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Investigation of the D188V mutation in the SCN1A gene in patients with idiopathic generalized epilepsy

Hatice Seğmen[1], Osman Tanık[2]

[1]*Department of Neurology, İstanbul Kanuni Sultan Süleyman Training and Research Hospital, University of Health Sciences, İstanbul, Turkiye*
[2]*Department of Neurology, Apex Medical Center, İstanbul, Turkiye*

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ABSTRACT

Aims: This study aims to investigate the D188V mutation on the sodium channel protein type 1 subunit alpha (SCN1A) in selected patients with idiopathic generalized epilepsy (IGE). The mutation in the SCN1A gene is the most common gene mutation in ion channels and is believed to play an important role in the pathology of IGE.

Methods: This study included patients with IGE selected among patients with epilepsy admitted to the outpatient neurology department of Okmeydanı Training and Research Hospital. Medical history, clinical examination, electroencephalography (EEG), and imaging features of the patients were evaluated. IGE patients with no etiological cause were included in the study. The D188V mutation on the SCN1A gene was investigated by PCR method in the blood samples of the patients.

Results: D188V mutation on the SCN1A gene was investigated in a total of 65 patients, of which 31 were females and 34 were males. None of the cases had a D188V mutation on the SCN1A gene.

Conclusion: Increasing genetic research is promising to elucidate the etiology of many diseases. However, these studies require persistent repetition since they are complex and difficult. The role of genetics in elucidating the etiology of epilepsy is undisputed. Although existing studies support the genetic basis, further studies are still needed.

Keywords: Idiopathic generalized epilepsy, genetics, sodium channel, mutation

INTRODUCTION

Epilepsy is one of the most common neurological disorders, affecting approximately 1% of the general population.[1] Elucidation of the etiology of such a common disease has long occupied the scientific community, and the first problem encountered in this regard was the etiologic heterogeneity. Although there are many causes of epilepsy, the exact etiology cannot be identified in most cases. These cases with unidentified etiology are now classified as idiopathic. There is no informational medical history, familial findings, or clinical and laboratory findings to indicate the etiology. It is widely accepted that genetic factors contribute to the etiology of these idiopathic epilepsies, which account for 40% of all epilepsy cases.

Recent studies have focused attention on genetics by identifying the pathophysiology of several epileptic syndromes such as Benign Familial Neonatal Seizures (BFNS), Benign Familial Infantile Seizures (BFIS), Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE), and Autosomal Dominant Lateral Temporal Epilepsy (ADLTE). However, a suspect gene has only been identified in a very small number of epilepsies believed to be hereditary. These are the genes that code ion channels or functional proteins. Most syndromes of epilepsy show complex rather than simple inheritance. Therefore, the presence of genetic diversity and the challenges in determining the exact phenotype have complicated the search for candidate genes associated with these diseases. These genes can play a crucial role in understanding the causes of epilepsy and facilitate accurate diagnosis. They may help clinicians both in the treatment of seizures and in the prevention of epileptogenesis.

METHODS

The study was carried out with the permission of Ethical Committe of Okmeydanı Training and Research Hospital (Date: 12.01.2004, Decision No: 19-04). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. A total of 65 patients with IGE who were admitted to the outpatient clinic of the Neurology Department of Okmeydanı Training and Research Hospital in 2004-2005 and who had no etiologic cause based on history, EEG, and imaging features were prospectively analyzed. Of these patients, 31 were female and

Corresponding Author: Hatice Seğmen, haticesegmen@hotmail.com

34 were male; 44 had their first epileptic seizure before the age of 16, while 21 had their first seizure at age 16 or older. Each of these admitted patient's personal medical history, family history, clinical progression, seizure attributes, medication and treatment records, neurological examination results, and imaging findings (including EEG, CT, and MRI scans) were meticulously analyzed, alongside laboratory findings such as hemogram, biochemistry, and antiepileptic drug blood levels. The patients were followed up for one year. A family tree was constructed for all patients, and consanguineous marriages and the presence of other family members with epilepsy were investigated.

Ten cc of venous blood with EDTA was collected from all patients with the consent of themselves or their first-degree relatives. These blood samples were taken to the Experimental Medicine Research Institute of Istanbul University (DETAE) for genetic research. Genomic DNA was extracted from peripheral blood lymphocytes of the members in the IGE patients.The coding region of the SCN1A gene were screened for mutation using polymerase chain reaction (PCR) method.

RESULTS

The study was conducted at the Neurology Department of the Ministry of Health Okmeydanı Training and Research Hospital between 2004 and 2005, involving a total of 65 patients, comprising 31 females (47.7%) and 34 males (52.3%) (Table 1).

The most common seizure type in both men and women is generalized tonic-clonic seizures (GTC). GTC was present in 54.8% of females and 76.5% of males (Table 2). A total of 8 females had the syndrome, of which 3 had generalized epilepsy with febrile seizures plus (GEFS+) (37.5%), 3 had generalized myoclonic epilepsy (GME) (37.5%), and 2 had childhood absence epilepsy (CAE) (25%). A total of 7 males had the syndrome, 4 with GEFS+ (57.1%), 2 with GME (28.6%), and 1 with CAE (14.3%) (Table 3). While GTC was observed in 61.4% of patients who had their first seizure at age 16 years or younger, the rate of GTC was 76.2% in patients whose age at first seizure was older than 16 years (Table 4). There was no statistically significant relationship between age at first seizure and medical history (p>0.05). No statistically significant relationship was found between age at first seizure and treatment response (p>0.05). It was observed that response to treatment was mostly seizure-free in patients both under and over 16 years of age, followed by a resistant response. No statistically significant relationship was found between age at first seizure and consanguineous marriage (p>0.05). Consanguineous marriages were found in 38.6% of patients younger than 16 years and 23.8% of patients 16 years and older. There was no statistically significant relationship between age at first seizure and the presence of other epileptic relatives (p>0.05) (Table 5). Among cases with a first seizure onset before the age of 16, 56.8% have a family history, compared with 66.7% of cases with a first seizure onset at age 16 or older. No statistically significant relationship was found between the presence of epilepsy among family members and medical history (p>0.05). There was no statistically significant relationship between the presence of family history and treatment response (p>0.05). The response to treatment was mostly seizure-free in patients with and without family history, followed by a resistant response. There was no statistically significant relationship between the presence of epilepsy in the history and clinical photosensitivity (p>0.05) (Table 6).

Table 1. Frequency table

		n	%
Gender	Female	31	47.7
	Male	34	52.3
Age at first seizure	≤ 16	44	67.7
	> 16	21	32.3
Syndrome type	GEFS+	7	46.7
	GME	5	33.3
	CAE	3	20.0
History	Have had FS	11	16.9
	Have not had FS	54	83.1
Seizure type	Ato-Myo	3	4.6
	GTC	43	66.2
	GTC-Abs	3	4.6
	Myo-GTC	5	7.7
	GTC-CP	1	1.5
	Myo	2	3.1
	Abs	2	3.1
	Tonic	3	4.6
	Ato-GTC	1	1.5
	Tonic-Ato-GTC	1	1.5
	Ato	1	1.5
Clinical photosensitivity	Yes	5	7.7
	No	60	92.3
Treatment response	Seizure free	35	56.5
	Resistant	19	30.6
	Decrease	8	12.9
Consanguineous marriage	Yes	22	33.8
	No	43	66.2
Another family member with epilepsy	Yes	39	60.0
	No	26	40.0

GEFS+: Generalized epilepsy with febrile sizures plus, GTC: Generalized tonic clonic, GME: Generalized myoclonic epilepsy, CAE: Childhood absence epilepsy, FS: Febrile seizure, Ato-Myo: Atonic myoclonic, GTC-Abs:generalized tonic clonic-absence, Myo-GTC: Myoclonic-generalized tonic clonic, GTC-CP: Generalized tonic clonic-complex partial, Myo: Myoclonic, Abs:absence, Ato-GTC: Atonic-generalized tonic clonic, Tonic-Ato-GTC: Tonic-atonic-generalized tonic clonic, Ato: Atonic.

Table 2.Seizure type distribution by gender

		Female		Male	
		n	%	n	%
Seizure Type	Ato-Myo	3	9.7	-	-
	GTC	17	54.8	26	76.5
	GTC-Abs	2	6.5	1	2.9
	Myo-GTC	3	9.7	2	5.9
	GTC-CP	-	-	1	2.9
	Myo	2	6.5	-	-
	Abs	1	3.2	1	2.9
	Tonic	3	9.7	-	-
	Ato-GTC	-	-	1	2.9
	Tonic-Ato-GTC	-	-	1	2.9
	Ato	-	-	1	2.9
Total		31	100.0	34	100.0

Ato-Myo: Atonic-myoclonic, GTC: Generalized tonic clonic, GTC-Abs:generalized tonic clonic-absence, Myo-GTC: Myoclonic-generalized tonic clonic, GTC-CP: Generalized tonic clonic-complex partial, Myo:myoclonic, Abs: Absence, Ato-GTC: Atonic-generalized tonic clonic, Tonic-Ato-GTC: Tonic-atonic-generalized tonic clonic, Ato:atonic.

Table 3.Distribution of syndrome type by gender

		Female		Male	
		n	%	n	%
Syndrome Type	GEFS+	3	37.5	4	57.1
	GME	3	37.5	2	28.6
	CAE	2	25.0	1	14.3
Total		8	100.0	7	100.0

GEFS+: Generalized epilepsy with febrile sizures plus, GTC: generalized tonic clonic, GME: generalized myoclonic epilepsy, CAE: childhood absence epilepsy

Table 4. Distribution of seizure types by age at first seizure

		Age at First Seizure			
		≤ 16		> 16	
		n	%	n	%
Seizure Type	Ato-Myo	2	4.5	1	4.8
	GTC	27	61.4	16	76.2
	GTC-Abs	2	4.5	1	4.8
	Myo-GTC	4	9.1	1	4.8
	GTC-KP	-	-	1	4.8
	Myo	2	4.5	-	-
	Abs	2	4.5	-	-
	Tonic	3	6.8	-	-
	Ato-GTC	1	2.3	-	-
	Tonic-Ato-GTC	1	2.3	-	-
	Ato	-	-	1	4.8
Total		44	100.0	21	100.0

Ato-Myo: Atonic myoclonic, GTC-Abs: Generalized tonic clonic-absence, Myo-GTC: Myoclonic-generalized tonic clonic,GTC-CP: Generalized tonic clonic-complex partial, Myo: Myoclonic, Abs: Absence, Ato-GTC: Atonic-generalized tonic clonic, Tonic-Ato-GTC: Tonic-atonic-generalized tonic clonic,Ato: Atonic.

Table 5. Comparisons by age at first seizure

		Age at First Seizure				p
		≤ 16		> 16		
		n	%	n	%	
History	Have had FS	7	15.9	4	19.0	0.752
	Have not had FS	37	84.1	17	81.0	
Treatment Response	Seizure free	23	54.8	12	60.0	0.877
	Resistant	13	31.0	6	30.0	
	Decrease	6	14.3	2	10.0	
Consanguineous Marriage	Yes	17	38.6	5	23.8	0.237
	No	27	61.4	16	76.2	
Other Epileptic	Yes	25	56.8	14	66.7	0.448
	No	19	43.2	7	33.3	

FS:febrile seizure

Table 6. Comparisons by presence of family history

		Other epileptic family members				p
		Yes		No		
		n	%	n	%	
History	Have had FS	8	20.5	3	11.5	0.344
	Have not had FS	31	79.5	23	88.5	
Treatment Response	Seizure free	19	52.8	16	61.5	0.534
	Resistant	13	36.1	6	23.1	
	Decrease	4	11.1	4	15.4	
Clinical Photosensitivity	Yes	3	7.7	2	7.7	1.000
	No	36	92.3	24	92.3	

FS:febrile seizure

Genetic Analysis

D188V mutation on the SCN1A gene was investigated in 65 patients, of which 31 were females and 34 were males. The D188V mutation on the SCN1A gene was not detected in any of the cases, including those with familial characteristics and those fitting a syndrome type in which this mutation can be found.

Statistics Analysis

SPSS (Statistical Package for Social Sciences) for Windows 10.0 software was used for statistical analysis of the findings obtained in the study. In addition to descriptive statistical methods (frequencies), the chi-square test and Fisher exact chi-square test were used to compare qualitative data in the study. The results were assessed with a 95% confidence interval and significance was determined at the $p<0.05$ level.

DISCUSSION

Many studies have been conducted to explain the etiology of IGE. Genetic studies are the most interesting among these studies. Genetic studies have demonstrated the role of ion channels in the pathophysiology of IGE. Rare epilepsy syndromes with monogenic inheritance have been associated with mutations in genes encoding subtypes of voltage-gated (sodium, potassium, chloride channels) and ligand-gated ion channels.[2,3] The long-standing focus of antiepileptic drugs on sodium channels has led genetic research to shift in this direction. Sodium channels are composed of pore alpha and regulatory beta subtypes, and specific mutations in these channels cause epilepsy syndromes ranging from benign, self-limiting conditions such as febrile seizures to severe epilepsies causing intractable seizures and intellectual loss.[4] Mutations in the genes encoding voltage-gated sodium channels cause a variety of epilepsy syndromes in humans, with most of the mutations occurring SCN1A.The present study investigates the D188V mutation in the SCN1A gene, which is one of the genetically inherited sodium channel pathologies that have a marked importance in the etiology of epilepsy. Regarding the etiology of epilepsy, several genetic studies have been conducted on channel pathologies. If we look at some of these studies, Patrick Cossette et al.[5] showed the D188V mutation in the SCN1A gene in a large family with GEFS+. Laura Saez-Hernandez et al. found a point break translocation in the 6p21 gene encoding potassium channels in a family with IGE.[6] In their study, Iori Ohmori et al.[7] showed SCN1A mutation in 24 of 29 patients with infantile myoclonic epilepsy (IME) J. Spampanato et al.[8] found a W1204R mutation in the SCN1A gene in their study of patients with GEFS. Ching Chou et al. found no association between SCN1A polymorphism and FS in their study of families with febrile seizures (FS).[9] In their study, N. Pineda-Trujillo et al. found a mutation in the SCN1A gene in a large South American family with GEFS+.[10] M. Ito et al. showed the presence of a missense mutation in the SCN1A gene in 2 families with GEFS+.[11] A large number of SCN1A missense mutations have also been identified in Dravet Syndrome (DS) patients.It is likely that many of these abolish channel function, possibly by altering the properties of the channel, trafficking or subcellular localization , or interactions with other molecules.Unlike GEFS+ mutations that segregate within affected families, most DS mutations are de novo in the affected child.[12] Xu XJ et al.[13] showed SCN1A

gene mutations in 4 of 39 families with GEFS+ . de Lange IM et al. investigated 87 patients with SCN1A-related epilepsy. But they could not fully explain the variable phenotypes caused by similar pathogenic SCN1A mutations.[14] This study, conducted on a large cohort of individuals with IGE, aimed to explore the role of genetics in the etiology of epilepsy in Turkiye and the significance of channel pathologies in its etiology. In our genetic study involving 65 patients with IGE, no correlation was found between IGE and the D188V mutation on the SCN1A gene.

In epilepsy genetics research, it has been proposed that the heterogeneity in etiology may be due to genetic heterogeneity, with a wide array of genes potentially contributing to epilepsy. It has been suggested that epilepsy may originate from different genes within different families and that a single genetic factor may manifest in different clinical presentations in different individuals. Since many factors influence the correspondence between genotype and phenotype, it is difficult to identify epilepsy genes. Pathology in a single gene or a single mutation can cause disease with different phenotypes, and pathology in different genes can cause the disease with the same phenotype. Some epilepsies may have a stronger genetic ground than others. Even among genetically identified epilepsies, the genes responsible may vary. The absence of mutation in our study may be due to the genetic heterogeneity in the etiology of epilepsy. However, the inclusion of numerous subtypes of IGE in the selected group, indicating insufficient homogeneity, coupled with the small sample size, may also have influenced this result.

Despite the considerable interest in this topic in Turkey, current conditions restrict studies to the detection of known genes and chromosomal abnormalities. Considering that the disease genes that cause epilepsy may be different even within the same family, the genes that cause the disease in our society may also be different from other societies. Considering these differences in disease genes between societies, it is clear that further studies are needed to determine the genetic profile of epilepsy in the Turkish population.

There is a risk of IGE in relatives of groups with IGE. Studies have shown that this risk is associated with age at the onset of epilepsy. The risk of developing epilepsy in relatives of individuals aged 35 years and older with IGE is not elevated compared to the general population. Therefore, it is more accurate to refrain from seeking a genetic basis for epilepsies that manifest after the age of 35.[15]

In their study, Eisner et al. found a remarkable familial tendency for epilepsy within groups whose seizures began before the age of 16.[16] On the other hand, W. G. Lennox showed that the incidence of epilepsy was high in relatives of patients with early-onset seizures.[17] In our study, the presence of family history was higher in patients with a first seizure age of 16 years and below than in those with a first seizure age of 16 years and above. However, no statistically significant correlation was found between medical history, response to treatment, consanguinity, and presence of other epileptic family members in those with age of first seizure 16 years or less compared with those with age of first seizure 16 years or more (P>0.05).

Similar to epilepsy, FS is heterogeneous and it is difficult to assess familial risks. The risk of these seizures increases in the children, siblings, and nephews of those who have experienced seizures. In population-based studies, the risk in siblings ranges between 6% and 20%.[18,19]

In our study, the rate of family history was high in patients with FS. However, the rate of having FS was not found to be statistically significant in patients with a positive family history compared to those without a positive family history (p>0.05).

CONCLUSION

The role of genetics in elucidating the etiology of epilepsy is undisputed. Although some studies support a genetic basis, further studies are still needed on this subject. Increasing genetic research promises a bright future in elucidating the etiology of many diseases. However, the complexity and difficulty of such studies require patience and persistent repetition. In this study, only the D188V mutation on the SCN1A gene was investigated in patients with IGE. The absence of this mutation in our study does not mean that there are no other genetic mutations in the etiology of IGE. The role of genetics in the etiology of epilepsy should be further studied in larger, more homogeneous, and more specific subgroups and on different genes.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethical Committe of Faculty of Okmeydanı Training and Research Hospital (Date: 12.01.2004, Decision No: 19-04).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Evaluation of sleep quality in children with allergic rhinitis

Özlem Kemer Aycan[1], Özlem Özcanlı Çay[2]
[1]Department of Pediatrics, Faculty of Medicine, Balıkesir University, Balıkesir, Turkiye
[2]Department of Pediatrics, Balıkesir City Hospital, Balıkesir, Turkiye

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ABSTRACT

Aims: Sleep disturbance in allergic rhinitis patients ranges from mild disturbance to sleep apnea. Sleep disturbance in children can lead to problems such as excessive daytime sleepiness, irritability, decreased immune system and memory problems. In our study, we aimed to reveal the factors affecting sleep quality by applying the level-2 dsm 5 sleep scale to the parents of children aged 6-17 years diagnosed with allergic rhinitis.

Methods: Between August 1, 2023 and April 30, 2024, 79 children between the ages of 6 and 17 who were diagnosed with allergic rhinitis and whose parents/guardians agreed to participate in the study and 80 children without allergic complaints who applied to the outpatient clinic for any reason were included as the control group.

Results: There was no statistically significant difference between the case group diagnosed with allergic rhinitis and the control group in terms of gender, age, body-mass index (kg/m^2), residential area, mother work status, father job status and household income. A statistically significant difference was found between the level-2 6-17 years sleep disorder scale administered by the parents and the level-2 11-17 years scale answered by the case group ($p<0.05$), while no relationship was found between the level-2 11-17 years sleep disorder scale answered by the children and the control group ($p>0.05$). No statistically significant difference was found between symptom duration, gender, body mass index, seasonal variability, residential area, mother work status, father job status, household income, and sleep disorder scale ($p>0.05$).

Conclusion: Our study revealed that sleep problems were observed more frequently in children with allergic rhinitis in accordance with the literature. When we classified the case group as persistent and intermittent AR, no difference was observed, but a significant difference was found compared to the control group. In the case group with allergic rhinitis, no difference was observed in terms of scale score as symptom duration increased.

Keywords: Sleep quality, children, allergic rhinitis, sleeping disorder

INTRODUCTION

Allergic rhinitis is a very common disease in the society. Although its prevalence is defined between 10% and 30% in adults, this rate approaches 40% in children.[1] Considering that the prevalence of common rhinoconjunctivitis in children varies between 8-15%, allergic rhinitis is a common disease that is not chronic but affects quality of life. The classic triad of allergic rhinitis is sneezing, nasal itching and nasal congestion. Although allergic rhinitis can be seen at any age, its frequency increases after the age of 2. Nasal congestion and runny nose in children with allergic rhinitis affect the quality of life. Sleep is a part of living a healthy life. Although sleep disorders are commonly observed in children, their prevalence varies between 11% and 47%.[2] Sleep disturbance in allergic rhinitis patients ranges from mild disturbance to sleep apnea. The assessment of sleep quality in children with allergic rhinitis may vary depending on the age of the child, the severity of symptoms and other underlying factors. Therefore, a combination of several different methods to assess a child's sleep quality is usually the most effective approach.[3] In addition, controlling the symptoms of allergic rhinitis with an appropriate treatment plan may improve the child's sleep quality. In our study, we aimed to reveal the factors affecting sleep quality by administering the level-2 6-17 years DSM-5 sleep scale to the parents of children aged 6-17 years in the case group diagnosed with allergic rhinitis and the control group and the level-2 11-17 years DSM-5 sleep scale to the adolescent age group. Sleep disturbance in children may lead to problems such as excessive daytime sleepiness, irritability, decreased immune system and memory problems. At the same time, sleep health should be taken into consideration and necessary precautions should be taken as it leads to problems such as depression, growth retardation, metabolic dysfunction and hypertension.

Corresponding Author: Özlem Kemer Aycan, ozlemaycan@outlook.com

METHODS

The ethics committee of the study was approved by Balıkesir University Faculty of Medicine Clinical Researches Ethics Committee with the decision E.346422. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study included 79 children aged 6-17 years with allergic rhinitis diagnosed with allergic rhinitis and 80 children without allergic complaints who applied to the outpatient clinic for any reason between August 1, 2023 and April 30, 2024 at Balıkesir University Health Practice Pediatrics outpatient clinic between August 1, 2023 and April 30, 2024 as the control group.

Allergic rhinitis was diagnosed with the presence of at least two of the symptoms of runny nose, nasal congestion, sneezing and nasal itching for more than 1 hour per day and at least 2 consecutive days. According to the frequency of symptoms, it was classified as intermittent in the presence of complaints shorter than 4 weeks and less than 4 days a week, and persistent in the presence of complaints longer than 4 weeks and more than 4 days a week (National Allergy and Clinical Immunology Society of Turkiye, Allergic Rhinitis Diagnosis and Treatment Guideline 2022) It was aimed to reveal sleep quality and sleep disturbance by using the sleep disturbance scale in children with allergic rhinitis complaints. Parents were administered the DSM-5 level 2 6-17 years sleep disorder scale and the adolescent group was asked to answer the DSM-5 level 2 11-17 years sleep disorder scale by themselves. The DSM-5 level 2 sleep disturbance scale was arranged as multiple-choice as never, very little, a little, quite often, often, and the degree of sleep disturbance in the last week. In this scale, a minimum score of 8 and a maximum score of 40 are obtained and the higher the score, the more severe the sleep disorder is. The reliability and validity of the DSM-5 level-2 sleep disorder scale (parent form for 6-17 years and child form for 11-17 years) have been shown in Turkish children.[4] The inclusion criteria for the case group were being younger than 18 years of age, having a diagnosis of allergic rhinitis, not using chronic medication, and agreeing to participate in the study; for the control group, being younger than 18 years of age, not having a diagnosis of allergic rhinitis and other allergic diseases, and not using chronic medication.

Statistical Analysis

SPSS 23.0 package program was used for statistical analysis of the study. Descriptive statistics of continuous variables were shown as mean, standard deviation, median, minimum and maximum values, and categorical variables were shown as frequency and percentage. The compatibility of continuous variables with normal distribution was examined by Shapiro Wilk test. One-way analysis of variance (ANOVA) was used for comparisons of 3 or more groups of normally distributed continuous variables. Mann Whitney U test was used for 2 group comparisons of variables that did not show normal distribution and Kruskal Wallis test was used for 3 or more group comparisons. Pearson chi-square, Yates corrected chi-square and Fisher exact chi-square tests were used for group comparisons of categorical variables. In all statistical comparisons in the study, comparisons with p values below 0.05 were considered statistically significant.

RESULTS

179 people were included in the study. The patient group consisted of 90 people who were diagnosed with allergic rhinitis and the control group consisted of 89 people who were admitted to the pediatric outpatient clinic for any reason and who were not diagnosed with allergic rhinitis. The age range of the people included in the study was between 6 and 17 years. The mean age was 11.1±2.1 years. Of the participants, 48% were girls and 52% were boys. 64.8% resided in the urban area. The survey questions were answered by 53.1% mothers. There was no statistical difference between the case and control groups in terms of gender, age, BMI (kg/m^2), residential area, mother work status, father job status and household income (Table 1).

Table 1. Demographic characteristics of the patient and control groups

Demographic data	Variables	Patient, n (%)	Control, n (%)	p
Gender	Female	43 (24)	43 (24)	0.8
	Male	46 (25.6)	47 (26.4)	
BMI (kg/m2)	<3p	2 (1.1)	9 (5)	0.13
	3p-10p	15 (8.3)	27 (15)	
	10p-25p	43 (24)	32 (17)	
	25p-50p	23 (12)	21 (11)	
	50p-75p	6 (3,3)	1 (0.5)	
Residential area	City	59 (32)	57 (31.8)	0.2
	Rural	30 (16)	33 (18.4)	
Mother work status	Working	38 (21.2)	42 (23.4)	0.08
	Not working	51 (28.4)	48 (26.8)	
Father job status	Working	82 (45.8)	88 (49.1)	0.11
	Not working	7 (3.9)	2 (1.1)	
Household income	Low (<20,000 TL)	35 (19.5)	42 (23.4)	0.15
	Middle (20,000-50,000 TL)	32 (17.8)	27 (15)	
	High (>50,000 TL)	22 (12.2)	21 (11.7)	

Among the participants, 89 people constituted the case group diagnosed with allergic rhinitis. Allergic rhinitis symptom duration was over 1 year in 15% of the patients. Antihistamine use was 45% and nasal steroid use was 67.4%. Nocturnal snoring was present in 60% and sleeping with open mouth in 48.3%. No significant correlation was found between symptom duration and sleeping with open mouth, night snoring, antihistamine and nasal steroid use in the patient group (p>0.05). Total IgE values were 158±212.3 kU/L. In the skin prick test performed in the group diagnosed with allergic rhinitis, 56% had no specificity, 28% were sensitized to pollen, 5% to cat dander and 11% to house dust mites. In terms of other concomitant allergic diseases, 46% had no comorbidities while 28% had asthma (Table 2).

A statistically significant difference was found between the level-2 6-17 years sleep disorder scale administered by the parents and the level-2 11-17 years scale answered by the case group (p<0.05), while no relationship was found between the level-2 11-17 years sleep disorder scale answered by the children and the control group (p>0.05) (Table 3).

Table 2. Characteristics of the patient group diagnosed with allergic rhinitis

Variables (Fact)		n (%)
Symptom duration	<1 ay	11 (6.1)
	3 ay-6 ay	18 (10.1)
	6 ay-1 yıl	32 (17.9)
	>1 yıl	29 (15)
Antihistamine use	Yes	45 (50.5)
	No	44 (49.5)
Night snoring	Yes	54 (60.6)
	No	35 (39.4)
Sleeping with mouth open	Yes	43 (48.3)
	No	46 (51.7)
Nasal steroid use	Yes	60 (67.4)
	No	29 (32,6)
Concomitant allergic disease	Asthma	25 (28)
	Atopic dermatitis	18 (20.2)
	Food allergy	5 (5,6)
	None	41 (46)
Symptoms ≥4 days per week	Symptoms ≥4 days per week	48 (53.9)
		41 (46.1)

Table 3. DSM-5 level-2 sleep disorder questionnaire parent and child form comparison

	Case (mean±SD)	Control (mean±SD)	p
Level-2 6-17 years sleep disorder scale (Parent form)	24.9±3.2	18.07±1.9	<0.01
Level-2 11-17 year old sleep disorder scale (Child form)	21.8±4.4	21.1±4.2	0.7

No statistically significant difference was found between symptom duration, gender, body mass index, seasonal variability, parental employment status, family income, place of residence and sleep disturbance scale ($p>0.05$). No significant difference was found when allergic rhinitis patients were categorized as intermittent and persistent ($p>0.05$).

DISCUSSION

The classic manifestations of allergic rhinitis are a constellation of symptoms including sneezing, runny nose, itchy nose and nasal congestion. Sleep apnea may accompany or worsen the underlying symptoms in these children. Sleep apnea frequently accompanies sleep apnea in children, and its frequency was found to be between 1-5% in a study conducted in children aged 2-8 years.[5] When obstructive and non-obstructive causes were examined, obstructive causes were frequently shown. When the pathophysiology of allergic diseases is investigated, Th_2 cells start to differentiate after stimulation by any antigen and antigen-presenting cells (APC), T cells and other cytokines (IL-4, IL-5, IL-13) and Th_2 lymphocytes bind to B lymphocytes via MHC-II. IL-4 and IL-13 are secreted. IgE production starts by B lymphocytes. Th_2 lymphocytes secrete various cytokines that stimulate eosino-phylopoiesis (IL-5), mast cell development (IL-9) and goblet cells in addition to IgE production.[6]

Allergic rhinitis is a common disease, with a prevalence of 10% to 30% in adults and up to 40% in children.[7] Allergic rhinitis can occur at any age, but its prevalence increases after the age of 2 years.[8]

In many studies, sleep disturbance has been found to be associated with allergic rhinitis in both adults and children and a decrease in sleep scores has been shown in polysomnography. In addition to nocturnal sleep disturbance, allergic rhinitis has also been associated with nocturnal enuresis, snoring, obstructive sleep apnea, snoring and daytime sleepiness.[9] In our study, snoring and sleeping with open mouth were observed more frequently in the group with allergic rhinitis compared to the control group. Nocturnal sleep disturbances cause excessive daytime sleepiness and fatigue in children and may lead to weakening of the immune system, attention deficit problems, irritability, depression, growth retardation, hypertension, metabolic syndrome, decreased academic performance and increased substance use.[10] Therefore, sleep disturbance associated with allergic rhinitis may lead to outcomes that are not directly related to allergic rhinitis.[11]

Many questionnaire studies have been conducted to detect sleep disorders in children with allergic rhinitis. In cases where polysomnography is not available, these questionnaires may be guiding. One of these questionnaires is the Children's Sleep Habits Questionnaire (CSHQ). It is a parent-reported questionnaire designed to evaluate sleep problems in school-age children aged 4-10 years.[12] The Portuguese version of the CSHQ (CSHQ-PT) was developed to detect sleep disorders in children aged 2-10 years with the addition of psychometric measures.[13]

Allergic rhinitis may disrupt sleep mechanisms through various mechanisms. Increased airway resistance also poses a risk for obstructive sleep apnea. In addition, allergic rhinitis may lead to hypertrophy of the tonsils and adenoid gland. All these factors may contribute to sleep disturbance.[14] In allergic rhinitis, an increase in nasal turbinate edema also occurs in the typical lying position.[15]

Increased levels of histamine, IL-1b, IL-4, IL-10 and bradykinin have been found to be associated with poor sleep hygiene in patients with allergic rhinitis.[16] Increased levels of histamine, the basic architect of the sleep-wake cycle, contribute to sleep problems. Sleep problems associated with increased histaminergic response benefit greatly from antihistamine treatment.[17]

In a study investigating the relationship between allergic rhinitis and sleep disturbance, it was found that IL-1b, IL-4 and IL-10 levels were higher in patients with allergic rhinitis and were associated with shortened REM sleep with rapid eye movements.[18]

Increased free oxygen radicals and lipid peroxidation have been observed in children with obstructive sleep apnea. Increased oxidative stress, which is thought to be the result of chronic inflammation, may be similar in patients with allergic rhinitis.[19]

Our study revealed that sleep problems were observed more frequently in children with allergic rhinitis in accordance with the literature. When we classified the case group as persistent and intermittent AR, no difference was observed, but a significant difference was found compared to the control

group. A scale that had not been used before on patients with allergic rhinitis was administered. In children with attention deficit hyperactivity, the level-2 6-17 years DSM-5 sleep scale was administered to the parents of children aged 6-17 years and the level-2 11-17 years DSM-5 sleep scale was administered to the adolescent age group, and a correlation was found with eating disorder as the scale score increased.[20] Similarly, in our study, higher scores were recorded in patients with allergic rhinitis, while no difference was observed in terms of scale score as symptom duration increased in the allergic rhinitis case group.

CONCLUSION

Our study revealed that sleep problems were observed more frequently in children with allergic rhinitis in accordance with the literature. When we classified the case group as persistent and intermittent AR, no difference was observed, but a significant difference was found compared to the control group. In the case group with allergic rhinitis, no difference was observed in terms of scale score as symptom duration increased.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Balıkesir University Faculty of Medicine Clinical Research Ethics Committee Decision No: E.346422).

Informed Consent

The study was designed a cross-sectional study

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

*Cross-sectional article

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Oral health and periodontitis: why should we care?

Kubilay Barış, Tolga Aydoğan, Meltem Karşıyaka Hendek, Ebru Olgun

[1]Department of Periodontology, Faculty of Dentistry, Kırıkkale University, Kırıkkale, Turkiye

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ABSTRACT

Periodontitis is an inflammatory disease characterized by symptoms such as bleeding gums and bad breath. Severe periodontal disease is associated with systemic diseases. Diabetes is a group of diseases characterized by high blood glucose levels and can cause oral manifestations such as dry mouth, burning and susceptibility to candidal infections. There is a reciprocal relationship between diabetes and periodontitis. Various diseases such as hypertension, kidney disease, multiple sclerosis, liver disease and inflammatory bowel disease are also associated with oral health. Periodontal treatment can play an important role in the management of these diseases.

Keywords: Periodontitis, oral disease, other disease

INTRODUCTION

The mouth is an integral part of our body and one of the parts that contains many microorganisms. Periodontitis is an inflammatory disease characterized by clinical loss of attachment, gingival bleeding, bad breath, tooth mobility and swelling of the gums. Attachment loss can be defined as the loss of periodontal ligament cells and supporting alveolar bone. Severe periodontal disease affects approximately 11.2% of the world. Scientists recognize that there is a relationship between oral diseases and systemic diseases. Systemic diseases can be defined as diseases that affect a person's life and require medical treatment. In this chapter, the relationship between oral diseases and diseases such as heart diseases, respiratory diseases, cerebrovascular diseases, metabolic diseases, hypertension, kidney diseases, rheumatoid arthritis will be discussed.

DIABETES MELLİTUS

This is a group of diseases characterized by high blood glucose levels caused by a lack of insulin production, ineffective insulin or both. There are two main types of diabetes. Type 1 diabetes or insulin-dependent diabetes mellitus is an autoimmune disease that causes the destruction of insulin-producing β cells in the pancreas. Type 1 diabetes occurs primarily in children and young adults and accounts for about 5% of diabetes cases. Type 2 diabetes, or non-insulin-dependent diabetes mellitus, is characterized by resistance to insulin and insufficient insulin production. Type 2 diabetes is the most common form of diabetes in adults, accounting for 90% to 95% of cases.[1] Patients with diabetes may present with dry mouth and burning in the mouth as oral symptoms. There may also be increased susceptibility to oral candidal infections.

Disorders of collagen metabolism, neutrophil dysfunction and vascular changes in diabetes increase susceptibility to periodontal disease. Poor glycemic control in diabetes is associated with worsening of existing periodontal disease. On the other hand, periodontitis is associated with increased risk of diabetes complications such as dysglycemia and increased insulin resistance in patients with diabetes. Interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-6, receptor activator of nuclear factor-kappa B/osteoprotegerin ratio, oxidative stress and Toll-like receptor 2/4 have been implicated in the mechanisms associated between oral diseases and diabetes.[2] Advanced glycation end products (AGEs) are a heterogeneous, complex group of compounds formed by the non-enzymatic reaction of glucose with amino acids in proteins and other macromolecules. They can also be exogenously ingested through food. As a result of the accumulation of AGEs in diabetes, there is an increase in the parameters mentioned above due to their interaction with RAGE. Another mechanism is that periodontal bacteremia/endotoxemia resulting from daily activities such as eating and tooth brushing causes low-grade systemic inflammation through CRP and neutrophil oxidative stress responses. Increased inflammation is associated with increased glucose. In patients with diabetes, periodontal treatment can reduce HbA1C by 0.36% after three months. Hyperglycemia increases the risk and severity of periodontitis and adversely affects the outcomes of periodontal treatment. The magnitude of short-

Corresponding Author: Kubilay Barış, Kubilaybaris60@hotmail.com

term HbA1C reductions achieved following periodontal interventions is similar to that usually achieved by adding a second drug to a pharmacologic regimen. Emerging evidence also suggests that people with severe periodontitis have an increased risk of developing type 2 diabetes.

All patients with diabetes should receive oral health education as part of their general education program. It should be recognized that diabetes increases the risk of periodontal disease and if left untreated, periodontitis can have a negative impact on metabolic control and increase the risk of complications of diabetes. Successful periodontal treatment has a positive impact on metabolic control and complications of diabetes. Physicians should ask patients with diabetes about a previous history of periodontal disease. If a positive diagnosis of periodontitis is made, they should refer the patient to a periodontologist to ensure that periodontal care and maintenance is provided. Questioning the presence of periodontal disease should be an integral part of the diabetes care visit. Patients with diabetes should be asked about positive signs and symptoms of periodontitis, including bleeding gums during brushing or eating, loose teeth, gapping or angulation of teeth, foul odor in the mouth, presence of abscesses in the gums, swelling, redness of the gums. Periodontal assessment should be recommended for all newly diagnosed diabetics as part of ongoing diabetes management.

CARDIOVASCULAR DISEASES (CVD)

CVD are among the leading diseases that place a significant burden on global health services. Ischemic heart disease, rheumatic heart disease, cardiomyopathy and atrial fibrillation cause more than 95% of CVD-related deaths. The term CVD is used as a general term for atherosclerotic diseases, particularly coronary heart disease, cerebrovascular disease and peripheral vascular disease. Diseases such as rheumatoid arthritis, psoriasis, systemic lupus erythematosus and periodontitis are associated with an increased risk of developing CVD. Although there is evidence that more than 50 gene polymorphisms are involved in the modulation of atherogenesis, the main traditional risk factors are smoking, dyslipidemia, impaired glucose metabolism, hypertension and lifestyle factors.[3]

An association between periodontitis and CVD has been shown in studies in several different populations. In populations with multiple morbidities, such as co-morbid diabetes and chronic kidney disease, periodontitis is significantly responsible for cardiovascular mortality. It appears that periodontitis may be a modifiable non-traditional risk factor for CVD. The mechanisms associated between periodontitis and CVD are thought to be mediated by elevations in bacteremia, CRP and oxidative stress. The periodontopathogenic bacteria present in periodontitis and the systemic inflammation caused by periodontitis pose strong risks for atherosclerotic CVD. In addition, it can directly or indirectly induce systemic inflammation that influences the development of atherothrombogenesis.[6] Bacteria in the oral microbiota can translocate into the circulation. *Porphyromonas gingivalis (P. gingivalis)* and *Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans)*, which are potent periodontopathogens, have been shown in atheroma plaques.[7] Dyslipidemia may increase the risk of CVD by increasing oxidative stress. In a study, it was found that decreased CRP decreased inflammation in brachial artery endothelium. *P. gingivalis* has been shown to accelerate atherosclerosis in murine models, induce fatty streaks in the aorta of rabbits and induce aortic and coronary lesions after normocholesterolemia. A polymicrobial infection such as periodontitis has been shown to induce an enhanced oxidative stress reaction, Toll-like receptor and inflammatory signaling produced in aortic endothelial cells. *P. gingivalis* facilitates the entry and attachment of Hag a-expressing bacteria into coronary artery endothelial cells. Periodontal treatment is known to cause a decrease in IL-1β, IL-8, IL-6 and fibrinogen levels.[4]

It should be recognized that periodontitis may have a negative impact on CVD and may also increase CVD complications. Conversely, effective periodontal treatment has positive effects on cardiovascular health. Physicians should ask about a prior history of periodontal disease in CVD. If a positive periodontitis diagnosis is made, they should refer the patient to a periodontology specialist to ensure that periodontal care and maintenance is provided. In CVD, questions should be asked about signs and symptoms of periodontitis, including bleeding gums during brushing or eating, loose teeth, gapping or gapping/rotting of teeth, bad breath and/or gingival abscesses or suppuration.

HYPERTENSION

An arterial blood pressure higher than 140/90 mmHg on repeated measurements is known as hypertension. Hypertension is a systemic disease characterized by persistently high blood pressure and is an important health problem because it causes serious adverse conditions and is widely prevalent in the society.

Periodontitis and hypertension share risk factors such as old age, male gender, smoking, overweight/obesity, diabetes, low socioeconomic status and poor education. One of the mechanisms associated between hypertension and periodontitis is endothelial dysfunction. It is known that endothelial dysfunction can improve with periodontal treatment and a decrease of 1.3 mm Hg in blood pressure value has been reported in studies. Another mechanism is that periodontitis acts as a source of inflammation and oxidative stress and in the long term causes functional and anatomical vascular changes such as arterial stiffness and increased vascular resistance. It has shown that T cells play a central role in the development of hypertension. Specifically, following hypertensive stimuli, activated T cells accumulate in perivascular tissue. T cells are also known to be involved in periodontitis.[4]

The estimated surface of the periodontium is equal to the palm of one hand. The impact of this significant amount of local inflammation during generalized periodontitis can have a significant impact on systemic inflammation. The burden of periodontitis causes hypertension to worsen. Achieving periodontal health may provide effects equivalent to lifestyle modification in the control of hypertension. The effects of antihypertensive drugs that cause gingival enlargement should also be carefully evaluated and should not be confused with periodontitis. Calcium channel blockers among antihypertensive drugs may cause this effect. In such cases, gingival treatment should first be performed by a periodontologist and if there is no improvement, this drug group should be changed.

KIDNEY DISEASES

Chronic kidney disease (CKD) is defined by abnormalities in kidney structure or function and is characterized by persistent nephron loss and ultimately a decrease in glomerular filtration rate. CKD can be classified into glomerular, vascular, renal tubulointerstitial, cystic and other congenital diseases. Due to its generally poor prognosis, the CKD mortality rate has increased by 31.7% in the last 10 years, making it one of the leading causes of death worldwide.[5]

In periodontitis, red complex bacteria consisting of *Tannerella forsythia (T. forsythia)*, *Treponema denticola (T. denticola)* and *P. gingivalis* are the main causes of periodontitis. Oral bacteria can spread through the bloodstream and ingestion and use the circulatory system to induce inflammatory responses in distant tissues. One of the mechanisms associated between periodontitis and CKD is that oral bacteria reach kidney tissue via the bloodstream. One study showed an increased frequency of *P. gingivalis*, *T. forsythia* and *T. denticola* in CKD patients. The antibody titer of *A. actinomycetemcomitans*, which is also responsible for oral diseases, was found to be high in CKD. Indirect effects of inflammatory mediators in periodontitis are another mechanisms associated between CKD and periodontitis. Inducible nitric oxide produced in periodontitis may affect the kidney.[5]

Evidence supports the role of periodontal inflammation and elevated serum inflammatory mediators in the development of renal atherosclerosis, renal impairment and end-stage renal disease. Patients should be assessed by asking them about symptoms of periodontitis, including bleeding gums during brushing or eating, loose teeth, gapping or gapping/rotting of teeth, bad breath and/or gingival abscesses or suppuration.

MULTIPLE SCLEROSIS (MS)

MS is an acquired, chronic, immune-mediated, inflammatory condition of the central nervous system that can affect the brain, brainstem and spinal cord.[8] It occurs when autoantibodies attack the myelin sheath proteins that surround neurons. The resulting inflammation affects neuronal function and leads to scarring and plaque formation. Lack of oral care and difficulties in accessing a dentist have the potential to increase the risk of developing periodontal disease and tooth decay in patients with MS. The mechanism linking MS and periodontal disease is that periodontal disease affects MS patients because it is an inflammatory disease. Patients should be evaluated for symptoms such as gingival bleeding, bad breath, elongated appearance of teeth, and loose teeth that may be suspicious for periodontitis.[9]

LIVER DISEASES

Chronic liver disease (CHD) is a general term used to refer to a range of pathologies characterized by a progressive deterioration in liver function over a period of more than six months. Viral infections, toxin exposure, alcohol abuse, autoimmune diseases, genetic and metabolic disorders can lead to destruction of the liver parenchyma and increased AST and ALT release. The associated mechanisms between periodontitis and CHD are reactive oxygen products and oral dysbiosis. The oral cavity has the second largest microbiota after the gut and interacts with diverse microbial populations in different parts of the body. Oral dysbiosis can lead to intestinal dysbiosis. The resulting gut dysbiosis affects liver function. Several studies using rabbits have shown that the introduction of major periodontal bacteria, especially *P. gingivalis*, by oral gavage directly caused liver damage. Periodontal disease has been shown to increase MCP-1, TNF-α and IL-17 levels.[10] Periodontitis increased Galectin-3, the most important molecule that induces liver fibrosis as CHD progresses to cirrhosis. It is known that Smad2, Smad3 and ERK1/2 phosphorylations and TGF-β1 production are stimulated in hepatocyte cells infected with *P. gingivalis*.

INFLAMMATORY BOWEL DISEASE (IBD)

IBD is characterized by chronic recurrent intestinal inflammation and consists mainly of ulcerative colitis and Crohn's disease.[10] IBD morbidity has increased dramatically since the twentieth century. Studies suggest that environmental factors, genetic predisposition, gut microbiota and immune responses play a role in the development of IBD. Among these factors, gut microorganisms play a key role in the development and progression of IBD. The associated mechanism between periodontitis and IBD is oral dysbiosis. An unbalanced microecology affects the gut.[11] The second mechanism is that periodontitis produces inflammation that exacerbates IBD. Periodontitis has been suggested as a potential predisposing factor in IBD. *T. denticola* and other bacteria have been shown to be present as an opportunistic pathogen in the subgingival plaque in IBD.[12]

RAMATOID ARTHRITIS (RA)

RA is a systemic inflammatory autoimmune disease characterized by chronic inflammation and joint tissue destruction, potentially leading to functional limitation. Similar to periodontitis, anaerobic bacterial dysbiosis is seen in RA.[13] The association between RA and periodontal disease has been associated with higher periodontal disease compared to healthy controls, independent of the duration of RA disease or factors such as smoking. Periodontal disease is now recognized as a risk factor for RA and appears to play a central role in disease onset. The gram-anaerobic bacterium *P. gingivalis* is associated with RA and periodontal disease through its ability to induce citrullination of proteins via the endogenous peptidylarginine deiminase enzyme.[14] RA activity is significantly greater in patients with periodontitis and decreases with nonsurgical periodontal treatment.

LUNG DISEASES

The lung microbiome is important not only in the classic infection-related diseases, pneumonia, bronchiectasis and cystic fibrosis, but also in chronic non-infectious lung diseases such as chronic obstructive pulmonary disease (COPD), asthma and pulmonary lung disease. Studies have shown an association between periodontitis and asthma, COPD and pneumonia as a result of oral dysbiosis affecting the lung microbiome.[15] Periodontitis and respiratory diseases are public health problems and oral health is important in the management of respiratory diseases.

CANCER

Clinical studies have confirmed the impact of periodontal disease on the systemic immune response, showing that serum markers of inflammation, particularly CRP levels, increase with advanced periodontal disease. The link between systemic inflammation and cancer is well recognized. Interest in the role of inflammation in cancer has led to studies showing positive associations between periodontal disease and lung cancer risk. Associations have been found between oral cancers, gastrointestinal cancers, lung cancer, pancreatic cancer and periodontal disease.[16]

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a cerebral dysfunction associated with loss of cognitive function. It can be caused by many causes such as alcoholism and other toxic substances, vascular disease, malignancy, trauma, and metabolic disorders. The most important clinical findings of AD are memory loss, difficulty in performing daily tasks, impairments in language functions and visual perception. Hallucinations and depression are common at the onset of the disease. Periodontitis is common in the elderly and may become more prevalent in FH due to a reduced ability to pay attention to oral hygiene as the disease progresses. High antibodies against periodontal bacteria, increased systemic proinflammatory state may occur. Increased proinflammatory cytokines have been associated with an increased rate of cognitive decline in AD. Periodontitis may exert an increase in cognitive decline that may be mediated in AD through its effects on systemic inflammation.[17]

THYROID DISEASE

The thyroid organ regulates many functions of the body thanks to the hormones it produces. Too little or too much secretion of these hormones can lead to different diseases in the body. The thyroid is a typical organ in which organ-specific autoimmune disease and chronic inflammation often occur. Thyroid hormones play an important role in oxidative stress and inflammation in humans. In studies, periodontitis is associated with thyroid diseases through oxidative stress and inflammation.[18]

CONCLUSION

The World Health Organization has stated that oral diseases are serious health problems, and that oral health awareness worldwide should be considered as an important condition for overall health and quality of life. There is evidence that periodontitis is associated with approximately 60 non-oral diseases, including but not limited to cardiovascular disease, hypertension, obesity, atherosclerosis, diabetes and stroke. Physicians should consider the impact of periodontal disease when evaluating patients with systemic diseases and provide disease management.

ETHICAL DECLARATIONS

Referee Evaluation Process

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The dental perspective on metformin

Elif Tuğba Yollar

Department of Restorative Dental Treatment, Gülhane Faculty of Dentistry, University of Health Sciences, Ankara, Turkiye

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ABSTRACT

Metformin is a safe, non-toxic and well-tolerated drug most commonly prescribed for the treatment of diabetes. Additionally, metformin is a drug that has been reported to be used in the treatment of liver and kidney disorders and bone disorders, as well as in the treatment of diabetes. It has become popular in the field of dentistry with the discovery of the odontogenic, osteogenic and angiogenic effects of metformin in recent studies. With these properties, metformin was combined with many substances used in dentistry and its effects on teeth and surrounding tissues were examined. The purpose of this review is to provide an overview of the studies conducted with metformin in the field of dentistry.

Keywords: Metformin, odontogenic, osteogenic, dentistry

INTRODUCTION

Millions of diabetics take metformin as their first course of treatment for type 2 diabetes mellitus(T2DM).[1] It is secure, non-toxic, and well tolerated in its role as an insulin sensitizer.[1-3] By reducing gluconeogenesis in the liver, glucose absorption in the small intestine, and the production of free fatty acids in adipose tissue, metformin lowers blood glucose levels and increases glucose uptake by muscle.[4] Metformin has been examined for its ability to reduce blood sugar levels as well as for its cardiovascular system protection and anti-cancer properties in various malignancies.[4-6] According to Kim et al., the radiation sensitizing action of Metformin on hepatocellular carcinoma is caused by an increase in DNA degradation, cell cycle arrest, and apoptosis.[7]

Benefits of metformin have been documented in the treatment of liver illnesses,[8,9] renal damage and disorders,[10] neurodegenerative diseases[11-13] and bone abnormalities,[14] depending on the patient profile and different disease circumstances. Metformin has a number of important features that researchers have looked into ways to enhance. These properties include the potential for odontogenic, osteogenic, and angiogenic differentiation, which have a number of potential clinical uses.[15-17] Metformin can enhance osteoblast development of MSCs (mesenchymal stem cells) employed in tissue regeneration, according to in vitro and in vivo investigations.[15,18] This review aims to provide an overview of the various benefits of metformin and its uses in dental treatments.

MECHANISM OF EFFECT OF METFORMIN

Metformin's main target in eukaryotic cells is complex-I of the electron transport chain, which results in an accumulation of ROS (Reactive oxygen species) and oxidative damage to lipids, proteins, and DNA and can enhance the effects of ionizingradiation.[19,20] The initial energy conversion complex of several respiratory chains in eukaryotic cells, Complex-I (proton-pumping NADH), sets up the proton motive force necessary for energy-consuming pathways. The respiratory chain has complex-I homologues for many microorganisms.[21,22]

Metformin's suppression of complex-I causes eukaryotic cells to use less oxygen and produce less adenosine triphosphate (ATP). Adenosine monophosphate (AMP) levels rise in eukaryotic cells as a result of the reduction in ATP generation, and the energy sensor AMP-activated kinase (AMPK) is activated.[20] Two regulatory subunits (a and b) and a catalytic subunit (a) make up the serine/threonine protein kinase known as AMPK.[23]

AMPK is activated and AMP concentrations rise in response to dietary restriction, hypoxia, and metformin treatment when ATP concentrations are low.[24] Neutrophils or macrophages are more effective in killing bacteria when AMPK is activated. Innate immune responses that include the phagocytosis of microorganisms in the presence of neutrophils and macrophages are essential for regulating inflammation.[25]

Corresponding Author: Elif Tuğba Yollar, dt.tugbaaltiparmak@gmail.com

STUDIES IN DENTISTRY WITH METFORMIN

Metformin-containing resins were found to be promising in a study by Wang et al. for a wide range of dental applications, including deep caries and exposed pulp cavities, to encourage DPSCs (dental pulp stem cells) to synthesize new dentin and protect the pulp.[26] In a different study by Houshmand et al., metformin promoted osteogenic differentiation of dentin pulp stem cells in osteogenic medium, while metformin did not produce differentiation in conventional medium.[27] The odontogenic differentiation of dental pulp stem cells was greatly boosted by the addition of metformin to the calcium phosphate cement-chitosan composite, according to research by Qin et al., without impairing cell survival or proliferation.[28]

According to the findings of the study by Boreak et al.,[29] pretreatment with metformin increased the angiogenic ability of the DPSC secretome as seen by the growth of quaternary blood vessels in the chick embryo yolk sac membrane model after treatment with the DPSC secretome. The creation of vascular tubules in 3D cultures demonstrated that the use of a serum-free culture medium generating growth factors such as B27, heparin, and VEGF-A (Vascular Endothelial Growth Factor-A) improved the ability of DPSC for vasculogenesis.[30] Qin et al.[16] believed that metformin could play a significant pharmacological role in triggering odontoblastic differentiation and offer new perspectives for the treatment of pulp exposure in an in-vitro study that sought to investigate the effects of metformin on the proliferation and differentiation of DPCs.

Farnaz et al. found that 100 Mol/L metformin boosted dental pulp stem cell viability in their preliminary study evaluating the effects of metformin on both proliferation and osteogenic capacity of dental pulp stem cells cultivated on freeze-dried bone allograft granules. Metformin has also been demonstrated to improve dental pulp stem cell survival when cultivated on freeze-dried bone allograft granules.[31] Zhang et al. employed the CCK-8 assay to assess the proliferation potential of young and elderly DPSCs treated with different concentrations of metformin (10, 50, 100, 250, and 500 M) in order to choose the metformin concentration to be used in the investigations. It has been demonstrated to inhibit and promote DPSC growth.[32]

Dental professionals may use photodynamic therapy to treat and diagnose malignancies and mouth infections. A viable substitute for antibiotics that are more likely to develop resistance to the oral bacterial flora may be offered by photodynamic therapy's antibacterial function.[33] In the study of Afrasiabi et al., they found that the use of metformin in combination with photodynamic therapy would increase the effectiveness of photodynamic therapy and thus lead to its potential effect in reducing periodontal infections.[34]

The tumor of epithelial origin known as oral squamous cell carcinoma (OSCC) is malignant and aggressive, and it is now one of the leading causes of cancer-related fatalities.[35] Although there are many different treatment options, including surgery, chemotherapy, and radiotherapy, none have been proven to increase survival rates. A trustworthy therapeutic substance is urgently required for the detection and growth suppression of cancer cells.[36] MF has proven to have promising anti-cancer capabilities in the search for a workable agent.

The potential of metformin to target PI3K/mTOR (Fosfatidilinositol 3-kinaz/ Mammalian Target of Rapamycin) signaling for the prevention of head and neck squamous cell carcinoma was examined in a single-arm, open-label phase IIa clinical trial in patients with oral premalignant lesions by Gutkind et al. Clinical examination and biopsy were performed both before and after therapy on people with oral premalignant lesions who were otherwise healthy and did not have diabetes. For 12 weeks, participants took metformin. Blood, saliva, and pre- and post-treatment biopsies were collected for various biomarker studies. The results of this study support further research into metformin as a chemopreventive drug by showing that it increases histological responses and modulates the mTOR pathway when administered.[37]

According to the study by Liu et al. examining the effect of metformin on oral squamous cell carcinoma (OSCC) and the underlying processes, metformin reduced oral squamous cell carcinoma growth.[38]

Pyruvate dehydrogenase levels were assessed in patients with oral squamous cell carcinoma and oral dysplasia in the study by Guimares et al., which sought to determine the effects of metformin in hypoxic circumstances. To examine metformin's effectiveness in the presence of hypoxia, it was given intravenously. An oral squamous cell carcinoma cell line model showed that metformin decreased cell growth and migration.[39]

Locally applied metformin as an aid to scaling and root planing has been proven to be more advantageous than scaling and root planing alone in the treatment of periodontal abnormalities because of the significant role that metformin plays in bone growth and immunomodulatory function.[39] Better treatment outcomes for intraosseous defects have been observed in numerous clinical trials using different metformin gel doses.[40,41]

Five groups of twenty one rats each were randomly assigned to the Arajo et al. study to examine the effects of metformin on inflammation, oxidative stress, and bone loss in a rat model of ligature-induced periodontitis. The rats received different doses of metformin as well as metformin with and without ligatures for 10 days. It was determined that rats with ligature-induced periodontitis experienced less inflammation, oxidative stress, and bone loss when treated with metformin at a dose of 50 mg/kg.[42]

In the study of Kominato et al. to investigate the effects of metformin on gingival wound healing in insulin-resistant prediabetes, mice were fed a normal diet or a high-fat diet for 10 weeks; Half of the high-fat diet mice were treated with metformin (high-fat diet + met) for the past 2 weeks. Insulin and glucose tolerance tests were performed. The palatal gingiva (2.0 x 0.5 mm) was surgically removed adjacent to the maxillary molars. Postoperative wound closure was evaluated histomorphometrically for 1 week.

The mRNA expression of VEGF and endothelial nitric oxide synthase (eNOS) in tissue was measured by real-time polymerase chain reaction. In vitro proliferation and migration of human gingival fibroblasts cultured under high glucose or control conditions with/without metformin were analyzed. Metformin improved delayed gingival wound healing in insulin-resistant prediabetes by accelerating HGF(Hepatocyte growth factor) proliferation and migration through Akt phosphorylation in the insulin signaling pathway.[43]

The effectiveness of host modulators combined with non-surgical periodontal therapy in lowering probing pocket depth in individuals with periodontitis was examined in the review by Donos et al. They came to the conclusion that there was promise for therapeutic application of the local bisphosphonate and metformin gels in subbony deformities, but this needed to be verified.[44]

Bak et al.[45] examined the impact of metformin on osteoblast, osteoclast, and adipocyte development as well as alveolar bone loss in ligate-induced periodontitis. They came to the conclusion that through promoting osteoblast development, metformin may have a positive impact on alveolar bone in periodontitis.

In the systemic review of Ikbar et al.,[46] they aimed to evaluate the efficacy of MF containing Platelet Rich Fibrin (PRF) alone on Platelet Rich Fibrin in the treatment of periodontal bone defects. They demonstrated the complementary benefits of MF + PRF combination therapy over monotherapy in resolving periodontal bone defects. The quest to achieve maximum regeneration in periodontal bone defects, combination therapies such as MF + PRF have been reported to be better treatment options than other modalities.

In order to treat subbone abnormalities in patients with chronic periodontitis, Patil et al.[47] conducted a clinical and radiographic comparison and evaluation of the efficacy of 1.5% MF gel and placebo gel as an addition to scaling and root correction (SRP) and curettes. Using 1.5% metformin topically improved the clinical results of curettage and standard treatment (SRP).

The ability of MF to have favorable impacts on orthodontic tooth mobility is another noteworthy feature. To show how MF affects orthodontic mobility, Sun and colleagues conducted a study on Wistar mice with induced T2DM(Type 2 Diabetes mellitus) in 2017. The experimental and control groups of rats received orthodontic appliances, and two weeks later, the outcomes were assessed. Histological evidence that MF lowers the probability of unintended orthodontic tooth movement is provided by the fact that MF-treated rats showed increased tooth movement with normal osteoclast levels. Additionally, MF reduced the expression of sclerostin and enhanced the immunolocalization of the dentin matrix protein.[48]

Metformin monotherapy dramatically speeds up the osseointegration of intraosseous implants, according to studies in animal models. By blocking the negative effects of advanced glycation end products on osteoblastic cells, including interactions with receptors for advanced glycation end products, metformin's effects on wound healing are essential for implant survival.[49]

The utilization of stem cells from human exfoliated deciduous teeth (SHED) in tissue engineering and regenerative medicine is highly promising. According to research done in 2020 by Zhou et al., MF stimulates the AMPK pathway, which in turn induces osteogenic differentiation in SHEDs. It also has a beneficial impact on the production of osteogenic genes and proangiogenic growth factors in SHEDs.[50] According to a recent study by Deng et al., MF pre-treatment significantly increases the SHED-mediated angiogenesis in vivo of human umbilical endothelial cells in addition to promoting cell proliferation and inducing multiple forms of differentiation; these findings may pave the way for the use of SHEDS pre-treated with MF for tissue regeneration.[51]

CONCLUSION

Metformin can reduce inflammation, obesity, cardiovascular and renal illnesses, malignancies, polycystic ovarian syndrome, osteoporosis, and periodontitis, according to several cell culture research, animal studies, and clinical trials. Furthermore, it has been demonstrated that these effects involve a variety of molecular interactions. The advantages of metformin and its use in medicine are appropriate for dental procedures. To produce trustworthy evidence, however, it is probable to require repetitive and lengthy chapters. The precise dose and mode of action of metformin in dentistry can be ascertained by thorough in-vivo research.

ETHICAL DECLARATIONS

Referee Evaluation Process

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Conflict of Interest Statement

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Rehabilitation of total hip arthroplasty

Turgut Kültür, Ahmet Özkan

Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkiye

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ABSTRACT

THA, which is among the most frequently performed surgical procedures in the world; It is indicated for many diseases affecting the hip joint, especially for persistent pain that occurs at rest and at night and is unresponsive to conservative treatment. In this surgery, where cement, cementless and hybrid models are used, the existing methods have advantages and disadvantages compared to each other. However, no matter which method is used, patients should be followed carefully after the operations for possible complications. The surgical method applied may cause some differences in the rehabilitation process, and it is very important to pay attention to these differences in the treatment program.

Keywords: Total hip arthroplasty, hip, arthroplasty, rehabilitation

INTRODUCTION

Arthroplasty; it can be broadly defined as a reconstructive surgical intervention performed to correct the structure or function of a joint. Total hip arthroplasty (THA) has become one of the most frequently performed surgical procedures in the world. The main indication for Total Hip Arthroplasty has been reported as persistent pain that occurs outside of movement, at rest and at night, and is unresponsive to conservative treatment.The second reason is defined as the presence of severe or complete limitation of movement accompanied by pain, and as a result, the patient's daily life and work activities are negatively affected and the quality of life is impaired.

ENDICATIONS OF TOTAL HIP ARTHROPLASTY

The indications for total hip arthroplasty are very broad. Total hip arthroplasty can be applied in many diseases that cause hip pain and movement limitation.

Among these indications;[1-3]

- Osteoarthritis (primary, secondary) (Figure 1)
- Inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis)
- Femoral head avascular necrosis (Figure 2)
- Pyogenic arthritis or osteomyelitis
- Hip joint tuberculosis
- Bone tumors

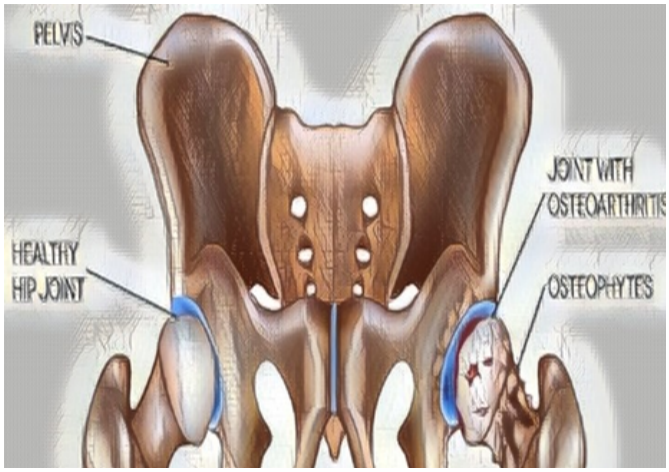

Figure 1. Osteoarthritis (primary, secondary)

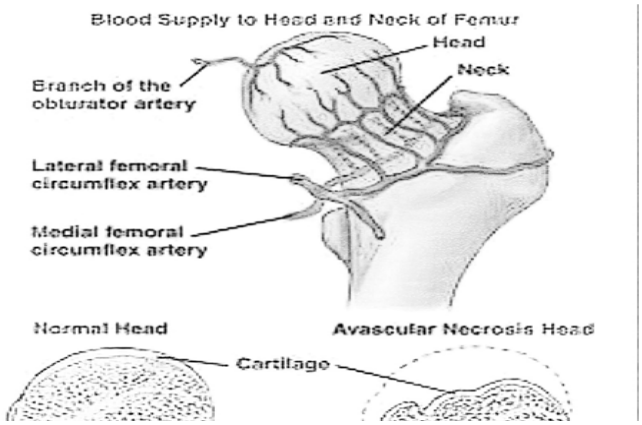

Figure 2. Femoral head avascular necrosis

Corresponding Author: Turgut Kültür, kurgut@hotmail.com

- Hereditary diseases
- Previous unsuccessful/complicated hip operations
- Hip osteotomies
- Slipped capital femoral epiphysis; can be shown.[1]

CONTRENDICATIONS OF TOTAL HIP ARTHROPLASTY

An active infection in the hip or other site, an unstable systemic disease that may increase morbidity and mortality; While it is considered as an absolute contraindication, any disease that rapidly destroys the bone, neuropathic arthropathy, abductor group muscle weakness and rapidly progressing progressive neurological disorders can be considered as relative contraindications.[2]

PREOPERATIVE EVALUATION IN TOTAL HIP ARTHROPLASTY

Careful evaluation of the patient before surgery is important in terms of complications. The most important point here is whether the level of pain requires such an elective operation. The patient's life expectancy and post-surgical expectation should also be taken into consideration. It is essential to make a comprehensive pre-operative evaluation, including laboratory tests. The medications used by the patient and his/her allergy history should be taken into consideration. Pyogenic skin infections must be treated. Likewise, genitourinary and dental problems should be resolved. During physical examination, the strength of the abductor muscles should be evaluated with the Trendelenburg test. If hip and knee replacement on the same side is required, the hip should be operated on first. In bilateral hip involvement, priority should be given to the painful one, and after 3 months or more, the other hip must be operated on. When a unilateral operation is performed, both hips can be operated in the same session in the presence of bilateral serious limitations and deformities that will affect the rehabilitation process. It has been shown that there are significant improvements in parameters such as pain, function, range of motion and psychosocial status in patients who practice exercises and receive training in the preoperative period.[3-5]

SURGICAL TECHNIGUES IN TOTAL HIP ARTHROPLASTY

There are three different methods used for component detection in Total hip arthroplasty. These are cemented (cemented), cementless (cementless) and hybrid model method. Both methods have advantages and disadvantages over the other. Operation with or without cement may affect the limitations regarding load bearing (Figure 3, Figure 4).

Total hip arthroplasty is one of the operations with the highest patient satisfaction. However, it should not be forgotten that postoperative complications such as thromboembolism, periprosthetic infection, hip dislocation, osteolysis and mortality may occur. Many studies comparing postoperative complications and mortality rates between operations performed with and without cement; It shows that there are no significant differences in the risks of mortality and postoperative complications between the two methods.[1,2-6-9]

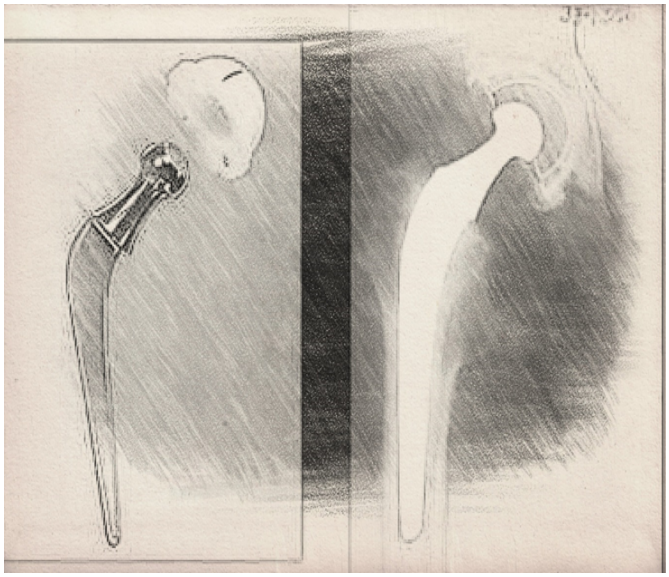

Figure 3. Operation with cement may affect the limitations regarding load bearing

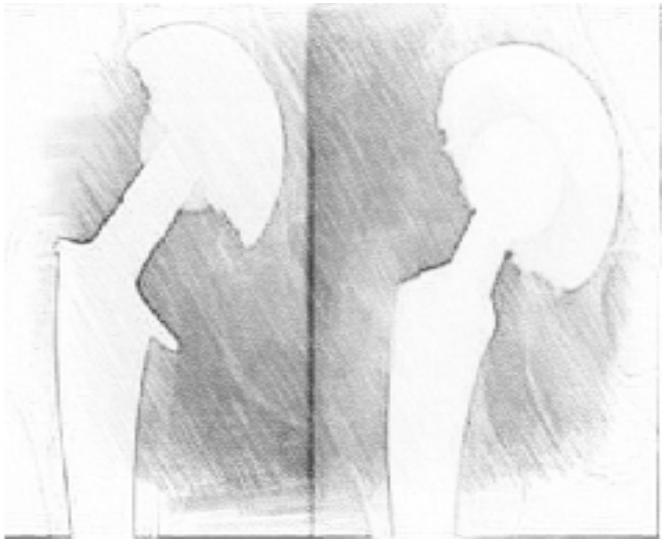

Figure 4. Operation without cement may affect the limitations regarding load bearing

REHABILITATION GOALS

The main rehabilitation goals in total hip arthroplasty are;

- Taking precautions against dislocation of the prosthesis,
- Mobilizing the patient as early as possible,
- To take precautions against complications that may be caused by long-term immobilization (deep vein thrombosis, pulmonary embolism, pressure sore, pneumonia),
- Ensuring independent transfer and ambulation with assistive walking devices,
- To provide pain-free hip joint movement within the permitted ROM degrees,
- Strengthening the muscles around the hips
- It can be considered as increasing the functional level of the patient to enable him/her to be independent in daily living activities and work life.[1]

If there is no special contraindication, full load pressing and ambulation are aimed for cemented prostheses starting from

the 3rd day. In cementless prostheses, the initial fixation of the implant is in the form of press fit. For this reason, maximum strength can only be achieved after sufficient bone advancement into the implant. Although it is thought that there is a sufficiently strong fixation at the end of the 6th week, maximum stability only occurs after 6 months.[1,2]

Total hip arthroplasty rehabilitation is very important to maximize functional level as soon as possible, especially in elderly patients.

POST-OPERATIVE REHABILITATION PROGRAM

Highlights;

- Initial muscle strength assessments,
- Sitting-standing transfers
- It includes balance and walking training.
- Transfer and walking training exercises are progressed depending on the patient's age, weight-bearing status, preoperative ambulation level and degree of recovery, and the transition is made from simple walking to climbing obstacles and ramps according to the patient's needs.
- Therapeutic exercises initiated at the first visit should include lower extremity isometric exercises (quadriceps, hamstring, and gluteal sets) and ankle pumping exercises.

On the 2nd day; while continuing the previous exercises, range of motion (ROM) exercises and heel slide exercises are performed within the allowed limits in the supine position.

On the 3rd and 4th days; it is recommended to perform long arc quadriceps exercises with heel lift in a sitting position along with the previous exercises.

5-7. days; mini squats, 90 degree hip flexion, standing hip extension, and stepping forward are added to these exercises.

SITUATIONS TO BE CAREFUL DURING THE REHABILITATION PROGRAM

In the straight leg lifting exercise, a load of at least 1.5 times the body weight is created. For this reason, it should be applied when partial and full load bearing are passed. If pain occurs, it is recommended to place a support under the knee to reduce the stress on the hip and perform hip flexion and knee extension exercises separately. In the operated hip, the quadriceps is atrophic and the thigh flexors are weak. Even isometric contractions of the hip abductors should be performed very carefully during trochanter osteotomy. When climbing stairs, first the healthy leg, then the operated leg, and finally the crutches are carried to the upper step. When going down the stairs, the crutches are taken down first, then the operated leg, and lastly the healthy leg.

The amount of load to be given to the operated extremity should be determined according to the type of fixation of the components and the presence of trochanteric osteotomy or bone graft. It should not be forgotten that restrictions such as fingertip weight bearing or partial weight bearing applied after arthroplasty directly affect the level of functional independence after surgery. Although partial weight bearing represents 30%-50% of body weight, studies show that patients have difficulty in achieving this ratio. More than 10% of the body weight should not be applied during fingertip weight bearing.[2]

Weight bearing is of great importance for the exercise program to be applied to the patient. In the studies, the effects of the exercises performed with and without weight on functional performance, Harris hip score, muscle strength and muscle thickness were investigated. The results obtained showed that weight-bearing exercises were superior.[10]

POST-OPERATIVE REHABILITATION STEPS

It is very important to achieve rehabilitation goals after surgery. The rehabilitation program goals are summarized below;[2]

- At the end of the 6th post-operative week, full range of motion is achieved within the allowed limits; For example, in a patient undergoing a posterior approach, an attempt is made to achieve 90 degrees of flexion and 40 degrees of abduction at the hip.
- At the end of the 6th week, patients can drive and lie on the operated hip.
- After post-operative restrictions are removed, joint range of motion (ROM) can be increased to a better level with stretching exercises.
- In the next stage, functional strengthening is aimed with closed kinetic chain exercises and balance exercises.
- While independent ambulation is aimed at the 12th week, it is aimed to return to recreational and sports activities at the end of the same week.[2]

Things to Consider During Ambulation

After Total hip arthroplasty, the patient's gait pattern should be monitored after full load mobilization. The most important condition that will cause gait disorder in these patients is shown to be hip flexion. To prevent flexion contracture, it is useful to apply gentle stretching in the direction of hip extension by hanging the operated extremity down in the supine position. Again, in some studies, it has been reported that in cases where a cane is not used, the abductor muscles tend to directly overlap the trochanter major in order to balance the body weight of the patients, so the patient should walk with cane support for at least 6 months, even if his gait is smooth.[1]

Resistive Exercises

In the first year after Total hip arthroplasty, the deficits in the affected hip are 1-21% of the contralateral hip. Post-operative power loss; It is thought to be independent of hip pain, systemic infections and thigh edema. These approaches to prevent weakness and atrophy should be started immediately after surgery.

The maximum strength increase gained through resistive exercises after Total hip arthroplasty can be achieved within 4-5 weeks, and there are studies showing that the gain in strength increase can continue even after 11 months. It is thought that functional parameters such as walking

speed and stair climbing time are significantly improved by resistive exercises. In a study comparing resistive exercises, neuromuscular electrical stimulation (NMES) and conventional rehabilitation in patients undergoing THA, it was found that the hospital stay was significantly shortened in the group receiving resistive exercise.[11]

RETURNING TO SPORTS AFTER TOTAL HIP ARTHROPLASTY

In general, after Total Joint Replacement surgery, the return to sports and physical activities increases noticeably 1 year after the surgery. However, it should not be forgotten that the level of 5 years before the operation cannot be reached. And this situation varies from person to person.. The effect of physical activity on the durability of total hip arthroplasty cannot be denied. Exercise and physical activity are essential for maintaining overall health. While some sports activities can be done safely (Cycling(Most patients with previous cycling experience can cycle again within 3-6 months after total joint arthroplasty.), Bowling, Golf, Rowing, Sailing, Swimming, Walking, Aerobic exercises), some sports activities are controversial (Ballet, Fencing, Jogging, Tennis, Table tennis). Some sports are definitely not recommended (Basketball). , Football, Karate, Volleyball, Baseball).[17,19-20]

COMPLICATIONS OF TOTAL HIP ARTHROPLASTY

This complications are below; [2,12,13-16,18]

1. Mortality (reported as 0.33% for primary total hip arthroplasty and 0.84% for revision surgery)
2. Hematoma formation
3. Heterotopic ossification: Although heterotopic ossification (HO) is very common after Total hip arthroplasty, it rarely causes any symptoms. HO usually presents clinical findings as pain, stinging, jumping, tightness, instability and limitation of movement in the hip joint. Male gender, presence of enthesopathy, presence of ankylosing spondylitis or hypertrophic arthritis, presence of brain injury, presence of diffuse idiopathic skeletal hyperostosis, post-traumatic osteoarthritis, conversion of hip ankylosis to prosthesis, anterior and lateral hip approach, wide dissection and presence of preoperative HO, postoperative HO increases the risk for development).
4. Thromboembolism
5. Nerve injuries (there is a risk of nerve paralysis of 0.5% after primary total hip arthroplasty and 3.5% after revision surgery. Sciatic, femoral, obturator and superior gluteal nerves may be injured)
6. Vascular injuries
7. Limb length differences
8. Instability and Dislocations: Dislocations are shown as the most common reason for revision of total hip arthroplasty after aseptic loosening. Research has shown that the instability rate range after primary Total hip arthroplasty performed due to different etiologies is 0.5-11%, and the instability rate range in Total hip arthroplasty performed due to primary coxarthrosis is 0.3-3%.
9. Fractures (Femur and acetabulum fractures can occur during or after surgery. Women, elderly patients, patients with inflammatory arthritis, osteoporosis,(Patients with osteoporosis have a higher risk of periprostatic fracture) and metabolic diseases increase the risk of fractures.)
10. Infection (Treatment options for periprosthetic joint infection occurring after Total Hip Arthroplasty include antibiotic treatment, surgical debridement, single-stage revision, double-stage revision and resection arthroplasty/amputation.)
11. Relaxation (Figure 5)
12. Osteolysis can be considered

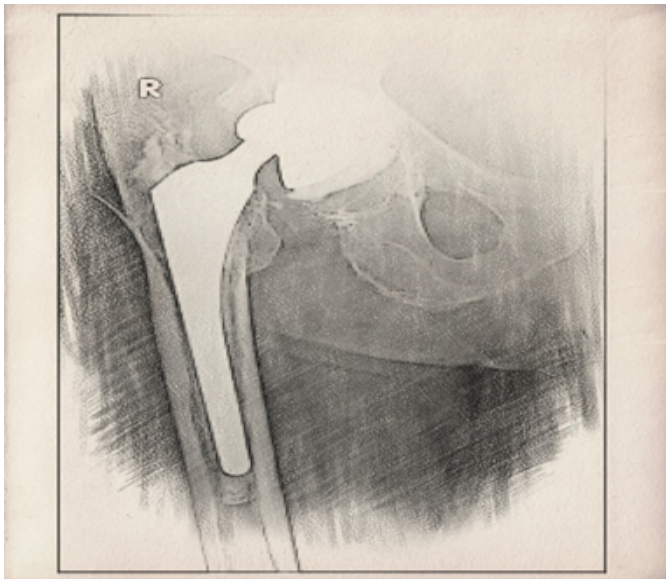

Figure 5. Relaxation

CONCLUSION

Arthroplasty, in its broad sense, is a surgical intervention performed to correct the structure or function of a joint. It is necessary to determine the right patient and the right indications before Total Hip Arthroplasty. A significant increase is observed in Daily Living activities of patients whose post-operative rehabilitation process is successful.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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