 8 or above was defined as an optimal cut-off score for comfort for both anxiety and depression. Data was analyzed by SPSS statistical package program version 23. In statistical evaluation, student's t-test was used for quantitative variables. The number, percentage, mean, standard deviation was calculated. Logistic regression analysis was used. P value <0.05 was considered for statistical significance.

RESULTS

The mean age of the studied groups was 54.21 ± 11.34 years old. The majority of the participants were above 50 years old (65.1%) and married (79.3%). 66.6% of the participants were below secondary educated, 85.4% of them had low-income and 79.6%

of them were not smoking cigarettes. 86% of the participants had surgery while nearly 61% of them had chronic illnesses.

Table 1: Patient's And Disease Characteristics

	Kidney (n %)	Prostate (n %)	Bladder (n %)	Testicular (n %)
Age				
<50	34 (43)	18 (13.1)	11 (19.2)	52 (92.8)
≥50	45 (57)	120 (86.9)	46 (80.8)	4 (7.2)
Marital Status				
Single	21(26.5)	3 (2.2)	2 (3.6)	32 (57.1)
Married	58 (73.5)	135 (97.8)	55 (96.4)	24 (42.9)
Education				
<Secondary	48 (60.7)	112 (81.1)	43 (75)	17 (30.4)
>Secondary	31 (39.3)	26 (18.9)	14 (25)	39 (69.6)
Income				
Enough	18 (22.7)	12 (9.5)	7 (12.3)	10 (17.9)
Not enough	61 (77.3)	125 (90.5)	50 (87.7)	46 (82.1)
Occupation				
Working	32 (40.5)	36 (26.1)	16 (28.1)	48 (85.7)
Not working	47 (59.5)	102 (73.9)	41 (71.9)	8 (14.3)
Smoking				
Yes	8 (10.2)	14 (10.2)	8 (14.1)	37 (66)
No	71 (89.8)	124 (89.8)	49 (85.9)	19 (34)
Surgery				
Yes	67 (84.8)	123 (89.1)	43 (75)	51 (91)
No	12 (15.2)	15 (10.9)	14 (25)	5 (9)
Chronic Illness				
Yes	57 (72.1)	106 (76.8)	32 (56.1)	6 (10.8)
No	22 (27.9)	32 (23.2)	25 (43.9)	50 (89.2)
Total (n=330)	79 (23.9)	138 (41.8)	57 (17.2)	56 (17.1)

In the current study, the prevalence of anxiety symptoms in kidney cancer group was 18 mild, 37 moderate and 24 severe, in prostate groups was 47 mild, 76 moderate and 15 severe, in bladder group was 6 mild, 27 moderate and 24 severe and in testicular group was 7 mild, 23 moderate and 26 severe, respectively. The prevalence of depression symptoms in kidney group was 22 mild, 41 moderate and 16 severe, in prostate group 41 mild, 88 moderate and 9 severe, in bladder group was 12 mild, 26 moderate and 19 severe and in testicular group was 10 mild, 24 moderate and 22 severe, respectively. The average of anxiety symptoms among uro-oncology cancer patients was moderate (47.5%) and the average of depression symptoms among them was moderate (51%). The symptoms of depression are slightly higher than the symptoms of anxiety among the patients.

Table 2: Distribution Of Anxiety And Depression Symptoms In The Cases Regarding HADS Scale

	Kidney (n %)	Prostate (n %)	Bladder (n %)	Testicular (n %)
HADS-Anxiety				
Mild	18 (22.7)	47 (34)	6 (10.6)	7 (12.6)
Moderate	37 (46.8)	76 (55)	27 (47.3)	23 (41)
Severe	24 (30.5)	15 (11)	24 (42.1)	26 (46.4)
HADS-Depression				
Mild	22 (27.8)	41 (29.7)	12 (21.1)	10 (18)
Moderate	41 (51.8)	88 (63.7)	26 (45.6)	24 (42.8)
Severe	16 (20.4)	9 (6.6)	19 (33.3)	22 (39.2)

It was found that there were significant relationships between kidney, prostate, bladder and testicular cancer groups, HADS-anxiety and HADS-depression scores. Anxiety and depression were found stronger predictors of causing psychological disorders among uro-oncology cancer patients.

Table 3: Relationships Between Uro-Oncology Cancer Types And Anxiety And Depression Measured By HADS

					95% CI	
	Covariates	B(SE)	Beta	P value	Lower	Upper
Kidney Cancer	HADS-A	-2.34 (0.40)	-0.63	0.000	-3.15	-1.93
	HADS-D	-1.72 (0.22)	-0.17	0.001	-3.68	-1.78
Prostate Cancer	HADS-A	-2.88 (0.46)	-0.13	0.000	-2.98	-0.74
	HADS-D	0.19 (0.41)	0.08	0.003	-1.57	0.41
Bladder Cancer	HADS-A	1.36 (0.63)	0.33	0.001	0.43	2.91
	HADS-D	-1.52 (0.36)	-0.59	0.000	-1.91	-0.63
Testicular Cancer	HADS-A	-2.96 (0.47)	-0.36	0.003	-2.49	-0.91
	HADS-D	1.23 (0.55)	0.21	0.000	0.53	2.57

HADS: Hospital Anxiety and Depression Scale

DISCUSSION

In the current study, the prevalence of anxiety and depression was high among uro-oncology cancer patients. The frequency of anxiety obtained by HADS-A, was 47.5% moderate and 32.5% severe among all the cancer patients while the frequency of depression obtained by HADS-D, was 51% moderate and 24.8% severe, among all the cancer patients, respectively. There was strong association between anxiety, depression and cancer patients. In the current study, significant relationships were found between uro-oncology cancer patients and

HADS-anxiety and HADS-depression scores ($p<0.005$). A systematic of observational studies about prevalence of psychological problems of cancer patients showed that cancer diagnosis and treatments interact with the anxiety level and psychological state of the patient, affecting the patient's current illness, combating the disease, compliance with treatment and the patient's quality of life negatively (Stacey et al., 2017). It has been reported that there is an increase in psychiatric morbidity among cancer patients and the prevalence of psychiatric diseases has been found to vary in a very wide range of 9-60% (Ochoa et al., 2017). The percentage of anxiety, depression and perceived stress among uro-oncology cancer participants in the current study was considerably higher compared to data in the literature for cancer patients. In the literature, most patients remain anxious due to process of treatment, stage of cancer, thoughts of death, extended hospital stays, and other health complications. The findings of the current study are important to contribute valuable information regarding uro-oncology cancer patients and psychological disorders since there is limited information and findings in the literature.

CONCLUSION

The prevalence of anxiety and depression among uro-oncology cancer patients was high and the statistical significant difference was found. Our research shows the importance of counseling for anxiety and depression to the cancer patients as means of effectively improving their psychological disorders and ultimately improving the quality of medical care provided in the field of uro-oncology.

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CHAPTER 6

AWARENESS AND ATTITUDES OF PATIENTS TO APPLY TO FAMILY MEDICINE FOR PERIODIC HEALTH EXAMINATION IN A THIRD LEVEL UNIVERSITY HOSPITAL SAMPLE

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INTRODUCTION

Periodic health examination (PHE) is the evaluation of healthy individuals at regular intervals using a series of procedures such as history taking, interview, physical examination, and laboratory tests (DiLorenzo et al., 2015). The purpose of PHE is to reduce the risk factors of illnesses and early signs of treatable disease by physicians on a regular basis. The PHE is a way of preventive health practice to reduce the mortality and morbidity of different diseases among people (Duan et al., 2020). Chronic diseases are the cause of death of two out of three people who die every year in the world (Sun et al., 2014). In addition to the increase in the mortality burden of chronic diseases, its effect on the deterioration of people's quality of life and comfort is one of the major problems. Family physicians are in a unique position to assist their population in maintaining and improving their health. The family doctor sees each person nearly 3-4 times a year. Family physicians per capita in Turkey is reported to be 2.9 years the number of applicants (Dikici and Şahin, 2013) Therefore, family physicians provide a great opportunity especially for the elderly people to obtain accessible health-care services. As the elderly people are more vulnerable to chronic diseases, family physicians establish a good relationship and health counseling in terms of prevention of disease as well early diagnosis (Ilesanmi et al., 2015). Many diseases can be diagnosed with the help of periodic health examination such as prostate cancer, bladder problems, kidney disorder, breast cancer, diabetes, hypertension, obesity, and diseases (Gan et al., 2018). With periodic health examination, the diseases can be detected in its early

stages and help decrease progression of later stages. Thus, early progression will save lives as well as decrease the economic burden for patients and communities. Although it is known that there are many screenings and tests performed in the field in family medicine practice, the importance and awareness of the patients about PSM are not sufficiently known. The aim of this study is to determine the knowledge, attitude and behaviors of patients applying to a tertiary university hospital regarding periodic medical examination.

METHODS AND MATERIALS

This descriptive study was carried out with the participation of 350 people determined from the universe by power analysis among those 18 years and older who applied to the Erciyes University Urology Polyclinic for any reason. In this case, the power of the study was obtained as 80%. With the form used in the study, the demographic information of the participants and their Awareness about Periodic Health Examinations to Family Medicine was obtained. Participation in the study was completely voluntary. Research data were evaluated through SPSS 23. Descriptive data are presented as mean, standard deviation, frequency and percentage distributions. The relationship between variables was evaluated using the chi-square test and logistic regression analysis. Statistical significance value was accepted as $p < 0.05$.

RESULTS

In our study with sample size of 350 participants, 215 (61.4%) of them were between 45 and 60, 233 (66.5%) of them were male, 207 (59.1%) of them had low income, 231 (66%) of them were married, nearly a half of the participants 171 (48.8%) were primary educated. The majority of the participants 213 (60.8%) were not smoking and using alcohol 309 (88.2%). Also, many of the participants 237 (67.7%) had no chronic illnesses and 239 (68.2%) of them had no chronic illness in the first- degree relatives. Among the participants, 139 (23.7%) of them applied to public hospital while only 26 (8.6) were applied to private hospital. Among the independent variables, age (p=0.001), gender (p<0.001), income (p=0.003), smoking (p=0.002) and chronic illness (p=0.001) were found statistical significant.

Table 1: Distribution Of Periodic Health Examination Applications With Descriptive Characteristics Of The Participants

		Never applied n (%)	1 or more n (%)	p value	x^2
Age	18-45	12 (13.6)	45 (17.1)	0.001	35.2
	45-60	48 (54.5)	167 (63.7)		
	61 and above	28 (31.9)	50 (19.2)		
Gender	Male	65 (73.8)	168 (64.1)	p<0.001	42.1
	Female	23 (26.2)	94 (35.9)		
Income	less than 2000TL	123 (61.8)	84 (55.6)	0.003	27.1
	more than 2001 TL	76 (38.2)	67 (44.4)		

Marital Status	Single	8 (9.2)	67 (25.5)	0.678	10.87
	Married	75 (85.2)	156 (59.5)		
	Widowed	5 (5.6)	39 (15)		
Education	Primary	46 (52.2)	125 (47.7)	0.432	3.781
	Secondary	27 (30.6)	79 (30.1)		
	High school and above	15 (17.2)	58 (22.2)		
Job Status	Working	56 (63.6)	89 (34)	0.287	4.781
	Not working or retired	32 (36.4)	173 (66)		
Smoking	Yes	61 (69.3)	76 (29.1)	0.002	8.712
	No	27 (30.7)	186 (70.9)		
Alcohol	Yes	7 (8)	34 (13)	0.371	7.412
	No	81 (92)	228 (87)		
Chronic illness	Yes	21 (23.9)	92 (35.2)	0.001	8.322
	No	67 (76.1)	170 (64.8)		
Chronic illness in the first degree relatives	Yes	34 (38.6)	77 (29.4)	0.655	4.112
	No	54 (61.4)	185 (70.6)		
Place to apply for PHE	Public Hospital	-	87 (23.7)	0.235	27.11
	Private Hospital		26 (8.6)		
	University Hospital		139 (39.7)		
	Family Health Center		98 (28)		

PHE: Periodic Health Examination

Among the participants, 88 (25.2%) of them stated that they never applied to a doctor for PHE and 262 (74.8%) of them stated that they applied at least once or more. Among the places, the university hospital was most frequently visited place by the participants 139

(39.7%) while private hospital was less frequently visited one 26 (8.6%). Reasons of PHE were mostly for urinate problems 77 (22.1). The majority of the participants stated other barrier for PHE and 189 (54%) of them were not satisfied for PHE due to various reasons.

Table 2: Practice Of Periodic Health Examination

	n	%
Number of frequency for PHE		
Never	88	25.2
1 or more	262	74.8
Reason of PHEs done		
Kidney problems	45	13
Prostate problems	66	18.8
Urinate problems	77	22.1
Infection problems	64	18.2
Sexuality problems	46	13.1
Other	52	14.8
Satisfaction of PHE		
Yes	161	46
No	189	54
Barriers of PHE		
Physical disability	28	7.1
Financial issues	34	9.7
Not prefer	78	22.2
Other	210	61

Multiple logistic regression analysis, which determines the degree of predicting the status of independent variables to apply to family health center for PHE was presented in Table 3. The statistical significance was found among age, gender, income, smoking and chronic illness ($p<0.005$).

Table 3: Applying to Family Health Center for Periodic Health Examination

	OR (95% CI)	p value
Age	1.09 (0.78-1.78)	0.003
Gender	2.12 (1.70-3.89)	0.001
Marital Status	1.42 (0.88-3.09)	0.615
Education	1.34 (1.26-2.98)	0.123
Job Status	1.10 (0.45-2.56)	0.617
Income	1.38 (1.08-2.59)	0.002
Smoking	1.35 (0.78-2.66)	0.001
Alcohol	1.55 (0.98-3.44)	0.389
Chronic Illness	1.98 (1.39-3.78)	0.006
Chronic Illness in the first degree relatives	1.45 (1.09-2.77)	0.761

DISCUSSION

Periodic health examination is usually a health service performed regularly by primary care physicians. In our country, periodic health examinations are carried out continuously and regularly, and because of the new application, there are not enough epidemiological studies on PHE (Yıldız et al., 2013). More than 20% of the population in developed countries regularly applies for PHE at least once a year to a family health center or doctor (Kelly et al., 2019). This rate is not clearly known in our country. Except for newborn and child check-ups and some cancer screenings from family health centers, there is no periodic health examination (Dikici and Şahin, 2013). The results of this study reported that one-third of the participants never done PHE and many of them reported different barriers for PHE. Also, age, gender, income, smoking and chronic illness were found statistical

significant among the participants' variables. In a study conducted, it was stated that the changes in lifestyles such as reducing smoking and alcohol consumption, regular exercise and healthy diet of people who go to PHE developed positively as a result of motivational interviews on these issues by primary care physicians. In our study, the participants believed that unawareness of the health service and the barriers are most important factors to do PHE in the community. The present study may increase awareness of PHE among the patients and obtain as much as possible benefits from PHE.

CONCLUSION

In Turkey, it is a new practice of family medicine physicians, and information on PSM, although to recognize the behaviors and attitudes that tried to determine how an awareness of the PSM in participating in this study. As a result of the data obtained, the frequency of the participants' applications for PSM purposes and the information on the purpose of their application seems unsatisfactory. It was concluded that most of the participants had insufficient knowledge about what PSM means, they should be informed about family medicine and the importance of PHE should be explained in the community.

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CHAPTER 7

FLUOROSIS AND TREATMENT APPROACHES

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INTRODUCTION

Fluorine is an element of the halogen group with atomic number 9, symbolized by F (Kaminsky et al., 1990; Li et al., 2001). Fluorine, one of the most reactive and electronegative elements, is rarely found in free or elemental form as it reacts rapidly with the surrounding elements(Agalakova and Gusev, 2011). Fluorine, one of the most reactive and electronegative elements, is rarely found in free or elemental form as it reacts rapidly with the surrounding elements (Agalakova & Gusev, 2011). Fluorine, which is found in different proportions in soil, water, atmosphere, plant and animal tissues, is one of the basic elements that participate in the formation of the earth's crust. Fluoride is also the 13th most common naturally occurring element in the earth. (Oğuz, 2013, Yang C, 2017).

Fluoride is present in the atmosphere in small amounts and comes into the atmosphere from a variety of sources. These sources include volcanic gases, industrial processing of fluoride-containing minerals, ocean spray, burnt coal smoke, various industrial processes. (Kaminsky et al., 1990, Bilgin, 2008). The concentration of fluoride ion in surface waters is generally between 0.01 and 0.30 mg / L. The fluoride ion concentration in groundwater depends on the geological, chemical and physical properties of the aquifer, the porosity and acidity of the soil and rocks, the temperature, the movement of other chemical elements and the depth of the wells. Fish and other seafood are rich sources of fluorine due to their presence in sea water. Fluorine is high in hard waters (Beyhan, 2003).

Plants also absorb gaseous fluoride from the air. Fluorine is in organic and inorganic compounds in plants, mostly in tea leaves.The amount of fluoride in a glass of tea is 0.19-0.31 mg. In places with fluorine waters, this amount taken daily with tea can increase to 8-10 mg (Ertürk, 2006). Fluoride accumulates in the bones and shells of animals that eat plants contaminated with fluoride (Bilgin, 2008).

Fluorine is used in medicine, industry and various fields. In some industries, fluorine is used in the production of teflon and in the refrigerator cooling mechanism. In terms of public health, a certain amount of fluoride is required in drinking water and some packaged water.

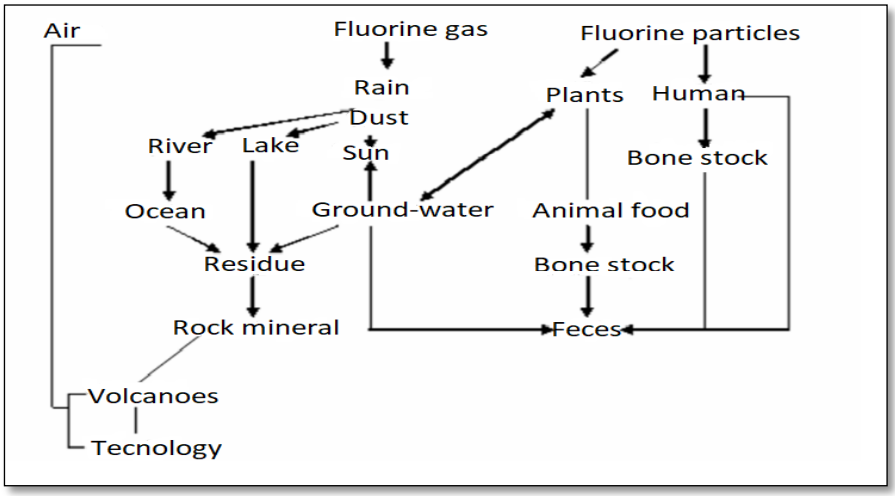

Figure 1: The Cycle Of Fluoride in Nature (Bilgin, 2008).

Long-term exposure to high doses of flora in humans and animals creates fluorine intoxication, namely Florizis. In fluorosis, many organs and tissues, including teeth, bone tissue, are damaged. (Öner, 2020, Song et al., 2014).

It has been stated that most cases of endemic fluorosis occurring in Asia and Africa are caused by drinking fluorinated water (Kharinar et al., 2015). Fan et al. (2015) reported that fluoride can also accumulate in brick tea and that brick tea-type fluorosis is more common in Tibet than in other regions.

Sherwood (2010) states in his study that florisis is a serious danger for India and 6 million children can be seriously affected by this danger. He also stated that most of the fluorosis incidents that occurred in his study were caused by drinking water.

Fluoride is abundant in the environment and can be ingested through a variety of mechanisms. Drinking fluorinated water is the primary cause of world fluorosis, as fluoride dissolves easily in water. Gao et al. (2016) showed in their study that the fluorine in coal is easily released into the atmosphere by burning and then it can be inhaled.

The first study on fluorosis in Turkey, Isparta in 1955 by Prof Dr Ata Pertev and drinking water, more than usual fluorine (4.03 ppm) were detected (Akyüz, 1997). In the studies and fluorosis studies, it has been determined that the fluorine content of the soil is quite high in the volcanic and earthquake regions. In this context, it has been reported that fluorosis is prevalent in the Eastern Anatolia Region, in

the districts of Van and Ağrı, which have a volcanic land structure (Şendil and Bayşu, 1974; Araya et al., 1990).

In later studies, they found a high fluorine ion concentration in Ağrı province Doğubayazıt district and villages, Van province Muradiye and Çaldıran districts and villages, as well as in Eskişehir-Beylikova / Kızılcaören village and Kırşehir-Kaman / Bayındır village where fluorite reserves are located, high fluoride in water, soil and plant samples, and urine samples in sheep that could cause fluorosis (Fidancı et al. 1994, Fidancı et al. 1998).

Fluorine poisoning is seen in two forms as acute and chronic fluorosis due to fluorine intake.

Acute Fluorosis

Acute fluorosis is a rare condition that occurs as a result of excessive intake of some insecticides, pesticides, anthelmintics, sodium fluoride tablets and rodenticides containing fluorine salts or as a result of contamination with sodium fluoride or sodium silicofluoride salt (Heifetz and Horowitz, 1984; Elbek and Sabah 2001).

It is characterized by nausea, vomiting, abdominal pain, diarrhea, dyspnea, increased salivation, tears, frequent urination, and a drop in body temperature (Şanlı and Kaya, 1995). Systemic symptoms are variable and severe, starting within 30 minutes and may continue for 24 hours. Death usually occurs as a result of stroke or heart failure in the respiratory system (Uslu, 1984; Heifetz & Horowitz, 1984).

Acute fluorine poisoning is characterized by sudden loss of appetite, weight loss, rumen atony, weakness, tremor, hyperesthesia, collapse, respiratory failure, and death in ruminants (Aytuğ et al., 1990).

In terms of acute poisoning, especially sodium fluoroacetate and sodium fluoride are considered dangerous compounds. Sodium fluoride, which is mixed with feed at 4-5% for anthelmintic purposes, creates a severe toxic effect. Sodium fluoroacetate and sodium fluoride, which are taken in measures that will cause acute poisoning, can permanently stop the activity of protoplasm and enzymes. Fluorine can lead to death by inhibiting lipase, phosphatase and cholinesterase enzymes with its molecular effect or due to metabolic disorders (Şanlı and Kaya, 1995).

Chronic Fluorosis

In normal conditions pets constantly take fluorinated compounds with feed and water to a extent that does not cause any negative effects. If the daily fluoride intake exceeds the safety threshold in a long period of time, chronic fluoride poisoning occurs. With exposure to high doses of flora for a long time, intoxication called fluorosis occurs in humans and animals (Şanlı and Kaya, 1995).

Chronic fluorosis is characterized by an increase in the amount of fluoride in urine, bones and teeth. In animals, first symptoms include tooth enamel stains and chalky lesions, erosion of tooth enamel, outward bone growth (exostosis) and other bone changes, as well as

systemic effects due to decreased appetite (Sel, 1991, Song et al., 2014; Öner et al., 2020).

Fluorosis and Oxidative Stress

There are several mechanisms that contribute to fluoride toxicity, but oxidative stress is one of the key mechanisms that can initiate fluoride toxicity. Superoxide anion (O_2^-) causes the formation of reactive oxygen species (ROS) such as hydroxyl radicals (OH) and hydrogen peroxide (H_2O_2).

The antioxidant defense system of our body neutralizes the enhanced ROS activity (Barbier et al.2011). Fluoride also forms peroxynitrite (reactive nitrogen species), which, when reacting with superoxide ions and cofactors of metalloproteins that have binding affinity with the thiol molecule, causes ER stress to form nitrosyl adducts that accumulate in the endoplasmic region (Flora et al., 2011).

The high electronegativity of fluoride increases its reactivity and therefore forms strong hydrogen bonds with the –NH and –OH moieties. Therefore, oxidation by various biomolecules can lead to chronic diseases such as cancer, age-related muscle degeneration, fluorosis, and cardiovascular disease (Chouhan et al., 2010).

Treatment Options for Fluorosis

Although there is no specific treatment available for fluorosis yet, its effects can be reversed by withdrawing the fluoride source. In addition, the intake of a diet rich in protein, calcium, vitamins and

other antioxidants may also benefit to some extent. The use of suitable substances with antioxidant properties and the least side effects can effectively solve the problem. Fluoride is a powerful oxidizing agent, treatment strategies have shifted towards the use of antioxidants in recent years.

Good results can be obtained with intravenous calcium infusions in acute fluorine poisoning (Aytuğ et al., 1990). Against the toxic effects of fluoride, giving more calcium than the normal amount of calcium needed by animals reduces the effect of fluorine and protects teeth (Ekambaram & Paul, 2001).

Intravenous administration of NaCl-glucose solutions for treatment, intravenous calcium gluconate injections are also beneficial against tetany, To precipitate the fluoride, a 0.15% Ca (OH) ^{2} solution should be used to lavage the stomach (Goodman and Gillman, 1980).

In chronic cases, frequent parenteral administration of calcium and adding 30 g of aluminum sulphate per animal to feeds every day reduces the accumulation of fluorine by 22% (Aytuğ et al., 1991).

Bulduk et al. (2020) studied the effect of resveratrol treatment on vascular responses caused by chronic fluorosis, showing that resveratrol provides a protective effect against increased blood pressure and potential endothelial damage caused by NaF. The protective effect of resveratrol is due to its capacity to reduce oxidative stress and endothelial tissue damage caused by fluorine.

Blaszczyk et al. (2012) showed in their study that methionine combined with vitamin E could have applications in the treatment of skeletal fluorosis. Methionine and vitamin E can reduce the effects of fluoride on soft tissues and prevent excessive fluoride accumulation in bone.

In a study on fluorosis and antioxidant-rich diet, it was concluded that the administration of calcium, vitamin C, and E may be beneficial based on the increase in lipid peroxidation and decrease in antioxidants in fluorosis (Susheela et al., 2002). In addition, it has been reported that the administration of vitamin C, calcium and vitamin D to young children may be beneficial in preventing fluorosis (Gupta et al., 1996).

Zhao et al. showed that choline attenuates the damage to chondrocyte matrix and degradation enzymes in fluoride-treated mice (Zhao et al., 2016). Choline may reduce fluorine toxicity by affecting the expression of relevant factors. Also, taurine causes restoration of fluoride-induced renal toxicity by enhancing thyroid gland function and renal antioxidant status in rats (Adedara et al., 2016). In addition, there are studies showing that pomegranate (Punica granatum) juice protects against fluoride-induced oxidative damage in liver tissues and erythrocytes of rats (Bouasla et al.2016).

Dey Bhowmik et al. 2020 claims that calcium and vitamin D supplementation gradually transforms fluorinated teeth into near-normal teeth, calcium and vitamin D supplementation effectively

reduce dental and skeletal fluorosis and maintain elemental homeostasis (Dey Bhowmik et al., 2020)

Liu et al. Showed that anti-hyperosteogenic drugs stimulate urinary fluoride and increase bone formation by 95.8% overall effective (Liu et al.2015).

Showing that acupuncture has good effects on the treatment of skeletal fluorosis, Chinese researchers reported that acupuncture improved range of motion and relieved pain caused by skeletal fluorosis (Zhou et al. 2013). Acupuncture has also been shown to stimulate urine fluoride, which is useful for removing fluoride from the body.

Based on the above studies, we understand that drugs to treat fluorosis are aimed at reducing fluoride toxicity in the body and repairing damage to the body by consuming tablets or foods. In addition, we can conclude that the substances given in the studies can lower the level of fluoride that occurs after the fluorosis formed, and even if it is not considered very effective in treatment, it may be successful.

CONCLUCSION

Providing safe drinking water can protect people against fluorosis. There are studies indicating that this material, which is referred to as $CeCO_3OH$ nanosphere, is a very suitable technology to remove fluoride from drinking water quite effectively (Zhang et al., 2016). Improving people's living standards will also help prevent fluorosis. Good living conditions will help people avoid fluoride intake from water, tea, and coal.

Studies in the last few years have shown that intake of calcium, vitamin C, vitamin E, and vitamin D are effective in the treatment and prevention of fluorosis (Shangguan et al., 1995; Ekambaram et al., 20 Konopacka et al., 2004; 01; Das and et al., 2006; Mittal et al., 2007; Błaszczyk et al., 2012; Yüksek et al., 2017; Dey Bhowmik et al., 2020; Öner et al.2020).

As a conclusion and recommendation, nutritional supplements can increase human immunity and contribute to treatment approaches. If these precautionary measures are taken, there will be a decrease in the number of people living in regions where fluorosis is seen at a high rate, endemic fluorosis rates and related diseases.

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CHAPTER 8

CONJUGATED LINOLEIC ACID IN ANIMAL RESOURCE FOODS AND ITS EFFECT ON HEALTH

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INTRODUCTION

Adequate and balanced nutrition, which is a basic need for people to be able to sustain a healthy life and perform their physical and mental functions, has a great importance due to the causes such as its increasing the effectiveness of medical treatment in the cases of illness and being effective alone in the treatment of some diseases. Because of these positive effects, in the recent years, the interest of consumers in the foods called "functional foods", which provide physiological benefits in metabolism other than its nutritive features, and which can reduce the risk of chronical diseases, has increased (Demirok and Kolsarıcı, 2010; Ulus and Gücükoğlu, 2017).

CLA is a group consisting of conjugated positional and geometrical isomers and while the major ones of CLA isomers 9, *cis*-11 (*c*-9, *c*-11); *trans*-9, *cis*-11 (*t*-9, *c*-11); *trans*-9, *trans*-11 (*t*-9,*t*-11); *trans*-10, *trans*-12 (*t*-10, *t*-12) and *trans*-10, *cis*-12 (*t*-10,*c*-12) octadecadieonicacid are, isomers that are present less are *cis*-10, *cis*-11, *cis*-12 and *trans*-12 octadecadienoic acids. It is reported that biologically active isomers of CLA are *cis*-9, *trans*-11 and *trans*-10, *cis*-12 and that a large part of isomers consists of *cis*-9 and *trans*-11 (O'Shea et al 1998; Fritsche and Steinhart, 1998a; Fritsche and Steinhart, 1998b; Khanal and Dhiman, 2004). *Cis*-9, *trans*-11 also called rumenic acid, due to its easy combination with phospholipids that are present in the structure of cellular membrane, is the most biologically active isomer, and due to its presence in the foods in the rate of 80%, the most present isomer

(McGuire and McGuire, 1999; Bessa et al., 2000; Mulvihill, 2001; Aydın, 2005; Schmid et al., 2006).

Biosynthesis of CLA

Biosynthesis of CLA in animals occur in the two different ways i.e. in rumen and tissues as endogen and in the first, bio- hydrogenation of unsaturated fatty acids in fodder in the rumens of ruminants is shaped and after absorbing in intestines, it reaches the other tissues. In the second step, it was reported that CLA synthesis occurred from *c*-9, *t*-11 and *t*-10, *c*-12 with desaturase enzyme in tissues (Turuni and Martin, 2001).

While the first metabolic way, seen in biosynthesis of CLA isomers, occurs in only ruminants, the second metabolic way is also observed in ruminants as well as monogastrics (Salminen et al., 1998; Glaser et al., 2000; Bessa et al., 2000; Loor et al., 2002; Turpeinen et al., 2002; Schmid et al., 2006). In the tissues of human body, CLA synthesis occurs but very little. However, it was reported that CLA was not enough for satisfying need of human body and, therefore, that this need should be met from the foods (Salminen et al., 1998; Bessa et al., 2000; Adolf et al., 2000; Turpeinen et al., 2002; Schmid et al., 2006).

The Effect of CLA on the Health

Although CLA is found to be present in edible oils in 1930s, in 1980s, with discovery of the presence of anti-mutagenic activity in grilled bovine meat, its physiological effect attracted attention and,

nowadays, it is known that besides anti-mutagenic effect, it has important effects such as anti-carcinogenic, anti-obesitic, antidiabetic, and antihypertensive (Pariza and Hargraves, 1985; Ha et al., 1987).

- **Anti -Carcinogenic Effect**

The anti-carcinogenic effect of CLA was introduced by the various studies carried out. It was reported that CLA inhibited the development of prostate tumor cells (Ip et al., 1991; Ip et al., 1994). However, when compared to omega-3 fatty acids such as EPA and DHA, whose anti-carcinogenic effects are well known, CLA is a stronger anti-carcinogenic effect. In vitro studies carried out of *c*-9, *t*-11, 18:2, *t*-10, *c*-12, 18:2 isomers of CLA, it was seen that CLA showed activity against cancer regardless of isomer used (Ip et al., 2002; Yamasaki et al., 2002; Chujo et al., 2003). CLA inhibits the development of the various cancer cells (Shultz et al., 1992; Schonberg and Erokan, 1995). Although the data obtained from clinical studies are highly less, the studies has a quality proving that CLA taken together with diet showed a protective effect against breast cancer in the people (Chajes et al., 2003).

- **Anti-Obesitic Effect**

Anti-obesitic effect of CLA is seen on the animals such as rat and pig and, although the results are not always clear, it is also met the effects reducing body fat accumulation on people (Park et al., 1997; Pariza et al., 2001). According to the results obtained from in

vivo and in vitro studies, these effects are associated with the factors such as increase of lipolysis in adipositis, increase of β-oxidation of fatty acids in adiposis and skeletal muscle cells,suppression of fatty acid synthesis in liver, and spending of oxygen and energy (Park et al., 1999; Pariza et al., 2000; Rahman et al., 2001; Nagao et al., 2003a).

Anti-obesitic effects of CLA are attributed to *t*-10,*c*-12,18:2 isomer rather than *c*-9, *t*-11,18:2 isomer, its effect mechanism is rather complex and is not still completely understood (Park et al., 1999; Nagao et al., 2003a; Wang et al., 2006).

In clinical studies, it was identified that the supplement of CLA made to diets reduced body fat; modified total serum lipids, and reduced glucose intake (Blankson et al., 2000; Thom et al., 2001; Smedman and Vessby, 2001). However, these effects on people are not clear due to intake dose, duration exposed to CLA, and obesity degree (Koba and Yanagita, 2014).

- **Anti-Diabetic Effect**

It is reported that CLA shows antidiabetic effect, regulating glucose mechanism. In a study carried out, it was concluded that when diabetic rats were fed by a diet containing CLA of 1.5%; glucose tolerance were recovered in two weeks and that the effect of CLA was similar to that of troglitazone that is a ormalisticagent (Houseknecht et al., 1998). It is reported that this antidiabetic effect of CLA results from *t*-10, *c*-12, 18:2 isomer and, that in Type-

2 diabetic patients, this isomer is a bioactive isomer affecting body weight (Ryder et al., 2001). On the other hand, there is some evidence in the direction that CLA negatively affect blood sugar control. In non-diabetic over weighed individuals, CLA develops insulin resistance and, thus, reducing insulin sensitivity, reveals the pre-diabetic state (Riserus et al., 2002; Larsen et al., 2003; Moloney et al., 2004; Riserus et al., 2004).

- **Anti-Hypertensive Effect (Blood Pressure Reducing Effect)**

Anti-hypertensive effect of CLA was introduced by the studies carried out and it was reported that this effect resulted from *t*-10, *c*-12, 18:2 isomer rather than *c*-9, *t*-11, 18:2 isomer. It was reported that this state arose from the feature of CLA to regulate the production of physiologically active adipocytokines such as angiotensinogen, leptin, and adiponectin (Nagao et al., 2003b; Nagao et al., 2003c; Inoue et al., 2004)

- **Anti-Inflammatory Effect**

It was revealed in the different studies that CLA reduced colon inflammation; reduced antigen–origin cytokine production in immune cells; and regulated the production of cytokine, prostaglandin, and leukotriene B4 and thus showed anti–inflammatory effect (Garcia et al., 1996; Belury and Kempa-Steczko, 1997; Bassaganya-Riera et al. 2002; Yu et al., 2002; Changhua et al., 2005; Bhattacharya et al., 2006).

- **Anti-Atherogenic Effect (Protective Effect Against Cardiovascular Diseases)**

In the various animal studies carried out, it was identified that CLA reduced atheroscloretic lesions and, while reducing total cholesterol (TG) and LDL cholesterol, increased HDL cholesterol (Nicolosi et al., 1997; Lee et al., 1998; Kritchevsky, 2000; McLeod et al., 2004; Kritchevsky et al., 2004).

- **Effect on Bone Health**

Although CLA, increasing bone density, bone mineral content, bone weight, bone length or calcium, magnesium or phosphor content of bone, developed bone mass stated in the various studies, it was also stated that the effects of CLA on body mineral or bone density were inconsistent (Berge et al., 2004; Weiler et al., 2004; Banu et al., 2006; Burr et al., 2006). The reason for this inconsistency is attributed to the interaction between calcium and CLA in diet (Park et al., 2008).

CLA Resources and Amount That Should Be Taken

The major resources of CLA are the meat and milk products and egg and it was reported that due to the fact that the bacterial activity in rumen is low in monogastric animals, amount of CLA is more compared to the ruminant animals (Khanal and Olson, 2004; Schmid et al., 2006; Huang et al., 2008).

Although the amount of CLA the people take together with their diets differentiate according to the countries, it was reported that in

Switzerland , amount of *c*9, *t*11 CLA taken from the meat and milk products was 0.16 g/day; in Germany, 0.36 g /day per women and 0.44 g /day per men and, as a result of a study carried out in United Kingdom, that when a person of 70 kg takes 3 g/day of CLA, he/she can benefit from biological effects (Fritsche and Steinhart, 1998a; Fritsche and Steinhart, 1998b; Mulvihill, 2001; Hur et al., 2007).

Amount of CLA in The Meat and Meat Products and Effective Factors

CLA content in the meat and meat products is affective a variety of factors such as season, genus, race, sex, bacteria population in rumen, Δ^9-desaturase enzyme activation level, rations having different compositions, and consumption duration of these rations (Mulvihill, 2001; Khanal and Olson, 2004).

In a study carried out, the effects of double muscled Piemontese bulls, fed with combined or uncombined with rumen-protected CLA and fed with rations having high or low raw protein density, on meat quality and CLA content were studied. As a result of the analyses made after animals are slaughtered, it was identified that rations combined with rumen–protected CLA statistically increased the concentrations of *c*9, *t*11-CLA and *t*10, *c*12-CLA in all tissues compared to control group. In addition, *t*10, *c*12-CLA concentrations was identified to be 20 times higher in muscles than that of adipose tissue (Schiavon et al., 2011).

It was reported that adding oil to ration was effective on amount of CLA and the level of this effect differentiates depending on the sort of vegetable oil (Schmid et al., 2006). As a result of literature review, it was identified that the various vegetable oil additions showed similar effects on the amount of CLA (Mir et al., 2000; Ivan et al., 2001, Sarries et al., 2009).

Addition of vegetable seed to ration is another application increasing amount of CLA in the meats. In a study carried out, it was reported that flaxseed added to diet raised the amount of CLA from 22% to 36% and that addition of flaxseed was the most effective method compared to the various factors used in the study such as the, genus, sex, and sort of muscle (De La Torre et al., 2006). In another study carried out, 50 lambs 50 steered lambs were fed with ration enriched with sunflower seed and, as a result of the study, it was identified that enriched ration (enriched ration:8969±643ppm; control group: 4050±643ppm) increased two times the amount of CLA in muscular tissues (Kott et al., 2003).

Another factor reported that it was effective on CLA content of meats is the weight of animals during slaughtering and sort of muscles obtained from carcass. In this study carried out, after the lambs in the weights of 11, 14, and 17 kg, fed with breastfeed, were slaughtered, amounts of CLA in *Longissimus dorsi* (LD), *Triceps brachii* (TB) and *Semi membranosus* (SM) muscles were tried to be identified. The animals slaughtered while they were 14 kg

and 17 kg in weight showed more rumen activity compared to the animals that were 11 kg in weight. While the content of *c*-7, *t*-9 CLA in TB and SM muscles significantly increased, ; *t*-7, *t*-9 CLA increased in only TB muscle and *c*-8, *c*-10 CLA in only SM muscle (Serraa et al., 2009).

As a result of enriching rations with commercial CLA resources, an increase also occurs in amounts of CLA of the meats. In a study carried out, commercial CLA at the level of 0.25% was added to ration and while in *Biceps femoris* muscles of pigs, the amount of *c*9, *t*11 CLA increased by 130%, and total amount of CLA by 180%, in adipose tissue, the amount of *c*9, *t*11 CLA showed an increase in the rate of 450% and total amount of CLA, 610% (Lo Fiego et al., 2005).

As result of literature review, it was seen that the various processes applied to meat such as irradiation, thermal process, cold storage, curing, and fermentation did not reduce the amount CLA (Du et al., 2000; Mulvihill, 2001; Du et al., 2002; Corino et al., 2003; Hur et al., 2004; Khanal and Olson, 2004; Schmid et al., 2006; Intarapichet et al., 2008; Martin et al., 2008; Sarries et al., 2009). In a study carried out, it was reported that while irradiation process, applied to *Longissimus thoracis* muscle of lamb, did not affect the amount of CLA of muscle, it led to increase in the concentrations of trans/trans isomers (Alfaia et al., 2007).

Amount of CLA in Milk and Dairy Products and Effective Factors

Foods, obtained from ruminant animals, due to the fact that they contain linoleic acid -I, which catalyzes isomerization of CLA, contains more amount of CLA. Therefore, milk and dairy products are also known as an important CLA resource (Akalin et al., 2007; Budiarsana et al., 2016). CLA content of cow milk is 5.4-7.00 mg/g and the factor affecting this amount the most rapidly is the content of linoleic acid of the animal ration (Schmid et al., 2006; Nudda et al., 2008). It was reported that animal ration was effective on CLA content and therefore, a study was carried out toward increasing the amount of CLA (Bauman et al., 2000; Nudda et al., 2005; Atti et al., 2006; Chilliard et al., 2007; Murphy et al., 2008; Castro et al., 2009; Daley et al., 2010; Mele et al., 2011; Siurana and Calsamiglia, 2016). In a study, it was identified that in animals, fed with cotton seed or extruded flaxseed, milk fatty acid profile of animals, fed with flaxseed, varied and amount of CLA increased (Nudda et al., 2008). Tsiplakou et al. (2008), in the study they carried out reported that the relationship between genus of sheep and animal ration affected the amount of CLA.

Another factor that are effective CLA amount of milk and dairy products is the seasonal changes (Kim et al., 2009; Chion et al., 2010). The effects of seasonal changes in fatty acid composition in fodder plants in pasture on CLA content of sheep milk were studied, it was identified that the amount of CLA that is 2.4% in May fell to 1.3% in August and rised to 2.6% in September ($p <$

0.001). The results of the study revealed that amount of CLA in milk was affected, depending on the seasonal differences in α-linoleic acid content of pastures (Mel'uchova et al., 2008).

During production of milk and dairy products, different methods are developed and CLA content of the final product is tried to be increased (Santo et al., 2012). Santo et al. (2012) identified that, in yogurt production, diet fibers, obtained from the fruits of apple, banana, passion flower, had an effect on fatty acid profile of yogurts. Among probiotic strains used with the sort of diet fiber, a synergic effect was observed on CLA and it was concluded that α –linoleic acid content of banana fiber increased. In another study, it was identified that keeping the yogurts obtained from cow and sheep milks at 5°C throughout 14 days had an effect on CLA contents of the yogurts and, during storage, it was observed that while CLA content in the yogurts obtained from cow milk statistically [significantly] decreased ($p < 0.05$), in the yogurts, produced from sheep milk, CLA content increased (Serafeimidou et al., 2013).Vieira et al. (2017) identified CLA production potential of probiotic *Lactococcuslactis* ssp. *cremoris* MRS 47 strain, isolated from kefir beans during fermentation of full fat cow milk. As a result, they reported that while *Lactococcuslactis* ssp. *cremoris* MRS 47 strain reduced saturated fatty acids in fermented milk at the significant level, it increased the contents of CLA and multiple unsaturated fatty acid.

CLA Content in Egg and Egg Products and Effective Factors

It was reported that CLA content obtained from animals was lower than CLA content ruminant animals contained (Hur et al., 2017). In similar with CLA content of meat and milk, CLA content of egg is also affected from the animal ration, from which it was obtained. While Chin et al. (1993) reported that there was CLA at the level of 0.1% in the fats of chicken and pigs fed with commercial ration, Raes et al. (2002) put forward that the chickens fed with commercial rations did not contain CLA. The studies carried out showed that via supplementation of animal rations with CLA, CLA contents in the eggs obtained from these animals could be increased (Chamruspollert and Sell, 1999; Jones et al., 2000; Schafer et al., 2001; Shang et al., 2004; Yin et al., 2008). It was identified that addition of CLA to ration at the level of 1% raised *c*9, *t*11-CLA content of egg from 0.06% to 2% (Zsedely et al., 2012). In addition, it was identified that CLA -supplement to ration fell cholesterol content of egg yolk at the significant level (Hur et al., 2007).

Enriching rations of animals, from which egg is obtained, in terms of CLA is quite important, since it makes it possible to improve, besides enriching nutritional value of egg, many technological values of it. In the studies related to this, the properties of mayonnaise such as rheological characteristics, emulsion stability, and cold storage obtained from eggs enriched in terms of CLA, was identified and, as a result, it was reported that mayonnaises

obtained from the eggs enriched from in terms of CLA had a more viscous structure and more stable emulsion (Shinn et al., 2015; Shin et al., 2016).

CONCLUSION

That animal resource food such as meat and egg and products obtained from these foods contain CLA, a natural component, increase the importance of these foods one time more. However, albeit these foods are accepted as CLA resource, for them to be able to show the biological effects such as anti–carcinogenic, anti–atherogenic, anti-obesitic, and antidiabetic, that they are not at the sufficient level reveals the fact that CLA content in animal resource products should be increased. In the literature, although there are many studies carried out on this subject, there is a need for further studies.

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CHAPTER 9

ARTIFICIAL INTELLIGENCE IN SURGERY

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INTRODUCTION

Developments in surgery have been effective on the management of both chronic and acute diseases, prolongation of lifetime and continuous expanding of survival margin. With the information age, there has been a transformation in workflow and productivity, and the field of medicine and particularly surgery seems to obtain striking gains from this information evolution. It is important for surgeons to understand the fundamentals of this technology in order to have a better insight about the effects of Artificial Intelligence (AI) on healthcare. Rapid developments in AI technologies have contributed to effective use of this technology in recent years. In surgical practice, AI technologies are used in clinical decision making, imaging interpretation, prediction of risks and complications and diagnostic purposes. However, the key point in the use of these innovative methods is the surgeon. Despite big data being used in AI applications and advancements in analytical models, accurate interpretation of AI depends on the accuracy of data and models used, which is a limiting factor for more widely using AI applications in clinical practice.

In this chapter, a brief description of AI is given, its functioning mechanisms are discussed and then medical applications of AI are focused. Following an historical perspective of AI in medicine, examples are provided for the use of AI subfield in medicine and particularly surgery. Given the dramatic evolution of AI technology, it is thought that the existing data on this issue should be updated

dynamically and continuously. This will be helpful especially for practitioning surgeons and positively affect learning curves.

1. ARTIFICIAL INTELLIGENCE

AI can be defined as algorithms that give machines the ability to fulfil cognitive functions such as problem solving, recognition of objects and words and decision making (Yurdaisik and Aksoy 2021). AI relies on the process of making accurate decisions that can be independently performed by a machine. Previously, AI has been defined as a scientific fiction, while it has gradually gained popularity in the academic literature, and rapidly introduced to the general application fields. Today AI is increasingly being used in many areas. The goal of AI technology is to design programs that can make decisions, and fulfill the desired tasks more effectively and with less errors. The place of AI in science depends on the ability to do tasks as well or better than humans (Kose et al. 2018). As in many industries, increased data are produced in the healthcare industry and health information systems become dependent on these data (Ching et al. 2018). The use of AI can facilitate improvements of data processing in medical applications. Medical AI uses main computer techniques for diagnostic and therapeutic purposes. AI has the ability to determine significant correlation in this big dataset and it has been used in numerous clinical situations for diagnosis, treatment and prediction of outcomes. Moder AI technologies have shown a great development, and are significantly helpful for diagnosis, treatment, prognosis and making decisions in projections.

1.1. Historical perspective of AI application in medicine

The use of AI in medicine dates back to 1956 when it was introduced following World Wide II (Russel et al. 2010). AI applications can be performed in medical fields both for diagnosis and treatment. Medical diagnosis programs serve as useful tools in today's overburdened healthcare systems. These medical applications enable physicians to effectively use patient's symptoms, laboratory data and imaging findings in order to make a decision between the "most possible clinical diagnosis and treatment options. Ultimate goal of these applications is to improve patient outcomes and reduce healthcare costs. Today, AI applications are being used increasingly in all fields of medicine. Programmable Universal Machine for Assembly (PUMA) 560 robotic surgical arm was used for the first time in 1985 and the first documented robot assisted surgical procedure was performed (Kwoh et al. 1988). Later, a cholecystectomy procedure was performed for the first time laparoscopically with a robotic system in 1987 (Jones and Jones 2001). The same PUMA system was used in robotic surgical transurethral prostate resection in 1988. In 1990, the Automatic Endoscopic System for Optimal Positioning (AESOP) system was the first system approved by the Federal Drug and Food Administration (FDA) for endoscopic procedures (Jones and Jones 2001). In 2000, da Vinci system became the first robotic surgical system approved by the FDA for laparoscopic surgery (Samadi 2016). Three dimensional magnification screen of the da Vinci system provides the surgeon to see the operation as high definition. The first AI techniques have focused on both recognition of

features for both preoperative planning and intraoperative guidelines and computer assisted intervention. Since that, surgical applications have exhibited a steady growth. On the other hand, the integration of AI with surgery is relatively new. This integration has evolved through active shaping models, atlas based methods and statistical classifiers (Vitiello et al. 2013). Perioperative interactions between surgeons and AI are shown in Figure 1.

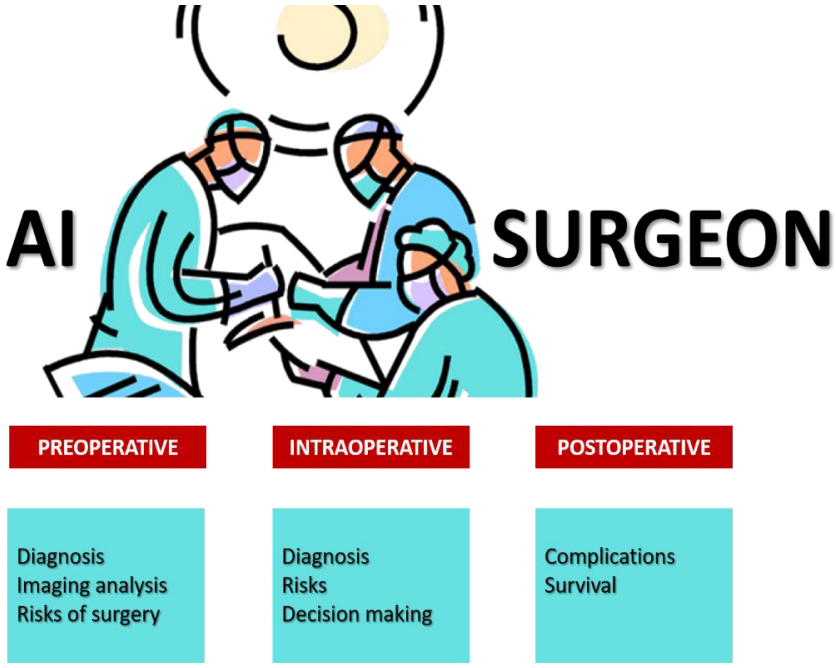

Figure 1. Perioperative interactions between surgeons and AI

1.2. Subfields of AI and surgical implementations

Roots of AI lies in many different areas such as robotic science, philosophy, psychology and statistics (Buchanan 2005). On the other hand, significant developments in computer science and increased information processing speed, have played a catalyzing role for the development of AI. Only in 2016, approximately 5 billion USD have been spent for AI investment in different industrial fields in the USA. The potential of AI techniques in surgical fields includes providing a laboratory for examination, organization and representation; cataloguing medical information; producing new tolls to support medical decision making, education and research; integration of the activities in medicine, computer, cognitive and other sciences; and providing rich-content disciplines for future medical specialties. Subfields of AI are listed below:

1. Machine Learning (ML)
2. Natural Language Processing (NLP)
3. Artificial Neural Networks (ANN)
4. Computer Vision (CV)

Technical contents of these subfields are beyond the scope of this chapter and their reflections in surgical areas will be focused.

1.2.1. Machine Learning

ML is a subset of AI that focuses automated computer systems predicting outputs through algorithms and mathematics (Jordan and Mitchell 2015). ML enable machines to learn and predict by recognition of patterns. There are numerous applications in surgical field. With the last advancement in ML, AI technology has led to creating decision support tools, optimizing postoperative outcomes and improving technologies used in operating room (Chang et al. 2020). In addition, owing to this technology, instrument motion can be detected, patterns can be recognized using video records, surgeons' physical movements, eye movements and cognitive functions can be tracked. This modality also helps advancement of robotic surgery education (Egert et al. 2020). Especially in telemedicine application that have become current during the last pandemic, ML can be used in voice recognition and remote healthcare delivery. ML constructs non-linear models by combining data sources such as diagnosis, treatment and laboratory investigation outcomes, and as a results, it performs logistic regression analysis for predicting surgical area infections (SSI) (Soguero et al. 2015). ML applications are also effectively used in reducing surgery related complications.

Another surgical field of ML applications is evaluation of the surgeon’s performance (Niitsu et al. 2013). Various approaches and algorithms are used in this evaluation, including transformation of ideo frames into a low-dimension representation and the use of ML to learn spatiotemporal features of the video. Tracking of the surgical

instruments accurately by detecting with videos enables a detailed analysis of instrument use, movement and autonomy (Khalid et al. 2020).

Predictive accuracy of the surgical case duration plays a crucial role in reduction of the operating room usage. Advanced ML algorithms have been used for this purpose. Studies conducted for this purpose have used datasets from multiple operation cases. These data include details about patients, operations, specialties and surgical teams. By this way, a large amount of case data and a wide variety of surgical procedures can be compared. The amount of total prediction errors in case operation times at hospital can be decreased using ML approach (Bartek et al. 2019)

1.2.2. Natural Language Processing

Medical NLP systems have been developed to identify, extract and encode information in the clinical narrative text. A large amount of medical record data are processed and recognized, and prediction of various preoperative, intraoperative and postoperative parameters is improved through NLP. A usual NLP program has a sensitivity between 94-99% and a positive predictive value between 92-98% (Al Haddad et al. 2010). NLP is a subfield that constructs the ability of a computer so as to understand the language of human beings, and is important for large scale analysis of electronic medical records such as narrative documentation of physicians. A successful NLP system should expand beyond simple word definition for a detailed analysis in order to obtain a language processing process at human level

(Nadkarni et al. 2011). NLP allows machines to process information and meanings from unstructured data. By this way, NLP enables clinicians to write more naturally than using specific narration sets or menu selection from the computer to recognize data. NLP has been used for the analysis of big data in order to determine adverse effects and postoperative complications with medical documentation (Murff et al. 2011).

Various NLP applications are effectively used in the surgical field. For example, NLP has been used in screening of electronic records of the words in the operation reports and prediction of anastomotic leakages following colorectal resection. Studies have found sensitivity of NLP as 100% and specificity as 72% in the prediction of leakages (Soguero et al. 2016). In addition, NLP has been utilized as an adjunct in the recognition of surgical site infections (Thirukumaran et al. 2019). Studies conducted on this issue have revealed NLP based models in the detection of surgical wound sites in a mixture of medical and surgical patients (FitzHenry et al. 2013; Taggart et al. 2018). The most important advantage of NLP is the elimination of surgical outcome documentation. Owing this, the management of postoperative complications is achieved more effectively. In a study with women undergoing ovarian cancer surgery, The use of NLP was reported to improve the ability of predicting postoperative complication and hospitalization rates (Barber et al. 2021).

1.2.3. Artificial Neural Networks

ANN, a subfield of AI and ML, has been inspired by the biological nervous system and has become crucial in many AI applications. ANN has drawn a special interest due to its ability to analyze non-linear complex data sets. Clinical significance of ANN has significantly surpassed traditional risk prediction approaches. For example, ANN has a sensitivity of 89% and a specificity 96% in the evaluation of pancreatitis severity, while these rates are 80% and 85%, respectively with APACHE II method (Modifi et al. 2007). ANNs predicted in-hospital mortality following open abdominal aortic aneurysm repair by 87% sensitivity and 96% specificity using clinical variables such as patient study, medications, blood pressure and length of stay in hospital (Monsalve et al. 2016).

ANN has been used also in the prediction of surgery related compression injuries in patients undergoing cardiac surgery (Chen et al. 2018). Again, NLP has been used for the prediction of surgical site infection after free flap reconstruction in patients undergoing surgery due to neck and head cancer, and shown the highest prediction performance compared to other methods. ANNs has been successfully used in the prognostic evaluation of postoperative complications in patients undergoing by-pass graft surgery (Souza et al. 2009).

In addition, ADDs have been used in the prediction of postoperative survival especially in cancer patients. In a study from Sweden in 2013, ANN was used in the prediction of survival inpatients undergoing radical surgery due to pancreas cancer. The ANN model used several

parameters, including lymph node metastasis, differentiation, body mass index, age, resection margin status, peritumoral inflammation, and American Society of Anesthesiologists (ASA) stage. The authors reported that ANN successfully predicted individual long term survival following radical pancreatic surgery (Ansari et al. 2012).

Another usage area of ANN is determining risk factors and predicting mortality in cardiac surgeries. Preoperative evaluation of patients' surgical risks is an important component in cardiac surgery. Risk stratification can provide information to patients and their relatives about the existing complications and mortality, guiding the selection among surgical, alternative or non-surgical treatment methods. It was emphasized in a study that the performance of ANN is superior in determination of patients' mortality risk independent from cardiac surgical procedures (Nilson et al. 2006).

1.2.4. Computer Vision

CV explain the ability of machines to understand images and videos, and significant advancements on this issue has resulted in computers having capability in the fields such as recognition of objects and scenes at human being level (Szeliski 2010). CV fields have undergone very fast advancements in recent years and have been used especially in the analysis of intraoperative videos. Even in some situations CV can determine intraoperative phases with an accuracy similar to surgeons. In this context, multiple surgical cameras are used in modern surgical practice to provide surgeons a rich visual data set to use in clinical decision making by visualization of surgical areas.

Health related studies in CV include image acquisition and computed assisted diagnosis, imaging guided surgery and interpretation at axial imaging with several applications such as surgical and virtual colonoscopy (Kenngot et al. 2015). In a study using CV, real-time analysis of laparoscopic videos showed 93% accuracy in automatic determination of gastric sleeve steps and recorded missing and unexpected steps (Volkov 2017). A high-definition surgical video of 1 minute include approximately 25 times higher data than a high resolution computed tomography image (Natajaran 2017). CV may be helpful in the real-time recognition and prediction of adverse events for intraoperative clinical decision making support.

2. Implications of AI for Surgeons

The first AI applications in surgery have been replication of human performance with computers. It is currently known that the interaction between physicians and machines improves the decision making process. AI improves the identification of high-risk patients and helps surgeons and radiologists to reduce the rate of lumpectomy by about 30% in patients who have lesions that were considered high-risk with biopsy, but determined to be benign following surgical resection (Bahl et al. 2018). In the future, surgeons will possibly analyze population and patient data provided by AI and will see improvement in every step of healthcare. AI can preoperatively monitor patients evaluated for bariatric surgery, using weight, glucose, meals and activities through mobile applications.

3. Role of Surgeons in AI

Big data analysis is estimated to save annually 300-500 billion USD only in the USA, and combining big data with multiple components in healthcare systems have significant economical impact (Groves et al. 2016). Surgeons should be actively involved in these innovations rather than waiting for these technologies to become beneficial. One of the most common contributions of surgeons in the development of AI is to ensure including records of all patients in clinical data records. Because, as is stated above, missing data limits predictions made by AI. Surgeons should be in cooperation with other data specialists in adoption of AI based technically and should be adapted to new forms of clinical data (Weber et al. 2014). Surgeons have clinical insight that can guide data scientists and data engineers to analytical problem solving.

Surgical practice where AI techniques are intensely used can contribute to surgeons' ability to improve surgical care quality. Considering studies have demonstrated that surgical technique and skill is associated with patient outcome (Scally et al. 2016), AI can help accumulation of surgical experience. Surgeons can support data scientists on seemingly simple issues such as anatomy and physiology, disease pathophysiology and the association between perioperative processes and postoperative complications. Herein, surgeons and engineers should ask transparency and interpretability in order to be held responsible for the predictions and suggestions of AI.

4. Limitations of AI

AI is a very new technology. As in all other technologies, unrealistic expectations from AI may lead to significant disappointment. Despite all dramatic developments in AI, there are some cases where conventional analysis methods are superior over this technology or AI can not improve outcomes (Bellman 2015).

First of all, outputs of AI analysis ate limited with the type and accuracy of the data used. Potential biases in the collection of clinical data may affect patterns or prediction determined by AI (Hopewell et al. 2009). This may especially affect ethnical minorities and the groups that are not sufficiently represented in clinical trials and populations.

NLP has been used in production of labels for chest X-rays by screening radiology reports, and these labels have been used in recognition of pathology for detection of pneumothorax. However, it has been found in a data analysis that some outcomes came from non-adequately labeled data. Majority of chest X-ray labeled as pneumothorax have a chest tube, and this has raised concerns that the used method has identified chest X-rays rather than pneumothoraces (Oakden and Oakden 2017). More importantly, despite the advancements in causal analyses, AI still can not determine clinical relationships at a level desired for clinical practice and can not provide an automated interpretation.

CONCLUSION

AI applications have been increasingly used in more fields from databases to video analyses. Surgeons are the focus point in this change process. Surgeons on one hand provides improved data quality ve thus, clinical outcomes by close cooperation with data engineers in order to increase efficacy and accuracy of AI applications, and on the other hand more easily adapt the development owing to improved learning curves with AI. Today, AI applications are increasing especially in medicine and surgical fields with the introduction of robotic surgery. From this viewpoint, the relevant literature should be always kept updated to provide dissemination of developments in AI more efficiently.

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CHAPTER 10

AN ALTERNATIVE APPROACH TO COVID-19: GINGER

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INTRODUCTION

Coming from the same family with severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV), SARS-CoV-2 was first seen in Wuhan, China in 2019. SARS-CoV-2, which spread to the world rapidly after China, caused the death of thousands of people in a short time (Pascarella, 2020). This virus was identified as 'Coronavirus Disease-19 (COVID-19)' by the World Health Organization (WHO) and was defined as an epidemic worldwide. In the December 2020 data of WHO were reported 68,165,877 confirmed cases and 1,557,385 deaths from COVID-19 (WHO, COVID-19, 2020). COVID-19 is an RNA virus and this virus shows cough, fever and flu-like symptoms similar to other coronaviruses (Wu, 2020). These symptoms might be seen in entire age groups, but the elderly and the individuals who have chronic disease history are defined as a high-risk group. After severe pneumonia, the virus can lead to acute respiratory distress syndrome and multiple organ failure, causing death in infected individuals (Pascarella, 2020). There is no specific medicine or vaccine to treat COVID-19. Because of the fact that there is no medical treatment or protection procedure, people can tend to utilize herbal remedies by acquiring immunity to viruses. Ginger (*Zingiber officinale*) is one of these medicinal plants. Ginger has been utilized due to various treatments of diseases for a long time in alternative medicine.

1. TRANSMISSION WAYS OF COVID-19

COVID-19 binding to angiotensin-converting enzyme 2 (ACE2) and spreads through the respiratory tract. The main source of human-to-human transmission is air droplets and hands. In a study conducted with people who are affirmed COVID-19 transmission in provinces without the exception Wuhan in China, was reported estimated incubation period of the virus is 2-12 days (average 5.1 days) (Lauer, 2020). Hygiene is the basic step in minimizing the risk of contamination. Mask and hand hygiene come first step in the protection measures against COVID-19 taken worldwide (Guopeng, 2020).

2. SYMPTOMS OF COVID-19

Symptoms of COVID-19 range from asymptomatic cases to severe acute respiratory failure (He, 2020). Common symptoms of the disease are fever, cough, tiredness, mild dyspnoea, sore throat, headache, and conjunctivitis (Chen, 2020). In a small percentage of patients have symptoms of dyspnea, severe acute respiratory failure and multiple organ failure. The majority of individuals who have symptoms and more severe clinical conditions coexist with medical conditions such as hypertension, diabetes and cardiovascular disorders (Yang, 2020).

3. GINGER (*Zingiber officinale*)

Ginger (Zingiber officinale) is a perennial, yellow, herbaceous plant from the Zingiberaceae family that has been used for healing purposes in Eastern medicine for thousands of years. Ginger rhizomes contain 60-70% carbohydrates, 3-8% raw fiber, 9% protein, 8% ash, 3-6% oleoresin and 2-3% essential oil (Srinivasan, 2017). Chemicals constitute 20-25% of oleoresins, mainly gingerols, gingerdions and shogaols (OSMANLIOĞLU-DAĞ). Ginger also contains plenty of phenolic and terpene active ingredients. In fact, among the active phenolic components of ginger, gingerols, shogaols and paradols are the leading ones. Fresh ginger contains also many polyphenolic ingredients except that 6-gingerol, 8-gingerol, 10-gingerol. Ginger contains various terpene components such as β-bisabolene, α-curcumene, zingiberene, which are considered to be the main components of ginger essential oils. Aromatic smell of ginger is also caused by these essential oils (Mao, 2019).

The primary pharmacological properties and health benefits of ginger components include antiemetic, anti-inflammatory, antitumorigenic, antihyperglycemic and antihyperlipidemic activities. Especially in the last decade, many studies have been done on the beneficial biological activities and bioactive components of ginger and new information has been obtained. In particular, the pharmacological effects and mechanisms of 6-gingerol active ingredient are corroborated by both in vivo and in vitro studies (Wang, 2014).

The U.S. Food and Drug Administration (FDA) classifies ginger as "Generally Recognized as Safe", German Commission Monographs report that ginger has no known side effects and no known drug-herb interactions (Blumenthal, 1999).

4. COVID-19 & GINGER

In a study investigating accepted alternative treatment methods for COVID-19 were reported some ginger mixtures and their remission times. In a mixture made by an elderly woman from Nigeria, ginger, 20 cloves of garlic and lime were made into a paste. A tea containing a spoonful of paste, liptone tea and 1000 mg of ground paracetamol was obtained. This tea was drunk every 4 hours and the remission period was reported as 3 days. A Nigerian family reported that the remission period was 3 days in a treatment method performed by inhaling the steam of a casserole containing turmeric powder, ginger, garlic and lemon. In the method applied by a former Nigerian governor, it was reported that the remission period was 1 day after boiling lemon, ground ginger, ground turmeric, ground black pepper and ground garlic in water and inhaling the steam for 20-30 minutes. In another method used by the Madagascar Applied Research Institute, it has been reported that the remission period is 7-14 days with boiling artemisia, neem leaves, claw leaves, garlic, ginger, lemon and orange peels and inhaling the steam (Orisakwe O. E., 2020). Nigerian home remedies have been reported to protect cells and cell membranes from damage (Amadi, 2019) (Orisakwe O. E., 2020).

The Ministry of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homeopathy (AYUSH), an organization that aims to research and develop the education, research and indigenous alternative medicine methods in India, has recommended Ayush Kwath to strengthen immunity and fight infection in the COVID-19 pandemic. Ayush Kwath is a formulation containing four herbs. These four herbs are basil, cinnamon, ginger, and black pepper. Ayush Kwath was aimed to boosting immunity of the public and reduce the burden on the hospital and health system. Ayush Kwath is an economically available mix. Advice to use is to prepare Ayush Kwath mixture by dissolving in 150 mg boiled water 1-2 times a day (Gautam, 2020).

The ingredients in ginger are known to inhibit viral replication. ß-sitosterol is contained in ginger; it is strongest inhibitor of the reverse transcriptase (RT) enzyme (Kharisma, 2018). Ginger contains tumor necrosis factor-α (TNF-α) which defined as cytokine of anti-influenza (Chopra, 1956). Gingers main components are gingerol and shogaols, and this components inhibit leukotriene and prostaglandin synthesis (Aggarwal, 2006).

in-silico studies conducted according with these known effects have also shown that the active ingredients of ginger have encouraging effects against COVID-19. Especially 8-gingerol and 10-gingerol components are active against COVID-19 (Rajagopal, 2020).

5. CONCLUSION

Alternative treatment methods have been developed among the public against COVID-19, which is a worldwide epidemic and currently has no treatment method. Ginger rhizome plant, one of the main ingredients of these immunity-enhancing mixtures, is known for its antiviral properties and is a safe herb. These properties should be provided by an ideal anti-COVID-19 agent; being safe for patients, ensuring antiviral immunity, increasing repair of tissue and demonstrating strong antiviral effects. Ginger that ensures whole these criterias will be preferred as an anti-COVID-19 until a medical treatment method for COVID-19 is found.

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