Current Researches in Health Sciences-I

Editor: Dr. Enes Karaman
Current Researches in Health Sciences-I

Editör
Dr. Enes Karaman
<table>
<thead>
<tr>
<th>Bölüm 1</th>
<th>Sayfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy and Thyroid Diseases</td>
<td>1</td>
</tr>
<tr>
<td>Ahmet Dundar - Enes Karaman</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bölüm 2</th>
<th>Sayfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoral and Radiographic Findings of Chronic Renal Failure</td>
<td>11</td>
</tr>
<tr>
<td>Yakup Şen - Sümeyye Coşgun Baybars - Merve Hacer Duran</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bölüm 3</th>
<th>Sayfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Arthritis; Covid19 Update</td>
<td>23</td>
</tr>
<tr>
<td>Nadide Koca</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bölüm 4</th>
<th>Sayfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artificial Intelligence Applications In Dentistry</td>
<td>51</td>
</tr>
<tr>
<td>Gaye Keser - Filiz Namdar Pekiner</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bölüm 5</th>
<th>Sayfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mineral Bone Diseases and Osteoporosis in Chronic Kidney Disease</td>
<td>69</td>
</tr>
<tr>
<td>Mehmet Biricik</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bölüm 6</th>
<th>Sayfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crush Syndrome: A Review of Current Knowledge</td>
<td>83</td>
</tr>
<tr>
<td>Mehmet Biricik - Üstün Yılmaz</td>
<td></td>
</tr>
</tbody>
</table>
Bölüm 7

Genetic Mechanisms of Chromosome Nondisjunction in Humans
Osman Demirhan

Bölüm 8

Preoperative Evaluation before Lung Resection
Elif Guliyev
Chapter 1

Pregnancy and Thyroid Diseases

Ahmet Dundar¹
Enes Karaman²

Abstract
Early diagnosis and effective treatment of thyroid diseases during pregnancy are the greatest priority. A delay in treatment can have severe adverse effects on the mother and unborn child. Thyroid-stimulating hormone (TSH) and T4 levels are checked as the first test to evaluate thyroid function during pregnancy. TSH levels are elevated, and T4 levels are depleted in hypothyroidism. About 2.5% of pregnant women experience it. Hypothyroidism, if left untreated, can cause neurological issues and developmental delays. 0.1-0.4% of pregnant women have hyperthyroidism. Graves' disease accounts for 80-85% of cases in pregnant women. Functional adenoma, thyroiditis, and thyrotoxicosis factitia are additional causes of hyperthyroidism in pregnant women besides Graves' disease (use of high-dose thyroxine hormone). Abortion, pre-eclampsia, premature birth, retardation in the baby's normal development, and intrauterine fetal death are possible outcomes if a pregnant woman with hyperthyroidism is not treated effectively.

Levothyroxine (LT4), used in treating hypothyroidism in pregnant women, should be started as soon as possible. During the follow-up period, it is appropriate to measure TSH every 6-8 weeks after the initiation of treatment. TSH levels should be maintained between 0.5 and 2.5 mU/L during the first trimester of pregnancy and between 0.5 and 2.5 mU/L during the second and third trimesters.

Medical therapy is the first line of treatment for hyperthyroidism during pregnancy. The goal of treatment is to maintain a serum fT4 level close to the upper limit of average values using the smallest effective dose of antithyroid medication. Due to potential side effects, treatment with propylthiouracil is preferred among antithyroid drugs. Propylthiouracil can be started at 100–150 mg per day. With 4-6 weeks of follow-up, the serum fT4 level to be used in the follow-up should be checked.

¹ Dr., Savur Prof. Dr. Aziz Sancar District State Hospital, Internal Medicine Clinic, drahmetdundar@hotmail.com, Orcid: 0000-0002-8106-7447
² Dr., Savur Prof. Dr. Aziz Sancar District State Hospital, Gynecology, and Obstetrics Clinic, dr.eneskaraman@gmail.com, Orcid: 0000-0003-1459-0606

https://doi.org/10.58830/ozgur.pub91.c380
1. INTRODUCTION

While thyroid problems can negatively affect both mother and fetus during pregnancy, early diagnosis, follow-up, and therapy are crucial. Otherwise, a situation with severe consequences for the mother and baby may occur. Free T4 and TSH are utilized in normal pregnancy to evaluate thyroid function.

During pregnancy, the thyroid gland in women undergoes several physiological changes. Human chorionic gonadotropin (hCG), which rises in the first trimester, has a comparable action on TSH receptors and produces an increase in serum total thyroxine (T4) and tri-iodothyronine (T3) levels. Thyroid stimulating hormone levels in the serum fall (1). Serum levels of thyroxine-binding globulin (TBG) are also elevated in pregnant women with high estrogen levels. By binding to total thyroxine (T4) in the circulatory system, serum thyroxine-binding globulin decreases fT4 levels (2). As a result of these modifications, tT4, and tT3 levels continue to increase until the eleventh week of pregnancy, remain steady in the weeks that follow, and remain comparable until the conclusion of the third trimester (1,2). Iodine, a necessary component of thyroid production, increases renal excretion due to elevated GFR (glomerular filtration rate) in pregnant women. As a result of the use of thyroid hormones in physiological synthesis and the use of iodine in the mother’s circulation in the fetus, there is also an increase in the need for iodine in pregnant women. Hence, during pregnancy, the serum amount of iodine falls (3). As a result, thyroxine (T4) levels in pregnant women decline, thyroid stimulating hormone (TSH) rises, and the growth of the thyroid gland becomes more noticeable in pregnant women. The risk of prenatal hypothyroidism increases in the fetus, which is more susceptible to the consequences of iodine deficiency (4,5).

The fetus needs the mother’s transplacental thyroxine hormone in the first trimester of pregnancy (1). As a result, changes in thyroid functions that may occur in pregnant women may negatively impact not only the mother but also the normal physiological development of the fetus. Hypothyroidism, which occurs at a rate of 25 per 1000 in pregnant women, is caused by increased TSH value. Overt hypothyroidism is an increased TSH value and a decreasing fT4 level (6,7). The baby may experience neurological issues and developmental delay due to hypothyroidism (8,9). On the other hand, subclinical hypothyroidism is a state in which standard free T4 is accompanied by an increase in Thyroid Stimulating Hormone levels (10). Subclinical hypothyroidism occurs at a rate of 40–85 per 1000 in the general population but only 20–50 per 1000 in pregnant women (11). Subclinical hypothyroid-
ism, like hypothyroidism, has been linked to neuropsychological issues in newborns in the future, according to specific research (12,13).

In pregnant women, the prevalence of hyperthyroidism ranges from 0.1% to 0.4%. (14). Graves’ disease is the most common cause of hyperthyroidism in pregnant women (15). The prevalence rate of Graves’ illness ranges from 80 to 85%. Besides Graves’ illness, functional adenoma, thyroiditis, and thyrotoxicosis factitia are other causes of hyperthyroidism in pregnant women (15). Abortion, pre-eclampsia, early birth, impairment in the baby’s normal development, and intrauterine fetal mortality are risks for a pregnant woman with hyperthyroidism (1,14).

2. EVALUATION OF THYROID FUNCTIONS IN PREGNANCY

When evaluating thyroid functions in a pregnant woman, it is necessary to consider the periods of pregnancy. Because the physiological changes that occur differ according to the trimester of pregnancy, TSH measurement should be done first in all pregnancies. Values of 0.1-2.5 mU/L for the first trimester, 0.2-3.0 mU/L for the second trimester, and 0.3-3.0 mU/L for the third trimester can be used (16).

3. HYPOTHYROID IN PREGNANCY

3.1. Diagnosis

According to reports, the prevalence of hypothyroidism during pregnancy ranges from 0.3% to 0.5% for overt hypothyroidism and 2% to 4% for subclinical hypothyroidism. In areas where adequate iodine is consumed, autoimmune thyroid disease is the most prevalent cause of hypothyroidism during pregnancy (17,18).

The symptoms of hypothyroidism can be mimicked by pregnancy. Symptoms include cramping muscles, anxiety, constipation, weariness, and weight gain. Symptomatic similarities can make diagnosing hypothyroidism during pregnancy challenging. Thus, every pregnant woman should be asked to undergo thyroid screening (19,20).

A pregnant woman with increased TSH should also have her fT4 level evaluated. Reduced T4 levels accompanying high TSH (>2.5 mU/L) levels during pregnancy suggest overt hypothyroidism. A patient with a 2.5-10 mU/L TSH level and an average fT4 level is diagnosed with subclinical hypothyroidism.
3.2. Treatment

Pregnant women should receive treatment as soon as feasible for hypothyroidism. The aim is to make the pregnant woman’s euthyroid as soon as possible (21). In treating hypothyroidism, levothyroxine (LT4) is commonly utilized. The physiological changes noted during pregnancy increase the need for thyroid hormone in pregnant women with hypothyroidism. There is an increase of 30-50% in the hormone output of the thyroid gland. Due to this requirement in pregnant women, mothers diagnosed with hypothyroidism should increase their Levothyroxine dosage. Given the lengthy half-life of thyroid hormones, increasing the daily dose by 25-30% would be prudent. Monitoring TSH at 6-8 weeks after commencing the treatment is suitable. TSH should be maintained for treatment between 0.5 and 2.5 mU/L. Serum Thyroid Binding Globulin-, T4, and T3 levels revert to pre-pregnancy levels 4-6 weeks after birth. The levothyroxine dose should be readjusted by looking at thyroid functions within 6-8 weeks following birth (22).

4. HYPERTHROID IN PREGNANCY

4.1. Diagnosis

With a rate of 1-4 in 1000 pregnancies, hyperthyroidism is present. The most common cause of hyperthyroidism during pregnancy is Graves’ disease with a rate of 80-85%. Thyroiditis, functioning adenoma, and excess thyroid hormone are further causes. Toxic nodular goiter is less common (23). An increased fT4 level and a decreased TSH characterize overt hyperthyroidism.

In contrast, subclinical hyperthyroidism is accompanied by normal fT4 levels despite a lowered TSH value. Diagnosing hyperthyroidism during pregnancy is a challenging illness. The clinical manifestations include tachycardia, heat intolerance, hand tremor, profuse perspiration, anxiety, weight loss, and irritability. These symptoms might also be noticed owing to pregnancy. The two most significant indicators of thyroid disease are the absence of weight gain despite an increase in hunger during pregnancy and a resting heart rate of more than 100 beats per minute (23). While these symptoms can be observed during a normal pregnancy, the diagnosis may be delayed. In addition, the fact that the reference values for thyroid function tests vary from trimester to trimester during pregnancy makes this diagnosis considerably more challenging.

Pregnancy and delivery may be impacted by hyperthyroidism. In these pregnancies, the risk of spontaneous abortion, pre-eclampsia, preterm birth, intrauterine growth retardation, low birth weight, and stillbirth also rose.
(24). The connection between subclinical hyperthyroidism and worse obstetric outcomes could not be established (25). Physiological changes, observations, and tests in the first trimester of pregnancy may mimic thyrotoxicosis, in which case no treatment is necessary.

Gestational hyperthyroidism (hCG-induced temporary hyperthyroidism) and Graves’ disease are the two most common causes of hyperthyroidism in regular thyroid function tests. Gestational hyperthyroidism is a disorder that occurs during the first trimester of pregnancy and is frequently asymptomatic and treated solely with TSH suppression. It is caused by an increase in hCG during early pregnancy, and no harmful pregnancy result is anticipated. Anti-thyroid medication treatment is not necessary.

Serum TSH levels below 0.1 mU/L or below 0.01 mU/L indicate a diagnosis of hyperthyroidism. The fT4 level should be evaluated if the TSH level is less than 0.1 mU/L. If T4 levels are normal, T3 levels can be measured. If the free thyroid hormone levels and TSH are inconsistent with clinical symptoms, the total T4 level should be determined. The thyrotropin receptor antibody (TRAb) test is 95% positive in Graves’ disease. It can be used when a clinical diagnosis cannot be made for a patient. If there are classic clinical indications of the disease (ophthalmopathy) and/or TRAb positive, the diagnosis of Graves’ disease is manageable.

4.2. Treatment

To prevent maternal, fetal, and neonatal problems, hyperthyroidism must be treated during pregnancy. Graves’ disease might spontaneously remit in the second and third trimesters of pregnancy. In the majority of individuals, the anti-thyroid medication can be discontinued. Medical treatment is the initial method of choice for treating hyperthyroidism during pregnancy. The goal of treatment is to reduce the serum fT4 level to the upper limit of the reference values as quickly as feasible and to maintain it at this level with the lowest dose of anti-thyroid medication therapy.

Anti-thyroid medications cross the placenta. Because methimazole in pregnancy has been linked to embryopathy and cutis ablation, propylthiouracil treatment is suggested. β-Blocker therapy can manage symptoms during pregnancy at low doses for brief periods. It should only be used for a few weeks. Prolonged use may result in miscarriage and fetal growth retardation, and use during late pregnancy may result in newborn hypoglycemia, apnea, and bradycardia. During pregnancy, PTU can be administered at a dose of 100 to 150 mg per day. Dose adjustments should be made to maintain the serum fT4 level at or near its maximum. High doses of anti-thy-
Pregnancy and Thyroid Diseases

Thyroid medications might cause fetal hypothyroidism and dose goiter. Serum fT4 levels should be maintained near the standard upper limit, and patients should be monitored at frequent intervals (26). The serum fT4 level should be tested every 4 to 6 weeks for the whole pregnancy. TSH serum levels return to normal within 6-8 weeks (26). Since it is known that the serum TSH level may remain suppressed for a long time, TSH should not be used as a foundation for follow-up. Even if the patient achieves euthyroid status, anti-thyroid medications should not be removed until 32-34 weeks have passed due to the danger of relapse (27). It is advised to check AST, ALT, and hemoglobin with thyroid hormones. With treatment with thionamide group medicines, transient leukopenia can occur at a rate of 10%. It typically does not necessitate discontinuing medication therapy. Agranulocytosis occurs in roughly 0.2% of patients. Drug therapy must be stopped for agranulocytosis. Agranulocytosis appears suddenly. It is independent of drug dose. Hence, recurrent leukocyte counts are unnecessary during treatment (27). The end of the second trimester is the ideal time for a thyroidectomy. Although it is the most predictable time, there is a risk of premature birth ranging from 4.5 to 5.5%. Thyroid surgery is contraindicated in the first trimester due to the risk of teratogenicity and fetal loss from the anesthesia used, and in the third trimester due to the risk of premature birth (29). Throughout pregnancy, radioactive iodine reaches the placenta and destroys fetal thyroid tissue. Pregnancy is categorically prohibited from using it (28).

In patients diagnosed with Graves’ disease during pregnancy, TRAb measurement should be performed at the time of diagnosis; if it is high, pregnant women should be constantly monitored, and the third-trimester antibody level should be assessed. A thorough fetal examination and ultrasonography (USG) should be undertaken in pregnant women who are found to be overweight. Owing to the placental transmission of antibodies, inhibiting antibodies may cause fetal hypothyroidism, and increasing antibodies may cause newborn hyperthyroidism (1-2%). In the postpartum period, the risk of recurrence and postpartum thyroiditis in the mother is significantly higher than average (30,31).

5. THYROID NODULES IN PREGNANCY

Thyroid nodules are widespread in the community. Sonographic imaging can detect thyroid nodules at 20–76%. These nodules, however, have a 5% malignancy rate (32-34). Due to the physiological changes during pregnancy, the size of the thyroid gland and its nodules increase. In pregnant and non-pregnant women, the suspicion of thyroid cancer is increased.
by the rapid expansion of the nodule, compression symptoms, a history of radiotherapy to the head and neck, and a family history of thyroid cancer (33-35). Ultrasonography should be used to find nodules. Examining the characteristics of the nodule is necessary. Regardless of the gestational week, a thyroid fine-needle aspiration biopsy (FNAB) should be performed if the nodule has worrisome signs such as uneven borders, hypoechogenicity, increased intra-nodular blood supply, and microcalcification and if the nodule size is 10 mm or greater (36,37).

10% of thyroid malignancies are detected during pregnancy or within the first year of life. Papillary microcarcinoma is the most prevalent histological subtype (38). A study conducted in California during 1991-1999 revealed that the prevalence of thyroid cancer was 14.4/100,000 in pregnancy. The most prevalent kind of papillary cancer was discovered (39). The patient and the fetus are at considerable risk when thyroid cancer is diagnosed during pregnancy. In terms of thyroid cancer monitoring and treatment, a balance must be struck so as not to jeopardize the mother’s health, and obstetrics must also consider maternal and newborn health. Sonographic follow-up is advised for each trimester if thyroid cancer is discovered in a thyroid nodule by thyroid fine-needle aspiration biopsy in the early stages of pregnancy and the disease is localized to the thyroid gland. If the size is stable, the surgery can be conducted after delivery. If the occurrence of extrathyroidal extension and/or metastatic LAP in the neck region, it is recommended that early surgery be performed during pregnancy. If an ultrasonographic follow-up reveals a considerable thyroid gland enlargement, thyroid surgery may be indicated. Surgery should wait until after delivery if thyroid cancer is discovered in the second trimester of pregnancy. If surgery is to be postponed following birth, thyroid hormone suppression medication may be considered, and levothyroxine therapy is initiated to maintain the TSH level between 0.1 and 0.5 mU/L. Even if surgery is to be performed, levothyroxine treatment should begin following the procedure. Similarly, TSH levels should be maintained between 0.1 and 0.5 mU/L. The outlook is identical to that of non-pregnant women.
RESOURCES


2. Ain KB, Mori Y, Refetoff S. Reduced clearance rate of thyroxine-binding globulin (TBG) with increased sialylation: A mechanism for estrogen-induced elevation of serum TBG concentration. J Clin Endocrinol Metab 1987;65(4):689-96


7. Andersen S, Bruun NH, Pedersen KM, Laurberg P. Biologic variation is important for interpretation of thyroid function tests. Thyroid 2003;13(11):1069-78.


Abstract
Renal failure is the reduced filtering function of the kidney as a result of damage to the function of many nephrons. Depending on the decrease in kidney functions, substances such as urea and creatine accumulate in the serum, thus the fluid-electrolyte balance in the body is disturbed. Kidney diseases give many radiographic and oral findings in the jaws, early diagnosis of these findings is very valuable in terms of patient health. Knowing that oral findings are distinctive in kidney patients, healthy oral environment should be created by eliminating the foci of infection that may be serious in the future by detecting the oral health condition early. In this manner, it is extremely important to evaluate the effects of chronic renal failure, to examine the oral and radiographic findings, to determine the treatment needs and to refer these patients to the necessary treatment immediately.

INTRODUCTION
The kidneys filter the blood, help to remove harmful substances (urea, uric acid, creatinine, toxins, drugs, etc.) from the body, while maintaining the body’s water and salt balance [1]. They also have many tasks such as vitamin D secretion, which increases the reabsorption of calcium and phosphorus, erythropoietin secretion, which increases the production of red blood cells, renin secretion, which plays a role in blood pressure control and also controlling the acid-base balance of the body [2].
Intraoral and Radiographic Findings of Chronic Renal Failure

The smallest structural unit of the kidney is the nephron and renal failure is a condition which the filtering function of the kidney is reduced as a result of many nephronal damage. Glomerular filtration rate (GFR) indicates the total amount of blood filtered from the glomeruli per unit time. Depending on the decrease in GFR, substances such as urea and creatine accumulate in the serum, thus the fluid-electrolyte balance in the kidney is disturbed [3]. When the GFR falls below 25, signs of chronic renal failure (CRF) occur. The findings may appear with a decrease in renal function and progress to mild, moderate and severe renal failure, respectively; renal failure may occur in the end-stage, which kidney functions are severely affected and transplantation is required [4].

Oral findings that may occur in CRF patients may become more severe and lead to further problems in patients who do not have adequate oral hygiene and do not visit the dentist regularly [5]. Therefore, it is extremely important to investigate the effects of CRF on oral health, to determine the treatment needs by evaluating oral and radiographic findings and to apply the necessary treatments urgently [6].

The aim of this review is to evaluate the causes and consequences of clinical and radiographic oral findings in patients with CRF, and to increase the awareness of patients and dentists on this issue.

ORAL FINDINGS OF CHRONIC RENAL FAILURE

As CRF has many systemic symptoms, it also gives many findings in the oral region. Knowing that oral findings are distinctive, it is extremely important to create a healthier oral environment by eliminating the foci of infection that may cause problems in the long term by evaluating the oral health status in the early period.

Periodontal problems (increase in the amount of plaque, bleeding on probing, gingival inflammation, gingival recession, tooth mobility, periodontal abscess and pockets, etc.), dental caries, enamel hypoplasia, xerostomia (dry mouth), taste disturbances, mucosal lesions, gingival enlargement and calculus formation are among the main oral findings frequently seen in CRF and related treatments [4,7].

Periodontal Diseases in CRF

Periodontal disease is an inflammatory condition that affects the tissues surrounding the tooth, resulting in pocket formation, loss of attachment, gingival recession and gingival bleeding. Inadequate and ineffective removal of dental plaque lead to serious periodontal problems, while the condition of
the host has great importance in terms of the degree of periodontal disease progression [8].

It has been observed that CRF patients face serious periodontal problems due to inadequate oral hygiene. The negative effects of CRF on periodontal tissues by modifying the host inflammatory and immune response, the altered biofilm, decrease in leukocyte function in patients receiving dialysis treatment and also the neglect of oral health of these patients due to their existing systemic diseases are factors that predispose to periodontal disease. Particularly, periodontal abscesses, which may constitute a potential focus of infection, are very common in these patients [9,10].

Bodur et al. evaluated the periodontal health status of CRF patients undergoing dialysis treatment and it was observed that all of the patients diagnosed with 27 chronic periodontitis and 18 gingivitis were periodontal unhealthy. Researchers have stated that increased C-reaktif protein (CRP) level may be a cause of inflammatory exacerbation. In these patients, the immune response against bacterial plaque decreased, but there was no significant difference between plaque index and gingival index values in the study and control groups. The reason for this is explained that even if the immune response is reduced, there is still a response to bacterial inflammation. The authors reported that the major cause of periodontal disease is microbial dental plaque and periodontal health worsening as dialysis treatment course increases [10].

Davidovich et al. examined the oral health status of patients with CRF and determined that bleeding on probing and the gingival index were at a higher rate in patients with CRF compared to the healthy control group, there also a statistically significant difference was obtained. Researchers have associated these results with prolonged dialysis time. In addition, unlike other studies, gingival recession and loss of attachment were also evaluated and a higher rate was found in CRF patients. Researchers have explained the progression of periodontal disease by the patient’s uremic status, duration of renal disease and poor oral hygiene [11].

Aydın et al. evaluated the oral findings related to CRF and they observed a significant increase in tooth mobility and tooth loss in CRF patients, along with an increase in periodontal problems (plaque index, gingival index, gingival recession, loss of attachment) [12].

In a study by Lütfioğlu et al., which the salivary dynamics and oral health status of pediatric patients with CRF were examined, plaque index and gingival index were found to be higher in the study group and they attributed
this to the thought that patients neglect their oral health as a result of their poor systemic health [13].

**Dental Caries**

Dental caries is the destruction of the tooth structure by bacteria as a result of the deterioration of the remineralization-de-mineralization balance in favor of demineralization in the oral cavity. The incidence of dental caries increases due to the deterioration of neglected oral health, decreased salivary flow, hypoplastic tooth surfaces, poor oral hygiene and weakened immune system in CRF patients, however the increase in pH above the critical de-mineralization value as a result of the increase in the amount of urea in the saliva in CRF patients also increases the buffering ability of the saliva and provides an anticariogenic effect. Accordingly, it is known that S.mutans and Lactobacillus levels decrease and the incidence of dental caries decreases. [8,14,15].

In the study of Barlak et al., which the oral and dental health status of CRF patients were examined, it was found that the prevalence of dental caries was lower in CRF patients and no caries was observed in 16 of the 55 patients examined [6].

Ertuğrul et al. evaluated the oral findings of terminal stage CRF patients and high salivary buffering capacity was found in 89.5% of the study group. Lower levels of S.mutans and Lactobacillus were detected in the study group and it has been reported that this may be due to increased levels of antibacterial agents [15].

Obry et al. examined the biochemistry of saliva in CRF patients, the DMFT index was found to be zero in 56% of the patients [16].

Al nowaiser et al. examined the oral findings of 70 healthy children and 70 children with CRF, no dental caries was detected in 40% of the patients. Researchers have associated this with high urea concentration, high salivary buffering capacity and low amount of S. mutans [8].

In the study of Thorman et al., unlike other studies, the DMFT index was found to be higher in adult patients at different stages of CRF. The authors attributed these results to the uremic status of adult patients, poor oral hygiene and concomitant medical endangerment with systemic disease [14].

**Enamel Hypoplasia**

Enamel hypoplasia is known as defective calcification areas that cause permanent marks on the surfaces of maturing teeth as a result of disruption
of enamel matrix secretion and may cause some problems such as increased sensitivity of the teeth, weakening of dental hard tissues due to decreased mineral content and deterioration of aesthetic appearance [17,18].

The major causative factor of enamel hypoplasia in CRF patients is hypocalcemia. In addition, increase in phosphate and parathormone and decrease in 1,25 dihydrocholecalciferol in serum can be counted among the factors that cause enamel hypoplasia. In CRF patients, dental enamel defects can be seen in many forms such as pits, grooves, transparent, diffuse nebula, etc. [18,19].

Aktören et al. evaluated oral symptoms in children diagnosed with CRF before and after the age of 6, enamel hypoplasia was observed in 20 of 23 children with CRF before the age of 6 years. This rate was found to be lower in children with CRF after 6 years of age. Researchers have associated this condition with renal failure coinciding with the developmental period of the teeth [20].

Nunn et al. examined the oral findings of 38 patients who applied to a local kidney diseases center, 20 of whom had a previous kidney transplant, 11 of whom had CRF and 7 of whom had other kidney diseases, the rate of enamel opacities (diffuse nebula areas, diffuse opacities, transparencies) was 83% and the rate of enamel hypoplasia (grooves, pits, large missing layers) categorized separately was 22%. Researchers have reported that this may be due to impaired calcium-phosphate metabolism [18].

Ertuğrul et al. evaluated oral findings in children with end-stage renal disease, enamel hypoplasia was found in 47.7% of the patients and researchers have reported that this may be associated with abnormal calcium-phosphate metabolism [l5].

Barlak et al. examined the oral and dental health status of 55 patients with CRF and reported that 28 of the patients had varying degrees of enamel hypoplasia in the existing teeth [6].

Davidovich et al. stated that the severity of hypoplasia in CRF patients may be related to age and the time elapsed since the onset of the disease, they also drew attention to the possible correlation between the location of hypoplasia on the tooth and the age of onset of renal failure [11].

Dry mouth (Xerostomia)

The state of being dehydrated as a result of the decrease in the amount and quality of the salivary fluid is defined as xerostomia. Factors such as uremic involvement of salivary glands, decreased saliva amount, medications
and decreased fluid intake may cause dry mouth in patients with CRF. Additionally, dry mouth brings with many problems such as an increase in caries, periodontal diseases and tooth loss [4,21].

Nascimento et al. examined oral symptoms in CRF patients and they noted that xerostomia was observed in 44.6% of the patients. Researchers have associated this situation with decreased kidney capacity and reduced fluid intake and they have suggested that drugs used in the treatment of kidney failure may also cause dry mouth. [9].

Lütfioglu et al. examined the salivary content of CRF patients undergoing dialysis treatment and reported that the cause of dry mouth is not only the decrease in saliva, but also the increase in protein concentration in the salivary content [13].

**Taste Disturbances**

Impairment of taste sensation is called dysgeusia and different tastes such as metallic, bitter or abnormal tastes in the mouth may be encountered in patients with CRF. The taste disturbances in these patients are thought to be due to urea concentration in the mouth, medications and salivary composition [9,22].

Nascimento et al. evaluated oral symptoms in CRF patients, taste disturbances were found 31.1% of the patients. Researchers have reported that dysgeusia may be associated with high concentrations of urea in saliva. In addition, it was stated that there was a significant relationship between the amount of drug used and dysgeusia [9].

**Mucosal lesions**

Petechiae, ecchymosis and hemorrhage can be seen in the intraoral mucosa due to aggregation disorders in platelets and heparin used in dialysis treatment in CRF patients. Oral mucosa is pale due to decreased erythropoietin secretion in CRF patients. Mucositis or glossitis may also occur due to low salivary secretion in CRF patients [4].

**Gingival Enlargement**

Gingival enlargement is increasing volume in the gingiva that develops due to many reasons such as hormonal changes, mouth breathing, ill-fitted dental prostheses, inadequate oral hygiene, systemic diseases and medications. Gingival enlargement in CRF patients may be due to poor oral hygiene and the drugs used (antihypertensive, immunosuppressive, anticonvulsant) [11].
Al nowaiser et al. examined the oral findings of 70 healthy children and 70 children with CRF; a significant difference was found in CRF patients compared to the control group in terms of gingival enlargement. In the study group, 11% gingival enlargement was detected and these patients were found to be used nifedipine continuously or intermittently during the study [8].

Davidovich et al. found a positive relationship between gingival enlargement and use of nifedipine in their study which examining periodontal findings in children and adolescents with CRF [11].

Barlak et al. examined the oral and dental health status of patients with CRF; no statistically significant difference was found between the study and control groups in terms of gingival enlargement [6].

Nunn et al. examined the oral health status of 38 pediatric patients with CRF; mild gingival hyperplasia was found in children, but no significant relationship was found between gingival enlargement and the use of nifedipine or cyclosporine. It has been reported that this situation is perceived as a result of irregularity in the gingival contours, since it is a transitional period between primary and permanent dentition [18].

**Calculus Formation**

Calculus is a mineralized structure with organic and inorganic content formed as a result of the precipitation of calcium and phosphate salts on the bacterial plaque which adhering to the surface of the teeth and existing dentures in the mouth. Decrease in magnesium level, increase in urea and phosphorus levels and precipitation of calcium and phosphate cause calcium oxalate formation in CRF patients. This accumulation causes calculus formation and the reduced amount of saliva also contributes to this accumulation [9].

Nascimento et al. evaluated oral symptoms in CRF patients, calculus was detected 52.7% of the patients. It has been suggested that patients with a low biofilm index may have a high amount of calculus and additionally it has been reported that lack of oral hygiene and reduced amount of saliva can cause calculus accumulation [9].

**RADIOGRAPHICAL FINDINGS**

Changes in bone metabolism and dental hard tissues can be seen on dental radiography are common in CRF patients and it is known that these changes are due to secondary hyperparathyroidism, which shows low calcitriol and high phosphorus levels. These changes can occur simultaneously
and cause resorption of the jaw bones [23,24]. Loss of the lamina dura and changes in the jaw bones (decreased bone density, decreased trabeculation, osteosclerosis, alveolar bone loss, soft tissue calcifications, thinning of cortical layers) are the most common radiographical findings [25].

**Loss of Lamina Dura**

In dental radiography, the radiopaque, thin layer of bone surrounding the tooth socket is called the lamina dura. While various systemic diseases cause loss of the lamina dura, loss of the lamina dura due to bone resorption under the periosteum as a result of hyperparathyroidism is a common condition in CRF patients [2,26].

Özel et al. compared the oral findings of CRF patients and healthy individuals, loss of lamina dura was evaluated using panoramic radiographs of 149 CRF patients and 200 healthy individuals. Lamina dura loss was found to be two times higher in the study group. However, it was pointed out that the invisible buccolingual surface of the teeth and the distortion in the two dimensional radiographic images can be misleading when detecting loss of lamina dura on panoramic radiographs [2].

Çağlayan et al. evaluated changes in teeth and jaw bones in CRF patients with using dental tomography and reported that the mandibula was more porous, also soft tissue calcifications, loss of lamina dura and radiolucent lesions were more common in CRF patients [27].

Kelly et al. examined changes in the jaw bones of CRF patients, 53% of patients had changes in the lamina dura and 45% of the patients had partial loss of the lamina dura, while only 8% had complete or near-complete loss of the lamina dura. [28]

Rai et al. evaluated the radiographical changes in the jaw bones of CRF patients, lamina dura loss was found to be higher in the study group and a statistically significant results were obtained [29].

**Changes in the Jaw Bones**

Since phosphate excretion is not adequately achieved in CRF patients, serum phosphate level increases, however vitamin D synthesis decreases and serum calcium level decreases. A low calcium level increases the secretion of parathormone and calcium transfer occurs from the bone to the blood. In this case, secondary hyperparathyroidism develops and a condition called renal osteodystrophy occurs. The findings of renal osteodystrophy in the jaw bones are varying; often a decrease in bone density is observed, but
sometimes an increase in bone density (Brown tumor) can also be observed. Changes in the number of bony trabeculae, enlargement of the maxilla, metastatic soft tissue calcifications or changes in the jaw bones giving a ground-glass-like radiographic appearance may be observed [30,31]. Another change that is thought to be caused by abnormal bone metabolism in hyperparathyroidism is Brown tumors, which are described giant cell-rich lesions and can cause symptoms in the jaw bones (32).

Coşgunarslan et al. evaluated the quality of mandibular bone in CRF patients through fractal analysis on panoramic radiographs and found that CRF and renal osteodystrophy adversely affected bone in terms of mineralization and volume, bone fragility increased and this situations significantly affect the clinical success of dental treatments (tooth extraction, implant, orthodontic treatment) [25].

Özel et al., examined oral and radiographic findings in 149 CRF patients, Brown tumor was observed in only 1 (0.7%) person in the study group, while Brown tumor was not found in the control group of 200 people [2].

Shaikabei et al. evaluated the radiographic changes in the jaw bones and teeth of 74 CRF patients that undergoing hemodialysis treatment. Thinning or loss of the lamina dura in 16 patients, changes in trabecular bone in 30 patients, changes in jaw bone density in 29 patients, and bilateral calcification in the stylohyoid ligaments in 13 patients were observed. It is not known whether these changes are related to the duration and frequency of dialysis [33].

**Conclusion**

It should not be forgotten that CRF patients need professional support in terms of oral and dental health, considering their systemic condition. Intraoral and radiographical changes should be evaluated on regular follow-ups, especially periodontal treatments should be performed at regular intervals. Since every CRF patient is a potential transplant patient, necessary dental treatments should be done as soon as possible. Especially in transplantation patients, all treatments should be done before the transplant procedure, because the patients will be in a state of immunosuppression after the transplantation and their body resistance against infection will decrease. For this reason, it has been recommended that dental treatments should be performed with a more radical approach in CRF patients in case of transplantation and that teeth with a poor prognosis which may cause problems in the future should be extracted.
References


13. Lütfioğlu M, Sakallioglu EE, Özkaya O, Açıklgöz G. Kronik böbrek yetmezliği olan çocuklarda tükürük sıvı dinamiği ve ağız sağlığı pro-


Chapter 3

Viral Arthritis; Covid19 Update

Nadide Koca

Summary

Viral arthritis is a self-limiting and non-destructive arthritis that occurs during or after various viral infections. The pathogenesis of viral arthritis is still not fully understood, but mechanisms such as direct invasion of synovial cells, immune complex formation and molecular mimicry (imitation) are emphasized. All over the world, the most common viruses causing arthritis are Parvovirus B19, Rubella, hepatitis B and hepatitis C virus and alphaviruses, and viruses such as Zika and Chikungunya are tropical viruses that cause arthritis in endemic areas. In addition, during the Covid-19 pandemic, which has been affecting the whole world since 2019, it has been determined that the SARS-CoV-2 virus also causes musculoskeletal symptoms such as arthritis and arthralgia. Many viral arthritis usually begin with nonspecific symptoms seen in viral infections. Joint involvement can be in different patterns. Although no major abnormality is usually observed in routine laboratory tests, they can sometimes lead to positivity of autoantibodies such as ANA, RF, Anti-ds DNA and ANCA. In addition, although it is usually a self-limiting form of arthritis, arthritis may become chronic, especially in immunodeficiency or in the presence of chronic persistent infection. Chronic rheumatic disease may be misdiagnosed in cases of long-lasting viral arthropathy. Viral infection may also be a triggering factor in the etiology of chronic rheumatic disease. It is important to make the differential diagnosis of viral arthritis, as the treatment modalities between the two disease groups are different.

INTRODUCTION

Viral arthritis are acute and self-limiting diseases. Viral arthritis is accompanied by fever, distinctive skin manifestations, hematological abnormalities, particularly in parvovirus B19, and other clinical features. Including parvovirus B19 chronic polyarthritis mimicking rheumatoid arthritis (RA) in adults, polyarthritis may occur also in other virus infections. It is necessary to know the epidemiology of viral infections and to perform laboratory examinations appropriate to the disease process for diagnosis. Different viruses can cause arthritis in a host by various mechanisms (immune complex

1 M.D., Department of Physical Therapy and Rehabilitation, University of Health Sciences, Ankara Training and Research Hospital, Orkid 0000-0002- 0839-5700

https://doi.org/10.58830/ozgur.pub91.c382
Viral Arthritis; Covid19 Update

The most common arthritogenic viruses worldwide are some tropical viruses such as Parvovirus B19, Hepatitis B virus - hepatitis C virus (HBV - HCV), Rubella, human immunodeficiency virus (HIV), Zika virus, Alphaviruses, and Chikungunya virus (CHIKV) 1-3. In the COVID-19 pandemic that started in 2019, the association of arthralgia and arthritis has been described after Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection 4, 5.

Most viral arthritis starts with nonspecific symptoms. There is headache, malaise, chills, fatigue, neck stiffness, nausea-vomiting, fever, sore throat, often macular or papular rashes. Mild fever and regional lymphadenopathy (LAP) may also be the only extra-articular finding. The absence of a single pattern of joint involvement is characteristic. In hepatitis B alone, the arthritis can be symmetrical, asymmetrical, migratory, or appended. Morning stiffness is usually in the affected joint. On the other hand, arthralgia may be the only manifestation of involvement 1, 6. Routine laboratory tests usually show few abnormalities. Some patients may have a mild anemia or a few atypical lymphocytes. Rheumatoid factor (RF) is usually negative except for Rubella. Antinuclear antibody (ANA) is negative. High erythrocyte sedimentation rate (ESR) is the most common abnormality. Patients with hepatitis B may also have cryoprecipitates and decreased serum complement levels in their serum. Synovial fluid studies are nonspecific and reflect varying degrees of inflammation. The general finding is a high white blood cell (WBC) count of 15000-25000 mm3, which is typical for rheumatoid arthritis (RA) and the predominant cell type is polymorphonuclear cell (PMN) 1-3, 6.

Little is known about how viruses induce arthritis (except for hepatitis B and hepatitis C, where immune complex-mediated pathogenesis is concerned). It has been shown that the virus can be replicated in the synovium by obtaining the virus from the synovial fluid of many patients in rubella. Since many findings are nonspecific, “how to recognize viral arthritis” or “how to suspect?” questions can be considered. Information on exposure is helpful in this regard. Conditions such as iv. drug use for hepatitis B, new immunization for rubella, history of going to an endemic area, seasonal onset for arboviruses and enteroviruses provide clues for diagnosis. However, the most well-known characteristic feature of viral arthritis is that they are of short duration. The short duration of arthritis without deforming changes is the major difference between known types of viral arthritis and RA. However, recent studies sometimes blur this distinction. Hepatitis B arthritis can last for months and can lead to vasculitis indistinguishable from polyarteritis nodosa (PAN). Direct radiographs of the affected joints may show progressive osteoporosis (OP) and significant loss of articular cartilage. Rubella arthritis with rubella virus vaccine (HPV77, DK12) may recur in as long as
three years, but each attack is short-lived. In addition, some reports indicate that the rubella virus causes chronic erosive arthritis. It is also stated that rubella, mumps and coxsackie viruses are associated with a condition similar to Still's disease. Although viral arthritis is mostly self-limiting and non-destructive, chronic form may develop in two cases. The first of these occurs when immunocompromised patients become infected with the agent. A short-term infectious agent in the normal host can lead to chronic and recurrent infection in immunodeficiency and cause chronic viral arthritis. In the second case; Chronic viral arthritis may develop in infections of the nature of chronic persistent viral disease. In the development of viral arthritis, besides host factors such as age, genetic predisposition and immunity, viral factors such as virus tropism, replication feature, ability to cause persistent infection, cytopathic effect, viral expression feature similar to host antigens and viral factors also play a role, for instance the ability to alter the host's immune response.

**VIRUSES CAUSED ARTHRITIS**

**Distinct Arthrogenic Viruses**

- Parvovirus B19
- Hepatitis B and C virus
- Rubella virus and vaccine
- Mumps virus
- HIV-1
- Human T-lymphotropic virus-1 (HTLV-1)
- Lymphocytic choriomeningitis virus (LCMVr)
- Alpha Viruses
  - Chikungunya virus
  - O’nyong-nyong virus
  - Igbo-ora virus
  - Ross-River virus (Australia’s epidemic polyarthritis)
  - Sindbis virus
  - Mayaro virus

**Rarely Arthrogenic Viruses**

- Adenovirus
• Herpes Viruses (Herpes Simplex virus type-1 (HSV-1), Epstein-Barr virus (EBV), Varicella Zoster virus (VZV), Cytomegalovirus (CMV))
• Rubeola
• Enteroviruses (Coxsackie virus, ECHO virus type 6-9, Hepatitis A)

**FINDINGS ACCOMPANYING VIRAL ARTHRITIS**

In addition to general symptoms such as sore throat, nausea-vomiting, myalgia, chills, malaise in hepatitis B infection; urticarial, macular, papular, petechial rashes, lymphadenopathy and low-grade fever may occur.

In rubella, flu, cough, sore throat, myalgia, malaise, as well as morbilliform eruptions, LAP and low-grade fever are seen. In cases of rubella vaccine-induced arthritis, colds, cough, sore throat, morbiliform rashes, LAP and low-grade fever may accompany.

Adenovirus may present with sore throat, maculopapular skin lesions, low-grade fever, pericarditis, and meningitis. In Varicella Zoster infection, malaise, vesicular skin lesions, and fever may occur. Vesicular skin lesions are seen in HSV-1. Epstein–Barr Virus infection often progresses with headache, malaise, sore throat, maculopapular rash and LAP. Coxsakie virus can progress with sore throat, pleuritic pain, maculopapular rash, fever, myopericarditis. Echovirus Type 6-9 can progress with fever, sore throat, vomiting headache, macular skin lesions, fever and meningitis.

**MUSCULOSKELETAL INVOLVEMENT IN VIRAL ARTHRITIS**

The rate of development of arthritis during hepatitis B infection is 10-30%. The duration of arthritis varies between 7-180 days. Joint involvement can be symmetrical, migratory or additive. Sometimes large joints can also be seen in the form of tendinitis or bursitis. The rate of development of arthritis in rubella is 15-35%, and arthritis is more common in adult women and rarely in children and men. The type of involvement is symmetrical, knees, wrists, proximal interphalangeal joints (PIF), carpal tunnel syndrome (CTS), tendinitis, and the mean duration of arthritis is 5-30 days. Rubella vaccine (HPV-77, DK12) induced arthritis is more common in women and affects 1-10% of children. The type of involvement is symmetrical (PIF joints) or monoarticular (knee) and CTS. The average duration of arthritis is 7-21 days. Chikungunya virus causes arthritis in the majority of cases, especially in large joints such as the knees and sometimes in small joints. Chikungunya virus recurrence can be seen in 5-7th months. Epidemic polyar-
Arthritis affects most adults and can be symmetrical, sometimes asymmetrical or additive. It occurs in the form of tendinitis and periarticular swelling in the joints, and can last for an average of 14-21 days and sometimes months. Mumps virus causes arthritis at a rate of 0.4% and lasts an average of 14(2-90) days. The type of involvement is in the form of large and small joints and tenosynovitis. Adenoviruses can cause large and small joint arthritis and can show recurrence in 7-35 days. VZV, HSV-1 and CMV mostly involve large joints such as the knee. Coxsackie virus and ECHO viruses can affect large and small joints.

LABORATORY FINDINGS IN VIRAL ARTHRITIS

In hepatitis B, an average of 25000 leukocytes per cubic millimeter are detected and the dominant cell type is polymorphonuclear (PMN) cell type. There is no virus culture, but HBsAg can be detected. Limited mononuclear infiltrate may be seen in the synovium. The leukocyte count in rubella is 30000 per cubic millimeter and the dominant cell type is mononuclear cells or PMN cells. Rubella has a cell culture, synovial hyperplasia, increased vascularity and mononuclear cells are detected in the synovium. In epidemic polyarthritis, the mean leukocyte count is 10000 and mononuclear cells predominate. In mumps, there is PMN cell dominance. Similarly, PMN cells and mononuclear cell dominance are observed in adenovirus infection. In Varsella Zoster, the leukocyte count is approximately 4000 and mononuclear cells are dominant. In herpes simplex-1 infection, the leukocyte count is on average 10000 and mononuclear cells are dominant. Epstein Barr virus, CMV and Coxsackie virus are the most common cells in PMN. In echo virus type 6-9, PMN and mononuclear cell dominance is present.

Autoantibodies detected in peripheral blood in viral infections: Parvovirus B19 has antinuclear antibody (ANA), rheumatoid factor (RF), antineutrophil cytoplasmic antibody (ANCA), Anti-double-stranded (ds) DNA antibody (Anti ds –DNA). Alphaviruses have RF and ANA, rubella has RF, EBV has RF and anti ds-DNA, anti-collagen and anti-cyclic citrullinated peptide (anti-CCP) antibodies. RF and ANA may be positive in HCV, RF and ANA may be positive in HBV, RF and ANA may be positive in HTLV_1 and ANA may be positive in HIV.
CLINICAL PRESENTATIONS

COVID-19 INFECTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has caused a pandemic that started in December 2019 and affected the whole world. Since the disease started in 2019, it has been named as Coronavirus disease-19 (Covid-19). Symptoms are mild to moderate in most patients, but in about 15% of cases, they progress to acute respiratory distress syndrome, severe pneumonia, multiple organ failure, and septic shock. This pandemic has caused more than 3 million deaths all over the world. While the respiratory infection pathogenesis of SARS-CoV-2 was being investigated all over the world in the midst of the epidemic, there has also been an increasing interest in the immune-mediated consequences secondary to the virus. Patients with a procoagulant state in Covid-19 infection and an inflammatory cytokine storm similar to that in macrophage activation syndrome constitute the most severe cases. A dysregulated hyperimmune response can lead to deepening of damage and autoimmune diseases in susceptible individuals. Many autoimmune diseases have been described in the literature after Covid-19 infections.

The pathogenesis of viral arthritis is still only partially understood. One of the known mechanisms in this regard is molecular mimicry. The virus causes autoimmune diseases in susceptible individuals through molecular mimicry. Molecular mimicry has also been found for SARS-CoV-2. This hypothetically plays a role in the pathogenesis of virus-related immune outcomes that develop both during and after acute systemic infection. Guillain Barre syndrome and Miller–Fischer syndrome, which occur through molecular mimicry after Covid-19 infection, have been reported. The mimicked epitopes are also present in the synovial membrane, and acute local inflammation occurs by a similar mechanism.

Ibanez et al. conducted a literature review on arthritis after Covid-19 infection for a 1-year period during the epidemic. They reached 30 articles on this subject and after excluding arthritis that may be due to other etiologies, the remaining 3 cases were discussed. The low prevalence of Covid-19-associated arthritis has been attributed to the use of hydroxychloroquine and corticosteroids, which are used in the cure of Covid-19 and also prevent or reduce inflammatory joint manifestations. The features that emerged in the examination of the remaining 3 cases were reported as follows: The time between the onset of arthritis and SARS-CoV-2 infection is variable, but occurs days after acute viral infection and often during the recovery period.
It mostly affects men and occurs as mono or oligoarthritis in the lower extremities. All patients with suspected post-Covid arthritis respond fully and rapidly to non-steroidal anti-inflammatory drugs (NSAIDs) and/or glucocorticoids. As a result, in the pathogenesis based on molecular mimicry, the condition that reveals joint inflammation is the antibody response against the virus. The rapid reduction of immunity within weeks after Covid-19 causes joint manifestations to fade. In addition, this pathogenetic hypothesis regarding immune system hyperactivation reveals why arthritis occurs in those with severe infections and that joint involvement is subclinical in milder infections.

Enginar AU. reported 2 cases of arthritis developing in the hand joints after Covid-19 vaccine and fully responding to glucocorticoid treatment. There are reports of elbow arthritis 1 week after SARS-CoV-2 vaccination and reactive arthritis cases developing 1 week after inactive vaccine. Watad et al. reported 27 cases with immune disease attack or new onset of disease after vaccination. Most vaccines are m-RNA vaccines. 21 patients had a previous autoimmunity or rheumatic disease. Disease exacerbation was detected in 17 patients, and new-onset immune disease was detected in 10 patients. Among these patients, polymyalgia rheumatica, myasthenia gravis, arthritis, and skin manifestations were found. Watanabe et al. They reported cases of inflammatory bowel disease, new-onset rheumatoid arthritis, anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis, and adult-onset Still’s disease after Covid-19 vaccine. Ono et al. They reported a case of reactive arthritis presenting with arthritis and mild Achilles enthesitis of the ankles 21 days after SARS-CoV-2 infection. On the subject, it is clear that more research is needed to understand the pathogenesis of the different clinical phenotypes of Covid-19 infection.

PARVOVİRÜS B –19

Parvovirus B19 is the smallest known DNA virus from the Parvoviridae subfamily and the Erythrovirus genus. This virus replicates autonomously in erythroid precursor cells. It is transmitted by respiratory secretions. Most infections are asymptomatic or in the form of undiagnosed nonspecific viral disease. Approximately 60% of adults have positive serology of a previous parvovirus B19 infection. Its appearance is usually late winter and spring. The disease is defined by its characteristic three-stage rash. Stage 1 is the stage that consists of a bright red rash on the face and includes the image of “slapped cheek”. In stage 2, lasting several days to weeks, “lace-like” eruptions spread to the extensor surfaces of the arms, buttocks, and legs. In stage
Viral Arthritis; Covid19 Update

3 lesions show recurrence in a period of up to 10 months. Parvovirus B19 virus may cause aplastic crisis on the basis of chronic hemolytic anemia. Parvovirus B19 infection may cause recurrent anaemia, thrombocytopenia or leukopenia in immunocompromised patients receiving chemotherapy for lymphoproliferative diseases, or in patients with AIDS. About 5% of children aged 10 years and younger develop arthralgia and 3% develop joint swelling. Joint pain and swelling in adolescents are 12% and 5%, respectively. However, in adults aged 20 years and older, joint pain and swelling are observed in 77% and 60%, respectively. Joint involvement is more common in women. The pattern of acute B19 arthropathy is different in children and adults. Asymmetric and pauciarticular involvement is seen in children. Joint involvement in adults is an RA-like picture with marked symmetrical involvement of the proximal interphalangeal joint (PIF), metacarpophalangeal (MCP), knee, ankle, and wrist. It is a symmetrical polyarthritis most often of acute onset, of moderate severity, that frequently begins on the hands and knees and spreads to the wrists, feet, elbows, and shoulders within 24-48 hours. Joint manifestations are usually self-limiting in adults. However, in a small proportion of adults, the findings can be seen as one of two patterns. In approximately 2/3 of the patients, the findings are seen as arthralgia with intermittent exacerbations and additional morning stiffness. In the other 1/3 patients, the patient is asymptomatic between exacerbations. Rheumatoid factor may be positive at low or moderate titers and often disappears. In the case of chronic disease, B19 arthropathy has been reported to last up to nine years.

Molecular mimicry, activation of antigen-presenting cells and viral persistence are emphasized as mechanisms of arthropathy. Parvovirus B19 infection may also be associated with immune-mediated syndromes. These; juvenile rheumatoid arthritis, rheumatoid arthritis, reactive arthritis, Remitting Seronegative Symmetrical Synovitis with Pitting Edema (RS3PE), Systemic lupus erythematosus (SLE), Still’s disease, Polymyositis, Dermatomyositis, Progressive systemic sclerosis (PSS), vasculitis, Sjögren’s syndrome, Raynaud’s phenomenon as well as a wide array of diseases, including carpal tunnel syndrome and fibromyalgia.

Considering the distribution and symmetry of B19 arthropathy, it may suggest the diagnosis of RA. About half of patients with chronic B19 arthropathy fulfill the American College of Rheumatology criteria for RA (symmetrical involvement, morning stiffness lasting more than one hour, involvement of the hand joints, and involvement of at least three joints). Joint erosion is not seen in these patients and rheumatoid nodules are not
found. The absence of joint destruction with rheumatoid nodules is important in the differential diagnosis of RA. It has been shown that viral infection is effective in the pathogenesis of RA, with the prevalence of parvovirus B19 DNA being high in patients with rheumatoid arthritis 36-38.

A 39-year-old female patient was identified as part of a large 1994 study on the suspicion that parvovirus B19 induces musculoskeletal disease. The patient had a flu-like illness with headache, myalgia, and axillary LAP lasting for two weeks, and a similar illness was found in her husband and two small children. In the patient who developed a painful, asymmetrical polyarthritis despite the recovery of other family members, laboratory outcomes indicated a new parvovirus B19 infection with high IgG and IgM levels. Two months after the onset of symptoms, the viral genome was noticed in serum by polymerase chain reaction (PCR) and continued positive for 10 months. The patient was first diagnosed with parvovirus B19 arthritis. However, because the symptoms could not be controlled with 3X50mg Flurbiprofen per day, Hydroxychloroquine 400 mg/day and Prednisone 10 mg/day were started in addition to the treatment. Hand and foot radiographs were normal at baseline, However, during the 8th month cortical erosions were seen in several small joints. Therefore, 20 mg/week Sodium aurothiomalate was started instead of Hydroxychloroquine and a gradual improvement was observed. In this study, it was concluded that the diagnosis of new parvovirus B19 infection, can be obtained with false low positive IgM results with some tests, should be made correctly. In addition, the relationship between parvovirus B19 and some forms of RA (particularly early in the process) was noted to merit further investigation 39. Another study found evidence of a new parvovirus infection in 4-5% of 199 patients with early RA, while those with nonspecific inflammatory arthritis A new parvovirus B19 infection was noticed in 12% of 190 patients 40.

Immune electron microscopy, finding of B19 DNA and anti-B19 IgM antibodies during viremia are the main laboratory tests. The most useful modality in rheumatology clinics is anti-B19 IgM antibody serology when the patient presents with polyarthritis/polyarthralgia. Anti-B19 IgM antibody is positive 2 months later the onset of joint symptoms. It can sometimes be noticed for 6 months or longer 1. It was conducted in a study investigating the role of parvovirus B19 in patients with arthritis of unknown origin. In this study, parvovirus B19 DNA was tried to be determined by PCR in the synovial fluid, synovial fluid cells, synovial membrane and bone marrow of 90 patients with idiopathic arthritis. Parvovirus B19 DNA was detected in the synovial membranes in 16.7% of the patients, while it was noticed in the
synovial fluid of only 1.4%. This result; developed a perspective against the background of reports reporting the presence of parvovirus B19 DNA in the synovial fluid cells and synovial fluid of patients with various arthropathy, as well as the inability to detect parvovirus B19 DNA in synovial fluid or synovial fluid cells obtained from patients with early RA diagnosis has shown 41. There is no specific treatment or vaccine. Symptomatic treatment with NSAIDs is carried out 1.

**RUBELLA**

The peak incidence of Rubella transmitted by nasopharyngeal secretions is late winter-spring periods. Infection in children and adults can be asymptomatic. The classic syndrome consists of low-grade fever, malaise, rash, common cold, and prominent postauricular, posterior cervical and occipital LAP 16, 17. Joint symptoms are common in women. The appearance of joint manifestations is one week before or after the onset of the rash. Similar to B19 arthropathy, arthralgias are more common than overt arthritis, and morning stiffness is more pronounced. Joint involvement is symmetrical or migratory and usually regresses from a few days to two weeks. PIF, MCP, wrist, ankle and knee are the most commonly involved joints. Tenosynovitis, periartritis and carpal tunnel syndrome can be seen. In some patients, symptoms may be observed for several months or years 1,42,43.

In a study investigating an association between chronic joint disease and rubella virus, synovial fluid samples or synovial membrane biopsies from 79 patients were tested for rubella virus. 79 patients diagnosed with RA, seronegative spondyloarthropathy, juvenile chronic arthritis, osteoarthritis, infective arthropathy, gout, unexplained monoarthritis and traumatic joint injury were included in the study. In this study, rubella virus was detected in the synovial fluid of only two patients. One of the patients was a patient with generalized immunodeficiency syndrome and mycoplasma hominis arthritis. The other was a 68-year-old female patient with RA. As a result, the data obtained were insufficient to confirm the association of rubella virus with chronic inflammatory joint disease. However, it has also been reported that rubella virus can persist in the joint and reactivate when cellular immunity is suppressed. Rubella virus is not associated with chronic inflammatory joint disease. Detection of rubella virus RNA in two patients has also been attributed to decreased immunity as a result of severe immunodeficiency or in advanced age 44.

In patients with rubella arthritis, the presence of an inadequate humoral immune response to specific epitopes allows persistence of the virus.
Rubella can be detected in the synovial fluid during arthritis exacerbations and then in lymphocytes for many years, although the findings subside. Rubella virus culture was performed from synovial fluid 3-4 months after the onset of symptoms in four patients following vaccination. Because of this isolation, it was hypothesized that the virus could invade the synovium and replicate there. However, detection of sequential and circulating antibodies, with the appearance of arthritis and rash following isolation of the virus from the pharynx and blood, is consistent with an immune complex-mediated arthritis. Circulating immune complexes have been found in patients with vaccine-induced rubella arthritis ⁷,⁴⁴.

**RUBELLA VACCINE**

Three rubella vaccines were developed in 1969 (HPV 77 DE 5, HPV 77 DK 12 and Cendehill). In a short time, it was seen that all three vaccines and especially HPV 77 DK 12 cause arthritis similar to that in natural infection ⁷. In a retrospective Cohort study with RA 27/3 vaccine, no relationship was found between rubella vaccine and chronic arthropathy or neurological disorder ⁴⁵. However, there are many studies reporting the relationship between rubella vaccine and arthralgia and arthritis ⁴⁶-⁴⁸.

Joint symptoms following rubella vaccine are similar to natural infection. However, isolated knee involvement and CTS are more common. Swelling, redness, and warmth are not common. Post-vaccine arthritis usually occurs in 2-4 weeks. Arthralgia lasts for a few days, arthritis for 1–3 weeks. However, those with knee involvement may show recurrent attacks for as long as three years ⁷,⁴⁹. It is well known that hormonal changes during pregnancy exacerbate or correct autoimmune disorders. Postpartum hormonal changes (eg, increased prolactin) may affect the immune response. Prolactin is immunomodulatory and abnormalities in prolactin level have been described in disorders such as arthritis, uveitis, and thyroiditis. In addition, it has been reported that the hormonal effect in the menstrual cycle may affect the susceptibility to rubella virus vaccine-associated arthropathy ⁵⁰.

Two neuropathic conditions can occur after natural infection or vaccination. In “Arm syndrome” there is brachial radiculoneuropathy, worsening at night, causing arm and hand pain, dysesthesia. “Catcher’s crouch syndrome” is lumbar radiculoneuropathy and is characterized by pain in the popliteal fossa that appears in the morning. Symptoms aggravate with knee extension, and pain gradually decreases with the “catcher’s crouch” position. Both syndromes, defined 1-2 months after vaccination, can be observed. Episodes may recur over a period of about 1 year but eventually resolve without se-
Rubella is easily cultured as a laboratory study from tissues and bodily fluids, including throat swab. Anti-IgG antibody seroconversion or Anti-Rubella IgM positivity is diagnostic for rubella infection. IgG and IgM are often present at the onset of joint symptoms. The IgM peak occurs 8–21 days after the onset of symptoms, and in most patients, this peak is not detectable after 5 weeks. Non-steroidal anti-inflammatories can be used to control symptoms in treatment. Some researchers state that low or moderate doses of corticosteroids are necessary to control symptoms and viremia.

**ALPHA VIRUSES**

Alpha viruses are mostly seen in endemic regions of the world. O’nyong-nyong virus, Ross river virus (Australia’s epidemic polyarthritis), Chikungunya virus, Barmah–Forest virus, Sindbis virus, Mayaro virus and Igbo-Ora virus are the arthritogenic viruses studied in this group.

Chikungunya virus causes epidemics in Asia, India, Indonesia, Africa and South America. It is transmitted by mosquitoes. Fever detected in chikungunya has a characteristic explosive onset, accompanied by severe arthralgia with fever. There is a maculo-papular rash, and the fever reaches 39-40 degrees. Widespread muscle pain, low back and shoulder pain are common findings. Stiffness and swelling, migratory polyarthralgia affects the wrists, small joints of the hand, feet and ankles. Large joint involvement is rare. Joint symptoms lasting up to one year may occur in 10% of patients. Destructive arthropathy has also occurred in a few patients with chronic symptoms. RF may be positive at low titer in patients with prolonged symptoms. Chikungunya IgM antibodies can remain positive for up to six months and are helpful in diagnosis in these endemic areas. Treatment is supportive. ROM exercises reduce stiffness during an acute attack. NSAIDs can be used, when insufficient, chloroquine phosphate 250 mg/day is used.

Clinically similar to Chikungunya fever, O’nyong–nyong virus is transmitted by mosquitoes. NSAID and ROM exercise are used in the treatment. Mosquito-transmitted Igbo-Ora virus is serologically similar to O’nyong-nyong and Chikungunya virus. Ross River virus (epidemic polyarthritis), another mosquito-borne virus, is endemic in warm and tropical areas of Australia. Sudden onset of polyarthralgia occurs after an incubation period of approximately 7-11 days. There may be a macular, papular, or maculo-papular rash. In most patients, arthralgia is severe and debilitating. The joint distribution is often wandering and asymmetrical. Involvement can be detected in the interphalangeal, metacarpophalangeal, wrist, ankle and knee joints. Big toes, elbows and shoulders may also be involved. Temporoman-
dibular, hip and axial involvement may occasionally occur. Tenosynovitis and polyarticular swelling are common, paresthesias may be present. 50% of the patients can return to their daily life activities in about 1 month. There may be residual polyarthralgia, joint symptoms may recur, and relapse episodes gradually decrease. Symptomatic treatment with aspirin or NSAIDs is used in the treatment 2, 8, 54.

Sindbis virus is common in South Africa, Russia and Finland. There is rash and arthralgia. Arthritis and arthralgia involve the small joints of the hands and feet, elbows, ankles, knees, and wrists. Cases are commonly confined to forested areas. Sometimes there may be axial skeletal involvement and tendinitis is common. The extensor tendons in the hand region and the Achilles tendon are involved. Chronic arthropathy is also observed as a common finding 3, 9, 53.

**HEPATITIS B VIRUS**

Hepatitis B virus can cause an immune complex-mediated arthritis. It starts suddenly and is often severe. Joint involvement is typically in the form of simultaneous, symmetrical association of several joints. Arthritis can be additive or migratory. Hand joints and knees are most commonly affected, but elbows, wrists, shoulders, and other large joints may also be affected. Morning stiffness often occurs. Urticaria and arthritis, which may appear days or weeks before jaundice, may persist for several weeks, usually after jaundice. The rash and arthritis often regress after the clinical manifestation of jaundice. Arthritis is limited to the preicteric prodromal period. Recurrent polyarthritis or polyarthritis may be observed in patients with chronic active hepatitis or chronic HBV viremia. There are publications showing a relationship between hepatitis B virus infection and autoimmune diseases such as autoimmune hepatitis, SLE, antiphospholipid syndrome, polyarteritis nodosa (PAN), multiple sclerosis, thyroid diseases and uveitis 55-57.

Presence of urticaria in the presence of polyarthritis suggests the presence of HBV infection. Asymptomatic Acute hepatitis may also occur. When arthritis occurs, bilirubin and transaminase levels are elevated. When arthritis occurs, serum HBs antigen (Ag) can also be seen at a peak level. Viral DNA, virions, polymerase and Hbe antigen can be detected in serum. AntiHBc IgM antibodies are present, indicating acute HBV infection 55, 56.

Immune complex deposition in the synovium is thought to be at the forefront in the pathogenesis of HBV arthritis. Complexes appear in the prehepatic period when HBs Ag is increased and the skin and joints are clin-
Arthritis often accompanies the rash, which is commonly urticarial but may be macular, papular, or petechial. All three types of rash may coexist in the same patient. When arthritis is present in the laboratory, HBs Ag is usually detected in the blood. However, several samples may need to be tested before a positive result can be obtained. As the arthritis heals, HBs Ag usually disappears and anti-HBs becomes positive. In the period of arthritis, cryoprecipitates can be detected in the serum of some patients. These precipitates are large immune complexes containing HBs Ag, anti–HBs, IgM, A, G, and complement (C) 19, C3, C4, and C5 7, 55, 57. Complement components can be rapidly depleted when arthritis first appears. During this time, C4 and CH50 levels were often markedly decreased. C3 level may be low or normal. Low complement levels are not found in all patients. The highest HBs Ag concentrations are associated with the lowest C19 and C4 levels 7. There is also ample evidence for the presence of circulating immune complexes to explain the extrahepatic findings in hepatitis B infection 57.

Acute hepatitis B may present as a polyarthritic syndrome with a symmetrical pattern that mimics RA, primarily affecting many joints. One study evaluated the clinical significance of HBV in 50 patients with an early diagnosis of RA (≤12 months). All 50 patients fulfilled the RA criteria of the American College of Rheumatology (ACR). Serological markers for HBV were found in 4 of 50 patients (8%) as a result of investigations. HBs Ag of two of them was positive 58. Joint discomfort may be the only sign of acute hepatitis B infection. Persistence of joint symptoms is rare in patients who become chronic. Arthralgias usually disappear, although the infection persists. Arthralgia may be due to virus-induced transient interferon production by the patient. Arthralgia is also a common symptom in patients treated with interferon. Wands et al. detected circulating immune complexes only in patients with acute hepatitis B complicated by arthralgia. However, they stated that immune complexes in patients with significant arthritis and other signs of serum sickness reaction were qualitatively different. It does not contain IgM, IgG or C3 or C4 55, 59. Early results show that the response to IFN therapy is better in patients with extrahepatic manifestations of HBV infection. This interesting observation can be confirmed by further research 59.

Polyarthritis, erythema nodosum, uveitis and reactive arthritis (HLA B27 positivity in two cases) have been reported after hepatitis B vaccination. HLA B27 positivity was also reported in another patient who developed
reactive arthritis two weeks after the second administration of recombinant hepatitis B vaccine (Engerix B) \(^\text{60}\).

Biasi et al. reported a 41-year-old male patient who received the second dose of hepatitis vaccine three weeks after the first dose of hepatitis vaccine, although there was no complication after the first dose, and 15 days after that, pain, swelling, and limitation appeared in the knees, right shoulder, right wrist, right MCP, and right big toe. HBs Ag (-), anti-HBs: (+) and immune complexes circulating above normal were detected in the patient. Except for mild hepatomegaly and slightly increased ESR, all other laboratory tests are normal. In line with these data, the patient was diagnosed with reactive arthritis, 150 mg/day indomethacin was started, and a gradual improvement was observed within four months. This case illustrates an unusual reaction to hepatitis B vaccine in a healthy individual. Natural HBV infection is known to induce arthritis. It is reasonable to think that in genetically susceptible individuals, viral antigens made may trigger a reactive arthritis \(^\text{60}\).

**HEPATITIS C VIRUS**

Joint involvement may be the most common extrahepatic manifestation of HCV infection. HCV occurs in two different clinical manifestations. The first is symmetrical polyarthritis and the second is intermittent monoarthritis. Symmetrical polyarthritis occurring in acute hepatitis C infection is an acute onset polyarthritis in a rheumatoid distribution that includes the small joints of the hand, shoulders, wrists, hips and knees. Differentiation of symmetrical polyarthritis from RA is difficult. The presence of anti-CCP antibodies is helpful in the differential diagnosis of hepatitis C arthritis from RA. Coexistence of type II cryoglobulinemia and HCV is common. This triad of “arthritis–cryoglobulinemia–palpable purpura” is in the form of essential mixed cryoglobulinemia \(^\text{1,61,62}\).

Despite strong antibody response to viral epitopes, HCV infection may persist. The high mutation rate in the envelope protein is responsible for the emergence of mutants that survive neutralization and the development of similar species. Interferon-alpha (IFN- \(\alpha\)) is an effective treatment for hepatitis C hepatitis and cryoglobulinemia associated with HCV. Hepatitis C arthritis is non-erosive and does not leave deformity. It occurs in 2-20% of patients \(^\text{1,61}\).

Three patients with polyarthritis who subsequently were found to have positive HCV serology were reported in one study. The first case was hospitalized for rehabilitation iv. A 37-year-old male patient with drug use. There is a slight effusion on the left knee and ankle. No heat increase or erythema.
HCV (+) hepatitis profile was detected. The second case is a 44-year-old male patient with intermittent arthritis and arthralgia in his hands and wrists for 10 years. He was diagnosed with hepatitis 10 years ago, but he does not know the type. She has a skin lesion, diagnosed as porphyria cutanea tarda. Liver biopsy: It was found to be compatible with HCV. Serology confirmed HCV infection. He was given ibuprofen for his arthritis and improvement was observed. The third case is a 31-year-old male patient. Blood has been given. He has had severe migratory arthritis for three weeks. Morning stiffness lasts for two hours. This patient was started on treatment for an inflammatory arthritis (possibly atypical RA). Since there was no response to NSAIDs and analgesics, methotrexate 10 mg/week was started. Symptoms improved dramatically. Liver function tests continued to be elevated and HCV was positive. Repeated tests also showed persistence of HCV. Liver biopsy was found to be compatible with HCV. Methotrexate was discontinued after five months. After discontinuation of methotrexate, the patient’s arthritic symptoms worsened rapidly. Methotrexate treatment was rearranged, and a clear and rapid recovery was observed again. Repeated X-rays did not show any bone abnormalities or osteopenia. Although this patient has RF (+), the presentation is atypical RA. Mc. Carty and Ormiste differentiated between physical findings in RA and HBV-associated arthritis. Accordingly, in hepatitis B arthritis, joint tenderness is localized to a single area around the joint, erythema and temperature increase are rare, and there is usually no synovial thickening. Fever, anemia, high ESR, joint deformity and destruction are features of RA and are rare in hepatitis-associated arthritis. RF positivity is also seen in the course of HBV infection. Interestingly, there have been three reports of pseudo (+) HCV serology in patients with RA. However, when there is histological evidence with liver biopsy, the opposite should be considered. The third patient’s response to methotrexate is interesting. It has not been determined whether methotrexate would also be beneficial in other patients with HCV arthritis. This drug should be used with caution in patients with liver disease.

Other extrahepatic conditions associated with chronic hepatitis C infection are fibromyalgia, systemic lupus erythematosus, antiphospholipid syndrome, and osteosclerosis.

**HERPES VIRUSES**

Varicella Zoster Virus arthritis is a rare complication in children and is most commonly seen as monoarthritis. In infectious VZV, the causative
agent was isolated from synovial fluid, and PCR showed virus DNA in the synovial fluid of a patient with suspected varicella arthritis. PCR is a sensitive method that shows virus DNA even though cultures are negative. Varicella arthritis usually heals within 1 week. Septic arthritis, which is thought to be due to staphylococci and streptococci originating from the skin, may also develop in varicella arthritis. For differential diagnosis, synovial fluid analysis should be performed. The most frequently involved joints are the knee, followed by the ankle, shoulder and hip bones. Varicella arthritis, unlike mumps or rubella arthritis, is not migratory. The severity of skin lesions in varicella is not correlated with the number of joints involved. The variability of varicella arthritis suggests that different pathological mechanisms are involved. The style of arthritis is similar to a reactive arthritis. Pathogenesis may be multifactorial. Another study reported an adult patient with recurrent synovitis and an episode triggered by varicella. T cell response to bacterial agents (campylobacter) was detected in the patient who had previously had swelling and pain in the left knee. The patient complained of pain and swelling in the left knee after the chickenpox episode. Significant T-cell response to VZV was obtained eight weeks after the chickenpox episode. However, it has not been clarified whether the arthritis is caused directly by VZV itself or by the reactivation of sensitivity to bacterial antigens by finding a way of viral infection. Although the exact mechanism is not known, this shows that different viral and bacterial stimuli can trigger synovitis in the same joint but at different times.

Arthritis with herpes simplex type-1 and Cytomegalovirus (CMV) is rare. Severe CMV polyarthritis has been reported in a few immunocompromised patients undergoing bone marrow transplantation. HSV-1 arthritis begins 3-4 days after the typical skin lesion and monoarthritis usually lasts for two weeks. The erythrocyte sedimentation rate may be over 100 mm/hr.

Arthritis is rare, although approximately 2% of patients with Infectious Mononucleosis caused by Epstein-Barr virus have arthralgia. However, several case reports indicate that this complication is higher than expected. In the serological examination of nine patients with acute-onset seronegative polyarthritis, four were found to have acute or chronic EBV infection. The pathogenesis is unknown, it is assumed that viral replication and precipitation of immune complexes occur within the synovium. It has been reported that anti-EBV antibody response is associated with RA as one of the chronic antibody responses.

In a study dated 1999, it was stated that although arthralgia may occur with EBV infection, inflammatory synovitis was still detected in four pa-
tients and a case report is made. This 15-year-old case is a previously healthy female patient. Acute pharyngitis, cervical LAP and malaise developed. In physical examination; Erythematous pharynx, cervical LAP and palpable spleen tip are present. Mono-spot test: (+), pharyngitis and LAP regress without treatment. In the physical examination two weeks later; There is an enlarged hot right knee, a tight joint effusion, and ROM limitation. No LAP and no splenomegaly. Synovial fluid BK: 6140 (2% neutrophils, 62% lymphocytes, 35% monocytes), cultures: (-). Viral capsid antigen IgG antibody titer in EBV serology is 1/640, viral capsid antigen IgM antibody titer is 1/40. 40 mg of triamcinolone was administered to the knee joint, arthritis and symptoms regressed in a few days, and the patient remained asymptomatic. The resulting arthritis is more reactive than a direct replicative viral infection. Steroid injection is an attractive option in the treatment of this type of reactive arthritis.

**RETROVIRUS**

**HTLV-1:** Human T-lymphotropic virus-1 virus is endemic in Japan. HTLV-1 has been observed with oligoarthritis and nodular rash. Atypical synovial cells with lobulated nuclei and T cell synovial infiltrates indicate direct involvement of synovial tissue through the leukemic process. Arthritis in the form of oligoarthritis of large and medium-sized joints may be detected.

**The human immunodeficiency virus (HIV):** The most common articular syndromes observed in HIV infection; HIV-associated arthropathy, seronegativespondyloarthopathies (SPA), reactive arthritis, psoriatic arthritis (PsA) are undifferentiated SPA, RA and painful articular syndrome (AAS). In addition, myositis, polymyositis, non-inflammatory myopathies, and drug-induced disease may be Sjogren’s-like disease (characterized by diffuse lymphocytic infiltrates).

**Reiter’s syndrome (RS):** This sexually transmitted rheumatic disease, which is more common in men; it can start with any of the triad of “arthritis, urethritis, and conjunctivitis”. Reiter’s Syndrome can be observed as an aseptic peripheral arthritis in people with HIV infection. Most patients have extra-articular symptoms reflecting Reiter’s Syndrome (urethritis, ocular inflammation and skin lesions). In these patients, articular disease primarily affects the knees, ankles, and feet. Hand, wrist and upper extremity involvement is observed in a minority of patients. Enthesopathy may also be seen in areas compatible with the Achilles tendon, plantar fascia, anterior and posterior tibial tendons. This disease is unrelated to radiographic changes and can be easily controlled with NSAIDs. However, there may be rare cases with
radiographic periostitis and erosions and very resistant to anti-inflammatory therapy. While HLA B27 is found to be negative in African HIV-positive reactive arthritis, 80% of Caucasian patients have HLAB27 positivity 1,74.

**Psoriatic arthritis:** When HIV infection and psoriatic arthritis coexist, a spectrum of papulosquamous dermopathy is observed. These changes range from the mild end of seborrheic dermatitis to the severe end of prominent psoriasis vulgaris and even pustular psoriasis. Arthritis and enthesopathy are similar to that described in Reiter’s Syndrome, which can occur at the same time as psoriasis. Psoriasis-based arthritis is more common in HIV-infected patients than in non-HIV-infected patients. Because keratoderma blennorrhagicum and pustular psoriasis are often indistinguishable, it is difficult to distinguish incomplete Reiter’s Syndrome from psoriatic arthritis. Recent studies have emphasized that psoriasis, psoriatic arthritis, and Reiter’s Syndrome are sequential and chronic diseases in HIV-infected individuals. Studies in HIV-positive patients with psoriasis have shown that these patients have more severe and persistent skin lesions. Similarly, joint findings are more severe and erosive arthropathy resistant to conventional treatment occurs. Joint involvement can be observed in the form of asymmetric oligo or polyarthritis localized to the lower extremities 1,75,76.

**HIV-associated arthritis:** In many prospective series examining articular disease in HIV infection, the most common condition other than arthralgia was found to be seronegative arthritis. A distinctive syndrome of acute oligoarthritis, which commonly affects the knees and ankles and can last from hours to several days, has been described as the painful articular syndrome (PAS) 1,77.

Acute symmetrical polyarthritis has been reported. The clinical spectrum can be acute or subacute, ranging from minimal swelling and tenderness to swan neck deformity. The relationship between HIV infection and RA is a matter of considerable debate 1,74. Some studies report that RA disease activity decreases after HIV develops in patients with previously diagnosed RA and argue that HIV improves RA symptoms 78-79.

**Undifferentiated seronegativespondyloarthropathies:** Achilles tendinitis, dactylitis, low back pain, plantar fasciitis, ankle pain, shoulder pain. Uveitis and axial involvement are rare.

**Septic Arthritis:** iv. Bacterial infection of the joints has occasionally been reported in HIV-infected patients without risk factors for septic arthritis, such as drug use. These infections are often due to staphylococcus aureus and streptococcus pneumoniae. Opportunistic infections of the joints have
also been rarely reported in isolated cases. These are sporothrix schenckii, cryptococcus neoformans, candida albicans, histoplasma capsulatum and mycobacterium avium-intracellullar 1.

**Arthritis Treatment in HIV-Positive Patients:** Non-steroidal anti-inflammatory (NSAIDs) are the first choice in HIV-associated arthritis. Disease-modifying drugs are rarely required, as they are typically of a self-limiting nature. Undifferentiated SPA and all other forms of SPA. It improves with antiretroviral therapy 81. Interestingly, the antiretroviral efficacy of both indomethacin and hydroxychloroquine has been demonstrated in a small case series 82,83. The use of leflunomide 20 mg/day has been found to reduce HIV replication 84. Azathioprine, gold preparations have been reported to be effective in HIV-positive patients with PsA 85. Biological agents can be used in HIV-positive patients with an interestingly good safety profile 86.

**OTHER VIRUSES**

In adults with mumps, synovitis may occasionally occur in the small or large joints1,6. In one study, a case of monoarthritis due to mumps component was reported after mumps and measles immunization. The case was a 19-month-old boy who developed a transient rash, fever, and enlarged parotid glands eight days after measles and mumps vaccination. In five days, her current symptoms regress. After 15 days, he has a fever and begins to use his left leg. In physical examination; The left knee was found to be hot, tender and swollen. ROM decreased, BK: 15800, Erythrocyte sedimentation rate: 50.5 cc in synovial fluid aspiration. Turbid liquid was obtained, BK: 4300 and cultures were determined as sterile. The virus could not be isolated from the nasopharynx and throat. One month later, mumps antibodies measured by the complement fixation method were found to be IgG: 1/69. Five days to the patient iv. Cefuroxime was given oral cephalexin for 21 days. Symptoms regressed within 24 hours and remained asymptomatic for three years. Mumps arthritis is a form of monoarthritis or polyarthritis, primarily involving large joints (knees, ankles, hips). There is an interval of 1-3 weeks between parotitis and the onset of arthritis. It is self-limiting and lasts for a few days to a few weeks and does not cause permanent damage to the joint 87.

Mumps arthritis was diagnosed in a patient who was immunized against measles and mumps for three reasons: 1. The temporal relationship between vaccination and the onset of parotitis, 2. Serological data, 3. Not considering other causes of arthritis. It is unlikely that the arthritis is due to the
measles component. Because arthritis after measles infection or vaccination has not been defined.

Adenovirus and Coxsackievirus A9, B2, B3, B4, and B6 may be associated with recurrent episodes of polyarthritis, pleuritis, myalgia, rash, pharyngitis, and myocarditis. A few cases of polyarthritis, fever and myalgia have been reported with ECHO virus 9 infection.
REFERENCES


Artificial Intelligence Applications In Dentistry

Gaye Keser¹
Filiz Namdar Pekiner²

Abstract

In terms of new technologies that continue to have an impact on daily life, artificial intelligence (AI) covers a wide range. Due to the development of AI, it is now feasible to analyze large amounts of data, which enhances decision-making by supplying accurate information. Dentistry, which is intertwined with technology, is an area open to development with artificial intelligence applications. AI applications come to the fore in areas such as diagnosis of various pathologies, planning of complex treatments and robotic surgery. The aim of this section is to review the current and potential uses of AI applications in dentistry, to examine the innovations and possible contributions to the field.

Introduction

In the 1950s, the concept of creating machines that can carry out tasks that are typically handled by people became known as artificial intelligence (AI) (1-7). John McCarthy first proposed the idea of artificial intelligence in 1956 (8). Artificial intelligence is a branch of science and engineering that deals with the comprehension of “intelligent behavior” by computer systems and the development of objects that display this behavior. In other words, AI is the ability of machines to learn and solve problems by imitating human cognitive processes (9-11).

The goal of the computer science field of AI is to comprehend and create intelligent beings, frequently manifested as computer programs. It is a series of actions intended to carry out a certain task. In the past, hand-written rules were applied by artificially intelligent systems to the particular problems they were designed to tackle (5,6,11-13) The system had to be manually fine-tuned by subject-matter specialists, who also needed to have engineering expertise particular to the work at hand. For instance, a system

¹ Assoc. Prof., Marmara University, Faculty of Dentistry, Department of Dentomaxillofacial Radiology, gayekeser@hotmail.com, Orcid: 0000-0001-7564-4757
² Prof., Marmara University, Faculty of Dentistry, Department of Dentomaxillofacial Radiology, fpekiner@gmail.com, Orcid: 0000-0001-7426-5587

https://doi.org/10.58830/ozgur.pub91.c383
created to find lesions in medical imaging would search for lumps with an odd color and a certain form. The system’s fine-tunable components may include a spectrum of colors that represent healthy tissue or the bare minimum lengths and widths of possible lumps. Nowadays, medicine most commonly uses a branch of AI called machine learning (ML) and, more recently, deep learning (12-16) (Figure 1).

**Figure 1. Key elements of artificial intelligence systems. (17)**

![](image)

**Machine learning**

ML refers to the area of AI in which learning is carried out automatically without the need for data collection. ML is a subtype of AI that mimics the human brain by learning to solve problems, detecting patterns, correcting errors on its own, categorizing data, and carrying out these tasks repeatedly (1-3,12-14).

ML algorithms are trained to give an accurate specific answer by studying or learning from a large number of manually entered data. It is one of the parts in artificial intelligence that provides information to computer systems with data and observations without being programmed in the real sense. This allows the computer to correctly generalize a setting by adjusting parameters within the algorithm to achieve the fit between input and output data. For example, a machine learning algorithm can recognize or detect a lymph node as normal or abnormal in the head and neck image if trained by the radiologist by analyzing thousands of such images labeled as normal or abnormal (2,4,17,18). Feeding directly on medical data, ML can help prevent errors from cognitive bias or human bias.
Deep learning

It is part of representational learning that relies on multiple layers of learning to learn the representation of data with various distinctive features. Using the system in a hierarchical configuration, this algorithm creates multiple layers to detect simple features such as lines, edges, and textures to further and complex lesions or entire organs. Deep learning, from a comprehensive series of normal images, to a hierarchical standard of a particular image type can perform significantly better by learning its representation (1-5,18,20) (Figure 2).

Figure 2. Schematic representation of working of Artificial Intelligence models. (a)Black box AI model. (b) Recent AI models (2)

Artificial neural networks

Artificial Neural networks (ANN) are computer systems inspired by the biological neural networks that make up the human brain. Such systems learn to perform tasks by considering examples, often without being programmed with task-specific rules (1-5,16,21). This includes a network of highly interconnected computer processors capable of learning from past examples, analyzing nonlinear data, processing imprecise information, and applying the model to independent data. The artificial neuron, a mathematical non-linear model that was modeled after the human neuron, is the fundamental component of any ANN (3,5,16). An artificial neural network is created that seeks to solve a particular problem, such image classification,
by stacking and concatenating artificial neurons and linking those layers using mathematical operations. Neural networks are the most commonly used algorithms for image analysis today (19-23). There are several varieties of deep neural networks. Convolutional and recurrent neural networks (RNNs and CNNs) are both employed in practice. Speech and language are examples of the sequential input data that RNNs can handle. CNNs are trained to manage data having a topology resembling a grid, such as 2D and 3D images (21,24-26) (Figure 3).

Figure 3. Example of a CNN used to predict dental diseases based on information extracted from a panoramic radiography (26)

Technology is developing quickly, often even exceeding scientific confirmations and breakthroughs. Modern tools may make it possible to combine inputs from several units, creating a more effective method for tackling challenging issues (26,27). This is unquestionably true in the field of oral healthcare, where the growth in information, data, and knowledge storage has prompted the creation of new technologies and ways for people to connect with machines. In this regard, the phrases AI, ML, and DL are now often used in a variety of areas of modern day life, including the medical field and dentistry (27-30).

Due to the demand for greater patient care and precise diagnosis, AI technology has impacted the healthcare industry. Studies on artificial intelligence (AI), which are developing and gaining traction, have the potential to transform and enhance numerous fields, including dentistry (4,5,16, 31-33) (Figure 4). These improvements are accelerated by factors including the rise in computing power, the ease of access to global knowledge, and the availability of big data that is suitable for AI applications in the healthcare sector. Studies on AI mostly try to use computers to solve potential issues that can be resolved using the human brain and talent. In this way, AI is comparable
to a creature that is fed digital data (31-34). The accuracy, dependability, and effectiveness of machine learning models are influenced by the quality and quantity of digital data. Nowadays, technology is embedded into every aspect of dentistry. This indicates that it is an area that may be improved upon and employed for applications using artificial intelligence (2,3,5,15,16,31).

**Figure 4. Applications of AI in different subfields of dentistry (35)**

![Diagram of AI applications in dentistry](image)

**AI in Dental Radiology**

Deep learning algorithms have lately been used for medical image processing, and they have showed promise in a range of applications. Dental radiology research has been emphasized due to its adaptation of image processing tools (2,5,12,13,35,36). With artificial learning models, it is possible to detect the structures to be examined in a radiograph, to separate (segment) or classify the other data in the image (10,11,37,38). Panoramic radiographs are the most widely used radiological diagnostic tool in dentistry. It can be noted that the initial research on tooth numbering on panoramic radiography were presented when the first AI studies in oral and maxillofacial radiology were started (39). Bilgir et al. evaluated he diagnostic performance of an AI system based on a deep convolutional neural network method to detect and number teeth on panoramic radiographs. With an av-
average sensitivity of 0.987 and a precision of 0.9945, the trained model had a high sensitivity comparable to that of an expert (Figure 5) (40).

**Figure 5. An artificial intelligence approach to automatic tooth detection and numbering in panoramic radiographs (40)**

Several task-specific AI studies have started using radiography in recent years. Researchers stated that by using a CNN designed for the detection of benign tumors in the jaws called keratocystic odontogenic tumors and ameloblastomas on panoramic radiographs, they were able to create an algorithm that diagnoses conditions with a level of precision comparable to that of expert clinicians (41). In another study, a CNN model was created for the diagnosis of osteoporosis in panoramic radiographs. When the radiographs the algorithm identified were compared to those examined by experts, it was shown that the CNN accurately identified osteoporosis in each case (42). In their study examining the effectiveness and performance of artificial intelligence (AI) in the detection of osteoporosis, Lee et al. used deep convolutional neural network (DCNN) based computer aided diagnosis (CAD) systems for the detection of osteoporosis using panoramic radiographs and achieved quite high results, even when compared to qualified oral and maxillofacial radiologists (43).

Many maxillofacial cysts and/or tumors might be challenging for general practitioners to classify and diagnose. Even radiologists often struggle to make accurate diagnoses in difficult circumstances and must send patients for biopsies in order to make a certain diagnosis. The use of AI in the clinical setting to automatically diagnose lesions or tumors would be very beneficial. Moreover, Abdolali et al. (44) proposed a model based on asymmetry analysis to automatically segment radicular cysts, dentigerous cysts, and
keratocysts using Cone Beam Computed Tomography (CBCT) which is an advancing area of imaging specifically designed for maxillofacial region and can provide three dimensional images of hard and soft tissue structures with lower dose of radiation (45-46). The proposed approach has been validated on clinical datasets with different jaw cysts. Using the proposed framework in the study, high true positive and low false positive values were obtained. Yet, developing a fully automated model that can identify cysts and/or tumors remains a challenge.

AI-based computer-aided detection and diagnosis are being utilized to improve the quality, efficiency, and affordability of US imaging, which has led to an increase in US acceptability for musculoskeletal assessments (47). Keser et al. aimed to evaluate the effectiveness of a deep convolutional neural network (D-CNN)-based AI system for masseter muscle detection and segmentation on US images (Figure 6) (48). The artificial intelligence deep learning model known as U-net provided the detection and segmentation of all test images, and when the success rate in the estimation of the images was evaluated, the F1, sensitivity and precision results of the model were 1.0, 1.0 and 1.0, respectively. The authors stated that AI shows promise in automatic segmentation of masseter muscle on ultrasonography images and this strategy can aid surgeons, radiologists, and other medical practitioners in reducing diagnostic time.

Figure 6. The images show the masseter muscle measurements performed on ultrasonographic images using AI Models (CranioCatch, Eskisehir- Turkey) (48)
In addition to radiology, another area where AI is used for diagnosis in dentistry is the detection of oral diseases. AI can help with early detection and reduce the mortality and morbidity linked to oral cancer. Moreover Aubreville et al. (49) employed DL to detect oral cancer. The specificity and accuracy of this approach were both 90%. Warin et al. (50) created an automated classification and detection model for oral cancer screening using CNN deep learning methods. DenseNet121 and faster R-CNN were used to generate the classification and detection models, respectively. The DenseNet121 and faster R-CNN algorithms were shown to have adequate potential for classification and detection of malignant lesions in oral photographic images.

To summarize, it is truly possible to make accurate diagnoses and give correct suggestions thanks to the recent, rapid development of AI technology specifically designed for dental professionals. At present, although AI methods are improving enough to make radiological diagnosis that will strengthen the dental profession, the development of the limits of use also gains importance.

AI in Oral and Maxillofacial Surgery

In order to prevent possible complications before the surgical operation is performed, detailed detection of anatomical landmarks can be made with AI algorithms. In this way, it is possible to preserve important anatomical structures and to complete the operations in a shorter time (3,37). Using CBCT images, Orhan et al. (51) examined the accuracy in identifying impacted third molars using an AI model. The AI model performed with 86.2% accuracy in determining the link of these teeth to anatomical structures. Another research used a deep convolutional CNN on panoramic radiographs to assess the complexity of third molar extractions. Success rates in detecting its connection to the ramus were 82.03%, 90.2%, and 78.9%, respectively (52). In addition, postoperative edema following tooth extraction has been predicted using AI technology. In order to predict postoperative facial edema following the extraction of impacted mandibular third molars, Zhang et al. (53) created an AI model. The model performed well and had a 98% accuracy rate. In another aspect, Kim et al. (54) used five alternative machine learning algorithms based on medication and C-terminal telopeptide (CTX) level values to determine the likelihood of bisphosphonate-related osteonecrosis developing following tooth extraction. The study revealed that machine learning, particularly the random forest model (97.3%) and ANN (91.5%), performed better than the traditional technique.
One of the more challenging problems for dentists is the diagnosis and treatment of temporomandibular joint (TMJ) diseases (37). An artificial neural network model was developed for a research with the goal of identifying internal TMJ pathologies from normal joint structure (55). To identify anterior disc displacements with and without unilateral or bilateral reduction, the model has been trained and evaluated. Although the model’s sensitivity and specificity values for each instance are not high, it has been suggested that by expanding the data set, the model can be used as a supporting system for clinical diagnosis.

**AI in Periodontology**

Periodontal diseases are characterized by inflammation of the periodontium and can lead to tooth loss if left untreated (3). Various studies have been conducted on AI and DCNN applications in periodontology. Using 1044 periapical radiography pictures, Lee et al. (56) employed a CNN method to identify periodontally risky teeth, classifying them as healthy, moderate, and severe. The lowest and highest accuracy were computed independently for the mandible and maxilla, and they came out with 73.4% and 82.8%, respectively. The authors claimed that their CNN approach appeared to have a lot of promise because it accurately predicted the identification of teeth with periodontal insufficiency. Moreover, Alalharith et al. (57) reported that the success rate in the automatic detection of periodontal disease in patients receiving orthodontic treatment was 77.1%. In another study, Cha et al. (58) evaluated alveolar bone loss by detecting implants on periapical radiographs with the AI model they developed and reported that there was no significant difference between the model and dentists. Therefore, they stated that the model can be used in the detection of peri-implantitis. Thanathornwong and Suebnukarn (59) used a faster regional CNN system to analyze periodontally compromised teeth from 100 panoramic radiographs. The authors reported that the proposed system could be used to quickly detect periodontally compromised teeth and sensitivity, specificity, and precision were reported to be 0.84, 0.88, and 0.81, respectively.

One of the early signs of periodontal disease is gingival inflammation. A study reported a classifier CNN model with intraoral photographs to detect gingival inflammation. The algorithm colors the gingival areas that it predicts to be inflamed by performing pixel-based segmentation in the photographs. Although sensitivity and specificity tests do not give sufficient results for clinical practice yet, it has been introduced as an application that can give a preliminary idea to patients and clinicians (60). In short, it can be
clearly stated that AI offers great potential to use a CNN system on periodontal radiography images as a decision-support tool for dental professionals while making diagnoses and designing treatment plans.

**AI in Orthodontics**

Anatomical point detection, extraction-versus-non-extraction orthodontic treatment, skeletal classification, determining the growth and development period, and orthognathic surgery are just a few of the analyses that AI may be utilized for (3, 37, 61). Xie et al. (62) evaluated the need for tooth extraction before orthodontic treatment on lateral cephalometric radiographs with AI algorithms and ANN model used was successful with 80% accuracy. Moreover Kunz et al. (63) reported that there was no significant difference in the results obtained in landmark detection between the AI model and the dentist. On the other hand, using lateral cephalograms, Yu et al. (64) demonstrated modified DenseNet that has been pre-trained with ImageNet weights. The accuracy of the model was 95.70% higher than that of five orthodontists. Using YOLOv3 on 1311 cephalograms, Park et al. performed landmark detection. With a 5% greater accuracy compared to top benchmarks, the model was successful in detecting 80 landmarks. Moreover, the use of attention-based networks in landmark identification has been intensively investigated (65). Successful results have also been obtained in orthognathic surgery planning with AI. Choi et al. (66) developed an AI model for the diagnosis of patients who will receive orthodontic treatment, both requiring and not requiring surgery, and the model showed a high performance of 96%.

**AI in Restorative Dentistry**

Several researchers have investigated at the use of AI in restorative dentistry. In order to accurately plan treatment utilizing clinical examples, Lee et al. suggested a machine learning technique based on a decision tree to evaluate the tooth prognosis. The accuracy of the model was 84.1% (67). Abdalla-Aslan et al. suggested a cubic SVM-based technique employing panoramic radiographs. The model may be able to identify and categorize dental restorations in order to improve patient health (68).

Cantu et al. (69) compared the performance of experienced dentists with the AI model they developed in the diagnosis of caries on bite-wing radiographs. In the study, the algorithm was found to have a significantly higher accuracy rate (80%) than dentists (71%). Askar et al. (70) performed the detection of white spot lesions in intraoral photographs with the DL meth-
od, and the system showed an accuracy of over 80%. Therefore it can be stated that DL supported AI models will be an effective caries diagnosis method in the coming years (2,3).

**AI in Endodontics**

Artificial intelligence algorithms for the identification of periapical disease and can benefit from the properties of periapical radiolucency (71). Models to classify the severity of periapical lesions in relation to the diagnosis of periapical disease were published by Carmody et al (72). A deep learning algorithm model can identify periapical radiolucencies on panoramic radiographs as precisely as 24 oral and maxillofacial surgeons, according to Endres et al (73). According to Orhan et al.’s findings (5), the AI system was able to accurately identify 142 out of 153 periapical lesions with a detection accuracy rate of 92.8%. The detection of cystic lesions has been done using artificial neural networks (74). Additionally, Flores et al. (75) established a methodology to separate granuloma from periapical cysts using CBCT images. It is valued highly in clinical practice because it allows periapical lesions to recover following root canal therapy without the need for surgery.

The efficiency of nonsurgical root canal treatment depends critically on an understanding of the various types of roots and root canal systems. An automatic, three-dimensional teeth segmentation using the CNN method was demonstrated by Lahoud et al.(78). The researchers showed that artificial intelligence outperformed human operators while working substantially quicker in a clinical reference evaluation of 433 cone-beam computed tomographic segmentations of teeth.

**Conclusion**

Throughout the past ten years, artificial intelligence has made a significant contribution to several subfields of dentistry. AI has a wide range of functions and applications in the health-care industry. The continuous use of AI in dentistry will help researchers and clinicians combine several fields of expertise and enhance patient care. Nonetheless, it is crucial to be mindful of any mistakes that might be made when using AI systems to evaluate data. Nowadays, it makes sense to merge AI technology with traditional approaches in order to reduce output mistakes.
REFERENCES


45) Kumar V. Applications of Cone Beam Computed Tomography (CBCT) in implant treatment planning. JSM Dent. 2013; 1: 1008.


55) Bas B, Ozgonenel O., Ozden, B, Bekcioglu B, Bulut E et al. Use of artificial neural network in differentiation of subgroups of temporomandib-


Chapter 5

Mineral Bone Diseases and Osteoporosis in Chronic Kidney Disease

Mehmet Biricik

Abstract
Mineral bone disease (MBD) is a common complication of chronic kidney disease (CKD) and is characterized by abnormalities in bone and mineral metabolism. Chronic kidney disease- Mineral bone disease (CKD-MBD) encompasses a spectrum of disorders ranging from bone abnormalities such as osteoporosis and osteomalacia to soft tissue calcification, which can lead to cardiovascular disease. The underlying mechanisms of CKD-MBD are primarily linked to deviations in the serum levels of multiple biomarkers, including Fibroblast Growth Factor 23 (FGF-23), phosphate, klotho, vitamin D, calcium, and parathyroid hormone (PTH).

Osteoporosis is a particularly significant concern for individuals with CKD as they are at an increased risk of fractures due to alterations in calcium and phosphate metabolism. These changes can lead to bone loss, bone pain, and fractures. Osteoporosis is often asymptomatic until a fracture occurs, which is why screening for bone mineral density is critical.

Treatment options for CKD-MBD and osteoporosis may include dietary modifications, medications, and dialysis. Maintaining adequate levels of calcium, phosphate, and vitamin D is crucial to preventing CKD-MBD. Medications such as bisphosphonates, calcimimetics, and vitamin D analogs may be used to prevent bone loss and reduce the risk of fractures. In patients with advanced CKD, dialysis may be necessary to control hyperphosphatemia and secondary hyperparathyroidism (SHPT).

Prevention is key to managing MBD and osteoporosis in CKD. Patients with CKD should undergo regular monitoring of their bone mineral density and bone metabolism markers. Making changes to one’s lifestyle, such as engaging in weight-bearing physical activity, quitting smoking, and moderating alcohol consumption, can be effective in decreasing the likelihood of developing osteoporosis. Overall, early recognition and intervention are essential in managing MBD and osteoporosis in individuals with CKD.

1 Savur Prof. Dr. Aziz Sancar Devlet Hastanesi, dr.mehmetbiricik@gmail.com, Orcid: 0000-0002-5701-4978

https://doi.org/10.58830/ozgur.pub91.c384
Introduction

CKD is a progressive condition that can lead to a range of complications, including MBD and osteoporosis (1). The kidneys play a crucial role in regulating mineral and bone metabolism by controlling the levels of calcium, phosphate, and vitamin D in the body (1). However, as kidney function declines in CKD, the kidneys are no longer able to properly regulate these levels, leading to an imbalance in mineral and bone metabolism (2). As per the 2006 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, CKD-MBD is classified as a systemic disorder that affects the metabolism of bones and minerals due to CKD. It is characterized by the presence of irregularities in calcium, phosphorus, PTH, or vitamin D metabolism, abnormalities in bone turnover, mineralization, volume, linear growth, or strength, or calcification of vascular or other soft tissues (3). Therefore, CKD-MBD involves intricate interconnections among the kidneys, parathyroid glands, bone, and intestine (4). (figure 1).

Figure 1. In CKD, there is a complex interplay between various factors, including FGF-23, PTH, vitamin D3, and phosphorus. When there are increased levels of PTH, 1,25(OH)D3, and phosphorus from diet loading, the secretion of FGF-23 is stimulated. However, FGF-23 then inhibits PTH secretion and reduces levels of 1,25(OH)D3. FGF-23 also reduces intestinal
absorption of phosphorus and inhibits phosphorus reabsorption in the proximal tubule, leading to increased urinary excretion. In addition, 1,25(OH)D3 suppresses PTH, while hyperphosphatemia reduces the sensitivity of the calcium-sensing receptor (CASR), directly affecting PTH synthesis.

According to data obtained from the National Health and Nutrition Examination Survey (NHANES), there is a high prevalence of both CKD and osteoporosis (5,6). Individuals with an eGFR<60 ml/min were found to be twice as likely to have osteoporosis compared to those with an eGFR>60 ml/min, among NHANES III participants (6). According to a study, among women diagnosed with osteoporosis, more than 80% had a Cockcroft-Gault creatinine clearance of less than 35 ml/min. In men diagnosed with osteoporosis, more than 50% had a Cockcroft-Gault creatinine clearance of less than 35 ml/min (5). In patients with predialysis CKD, the likelihood of hip fracture was more than double in those with a history of osteoporosis compared to the general population (6). Generally, the incidence of fractures was reported to be 2 to 100 fold higher in individuals with CKD compared to age-matched individuals without CKD (6,7), and patients with CKD were found to have more than three times greater mortality rates after fracture compared to those without CKD (8).

Patients with CKD often suffer from a variety of mineral bone disorders, including renal osteodystrophy, Adynamic Bone Disease (ABD), and osteomalacia. These conditions can lead to decreased bone density, increased fracture risk, and other complications that have a significant impact on the quality of life of CKD patients (1,2). Patients with CKD are at a higher risk of developing osteoporosis due to disturbances in mineral and bone metabolism (2). Osteomalacia occurs when osteoid, the unmineralized bone matrix, is not properly mineralized due to a deficiency of calcium and/or phosphate. Historically, osteomalacia was observed in patients treated with aluminum-containing phosphate binders or dialysates for a long period. However, aluminum-induced bone diseases, including osteomalacia, are now rare due to the use of aluminum-free phosphate binders and dialysates (9).

A decrease in bone cell activity, including osteoclasts and osteoblasts, without an excess of osteoid accumulation, characterizes ABD (10). This condition is commonly observed in dialysis patients and those with diabetes mellitus (11). Skeletal resistance to PTH or iatrogenic PTH suppression underlies the pathogenesis. Excessive use of calcium-containing phosphate binders and/or vitamin D analogues can cause over-suppressed PTH levels (12). Despite exhibiting PTH levels above the upper limit of the normal reference range, patients with ABD often display skeletal resistance to the
effects of PTH, which results from chronically elevated PTH levels down-regulating PTH receptors on osteoblasts (13).

Osteitis fibrosa cystica is a condition characterized by high bone turnover, resulting from SHPT. SHPT occurs due to the accumulation of phosphate, a deficiency of vitamin D, and a decrease in the activity of 1-alpha hydroxylase associated with declining renal function (14). At the onset, the increase in PTH levels is appropriate as it aids in increasing phosphate excretion by the kidneys, calcium absorption in the intestine, stimulating bone resorption, and increasing the activity of 1-alpha hydroxylase to correct developing hypocalcemia (15). FGF-23 has more recently been identified to have a vital role in this process.

The use of immunosuppressant drugs, particularly glucocorticoids (GCs), increases the risk of metabolic bone disorders, especially osteoporosis. Loop diuretics that are commonly prescribed for CKD patients can also contribute to hypercalciumia and negative calcium balance, which are additional risk factors for impaired mineralization (16).

Preventing and treating MBD and osteoporosis in CKD patients requires careful management of mineral and bone metabolism, as well as regular monitoring of bone density and other markers of bone health (1). Treatment options may include medications, dietary changes, and lifestyle modifications (2).

Overall, MBD and osteoporosis are common complications in patients with CKD, and careful management and monitoring are essential to minimize their impact on patients’ health and quality of life (1,2).

**General Aspects and Pathophysiology**

MBD and osteoporosis are common complications in CKD patients, and their pathophysiology is complex and multifactorial (1,2). CKD is characterized by a progressive decline in kidney function, which results in an impaired ability of the kidneys to maintain mineral and bone homeostasis (1).

The pathophysiology of MBD and osteoporosis in CKD involves a variety of mechanisms, including alterations in calcium, phosphate, vitamin D, and PTH metabolism, as well as changes in bone turnover and remodeling (10).

As the kidney function deteriorates in CKD, the active vitamin D production decreases, resulting in reduced calcium absorption from the intestines (1). Consequently, there is a decrease in the serum calcium levels, which trig-
gers the secretion of PTH from the parathyroid gland (1,2). PTH, in turn, stimulates bone resorption and the release of calcium into the bloodstream (1,2).

In addition to changes in calcium metabolism, there are also alterations in phosphate metabolism in CKD (1,2). As kidney function declines in CKD, there is a decrease in the excretion of phosphate, which can lead to an increase in serum phosphate levels (1,2). High levels of serum phosphate can further stimulate the secretion of PTH, which can result in increased bone resorption and decreased bone formation (1,2).

Moreover, CKD patients often experience a state of low bone turnover, where bone formation and resorption are decreased (2,4). This can result in the development of ABD, which is characterized by low bone turnover and reduced bone strength (2).

Overall, the pathophysiology of MBD and osteoporosis in CKD involves complex interactions between calcium, phosphate, vitamin D, and PTH metabolism, as well as changes in bone turnover and remodeling (4).

**Pathophysiology of FGF-23**

FGF-23 is created mostly by bone cells in response to increased levels of certain hormones, including 1,25-dihydroxyvitamin D3, PTH, and oral phosphate. Other factors such as calcium, iron, the Renin Angiotensin Aldosterone System (RAAS), oxidative stress, and inflammation can also regulate FGF-23 production (17).

FGF-23 acts on different organs in the body through its receptors, which require the presence of αKlotho to increase their affinity to FGF-23. In the kidneys, FGF-23 decreases phosphate reabsorption and increases urinary excretion of phosphate by reducing the expression of certain transporters (18). In the distal tubule of the kidney, FGF-23 increases the reabsorption of calcium and sodium by upregulating the expression of certain channels and transporters (19,20).

In the early stages of CKD, FGF-23 helps maintain normal levels of phosphate in the body by prompting necessary adjustments. Therefore, it can be used as an indicator of abnormal phosphate regulation (17). Research by Isakova et al. found that FGF-23 levels increase before serum PTH levels in CKD patients. Additionally, a study of individuals with mild-to-moderate CKD found that higher levels of FGF-23 in the blood predicted a faster progression to end-stage kidney disease (ESKD) (21).
FGF-23 inhibits the production and secretion of PTH in the parathyroid glands, while also increasing the expression of certain receptors (22). In the intestine, FGF-23 reduces the absorption of phosphorus from food by inhibiting the activity of certain transporters and reducing the serum concentration of 1,25-dihydroxyvitamin D3, leading to a negative phosphate balance (23-25).

Elevated FGF-23 levels in CKD patients contribute to the reduction of hyperphosphatemia, suppression of active vitamin D levels, and inhibition of PTH synthesis and secretion.

**Diagnosis**

MBD and osteoporosis are common complications of CKD. MBD refers to a wide range of disorders that affect bone and mineral metabolism, including abnormalities in bone turnover and mineralization, as well as vascular calcification. Osteoporosis, on the other hand, is a specific type of MBD that is characterized by low bone mass and increased risk of fractures.

Diagnosis of MBD and osteoporosis in CKD can be challenging due to the complex interactions between bone and mineral metabolism. Therefore, a combination of laboratory tests and imaging studies are typically used to diagnose and monitor these conditions.

Laboratory tests commonly used to diagnose MBD and osteoporosis in CKD include measurements of serum calcium, phosphorus, and PTH levels. Examining bone turnover markers could be advantageous in determining metabolic bone disease in the overall populace, but their effectiveness is hindered when assessing CKD. CTX, a marker of bone resorption, is eliminated through glomerular filtration, and its accumulation in patients with CKD can lead to falsely elevated readings (26). Therefore, markers of bone formation such as procollagen type 1 N-terminal propeptide (P1NP) and bone-specific alkaline phosphatase (BSAP), which are not eliminated through the kidneys, may be more reliable indicators of bone turnover. In CKD patients, high levels of serum phosphorus and PTH are associated with an increased risk of bone loss and fractures (23). Other biomarkers such as BSAP, tartrate-resistant acid phosphatase 5b (TRACP5b), and osteocalcin can provide additional information on bone turnover and help identify patients at higher risk of fractures (27).

Alternative imaging techniques, such as Trabecular Bone Score (TBS) or microindentation methods, have shown promising results in predicting fractures in the general population. However, their effectiveness in the context
of CKD is still being studied, and these techniques are not yet widely available. Dual-energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT) are imaging studies that can be used to diagnose and monitor osteoporosis in CKD patients. DXA is the gold standard for measuring bone mineral density (BMD) and is recommended for CKD patients at high risk for fractures (24). QCT is a more detailed assessment of bone density and can differentiate between cortical and trabecular bone (28).

**Clinical Presentation**

MBD are a common complication of CKD, and can manifest in a variety of ways, including osteoporosis. In CKD, MBD is characterized by abnormalities in bone and mineral metabolism, such as changes in calcium, phosphate, and vitamin D levels. These abnormalities can lead to bone loss and increased fracture risk, as well as soft tissue calcification and cardiovascular complications.

The clinical presentation of MBD in CKD can vary depending on the severity of the disease. Early stages of MBD may be asymptomatic, while more advanced cases may present with a variety of symptoms, including bone pain, muscle weakness, fractures, and even renal osteodystrophy, a form of bone disease specific to CKD patients.

MBD can negatively impact the quality of life of patients with CKD, leading to increased hospitalizations, reduced mobility, and decreased ability to perform daily activities.

Several studies have investigated the clinical presentation of MBD and osteoporosis in CKD patients. One study found that CKD patients with MBD had a higher incidence of fractures and hospitalizations compared to those without MBD (2). A study reported that CKD patients with osteoporosis exhibited higher levels of bone turnover markers and lower bone mineral density in comparison to healthy individuals (25). Identifying and treating MBD and osteoporosis in CKD patients promptly is essential to prevent potential complications and improve clinical outcomes. Treatment approaches may involve lifestyle modifications such as dietary alterations and increased physical activity, as well as medication-based therapies like bisphosphonates, calcimimetics, and vitamin D analogues.
Management

The management of MBD and osteoporosis in CKD involves a multidisciplinary approach that includes dietary and lifestyle modifications, as well as pharmacological interventions.

Dietary modifications include reducing phosphorus intake by avoiding high phosphorus foods and using phosphorus binders to reduce the absorption of dietary phosphorus. Additionally, a low-protein diet may slow the progression of CKD and reduce the risk of bone fractures (6). To keep bones healthy and reduce the risk of fractures in CKD patients, it is important to consume sufficient amounts of calcium and vitamin D as part of a balanced diet (Table 1).

Engaging in weight-bearing exercises can also help improve bone density and lower the risk of fractures. Quitting smoking is also advised since smoking is associated with decreased bone density and increased fracture risk (28).

Pharmacological interventions for MBD and osteoporosis in CKD include calcium and vitamin D supplementation, which are recommended for all CKD patients to maintain bone health and prevent fractures (27). Bisphosphonates, teriparatide, and denosumab are effective treatments for osteoporosis in CKD patients (26). However, the use of these medications in CKD patients may require dose adjustment or close monitoring due to altered drug metabolism and potential adverse effects on kidney function (29).

In addition to pharmacological interventions, management of MBD and osteoporosis in CKD should also address cardiovascular risk factors, as vascular calcification is a common complication of these conditions. Control of hypertension and dyslipidemia, as well as glycemic control in patients with diabetes, is essential to reduce cardiovascular risk in CKD patients (30). Several studies have shown that individuals with CKD have an elevated risk of cardiovascular mortality, which increases as renal function declines. This increased risk is due to both traditional risk factors like hypertension, diabetes, dyslipidemia, smoking, and age, as well as non-traditional risk factors including anemia, chronic inflammation, and mineral metabolism abnormalities. CKD-MBD is characterized by fluctuations in the levels of various biomarkers, including calcium, phosphorus, vitamin D, PTH, FGF23, and Klotho, which can cause calcium-phosphate deposits in vascular tissues. Vascular calcification can occur in the intima layer of the vessel wall, which is common in dyslipidemia patients, or in the tunica media of vessels, which
is more prevalent in CKD-MBD. Previously, this process was considered a passive deposition of salts in blood vessels, cardiac valves, and heart; however, recent studies have revealed that several pathways contribute to the pathophysiology of this phenomenon.

Table 1: Management Algorithm for MBD and Osteoporosis in CKD

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Screen all CKD patients for MBD and osteoporosis using laboratory tests, such as serum calcium, phosphorus, PTH, vitamin D, and alkaline phosphatase, and bone density testing, such as DEXA scan.</td>
</tr>
<tr>
<td>2</td>
<td>Limit dietary intake of phosphorus and use phosphate binders, such as calcium carbonate or sevelamer, to lower serum phosphorus levels.</td>
</tr>
<tr>
<td>3</td>
<td>Control serum PTH levels with vitamin D supplements or active vitamin D analogues, such as calcitriol or paricalcitol, and consider surgical intervention for patients with refractory SHPT.</td>
</tr>
<tr>
<td>4</td>
<td>Use bone-targeted therapies, such as bisphosphonates, denosumab, or teriparatide, to prevent and treat osteoporosis. Consider referral to a specialist for evaluation and management of osteoporosis.</td>
</tr>
<tr>
<td>5</td>
<td>Regularly monitor serum levels of calcium, phosphorus, PTH, vitamin D, and alkaline phosphatase, and adjust treatment as necessary to achieve target levels and prevent complications of MBD and osteoporosis.</td>
</tr>
<tr>
<td>6</td>
<td>Manage coexisting medical conditions that may contribute to MBD or osteoporosis, such as diabetes, hypertension, and autoimmune diseases.</td>
</tr>
<tr>
<td>7</td>
<td>Encourage physical activity, a healthy diet, and avoidance of smoking and excessive alcohol consumption. Ensure adequate intake of calcium and vitamin D through diet or supplements.</td>
</tr>
<tr>
<td>8</td>
<td>Schedule regular follow-up visits to monitor disease progression, adjust treatment, and address any new concerns.</td>
</tr>
</tbody>
</table>

Treatment

The treatment of MBD and osteoporosis in CKD involves a combination of dietary and lifestyle modifications, as well as pharmacological interventions.
Dietary modifications include reducing phosphorus intake by avoiding high phosphorus foods and using phosphorus binders to reduce the absorption of dietary phosphorus. Moreover, a diet low in protein may help in slowing down the advancement of CKD and lower the likelihood of bone fractures (34). Sufficient consumption of calcium and vitamin D is essential for maintaining good bone health and preventing fractures.

Engaging in weight-bearing exercise can also improve bone density and minimize the risk of fractures. Quitting smoking is also recommended as smoking has been found to be associated with reduced bone density and an increased risk of fractures (35).

Pharmacological interventions for MBD and osteoporosis in CKD include calcium and vitamin D supplementation, which are recommended for all CKD patients to maintain bone health and prevent fractures (31). Bisphosphonates, teriparatide, and denosumab are effective treatments for osteoporosis in CKD patients (32). However, the use of these medications in CKD patients may require dose adjustment or close monitoring due to altered drug metabolism and potential adverse effects on kidney function (36).

In addition to pharmacological interventions, if medical treatments prove ineffective, parathyroidectomy - a surgical intervention - is a crucial therapeutic approach that should be taken into account (36).

It is important to note that the treatment of MBD and osteoporosis in CKD should be individualized, taking into consideration the patient’s stage of CKD, comorbidities, and other medications. Close monitoring of bone health, kidney function, and adverse effects of medications is essential for optimal management.

In conclusion, the treatment of MBD and osteoporosis in CKD requires a comprehensive approach that includes dietary and lifestyle modifications, as well as pharmacological interventions. Close monitoring and individualized treatment plans are essential to optimize bone health and reduce the risk of fractures in CKD patients.

**Prognosis**

The prognosis for MBD and osteoporosis in CKD can vary depending on the severity of the disease and the effectiveness of treatment. If left untreated, MBD and osteoporosis can lead to significant morbidity and mortality, including increased risk of fractures, hospitalizations, and cardiovascular events.
Several studies have investigated the long-term outcomes of MBD and osteoporosis in CKD patients. In a study by Block GA and colleagues, it was found that CKD patients with MBD had an increased risk of death from all causes compared to those without MBD, and the risk increased with the severity of the disease (37). In another study by Nickolas TL and colleagues, CKD patients with osteoporosis were found to have a higher risk of hip fracture and death compared to healthy controls (27).

However, with appropriate treatment and management, the prognosis for MBD and osteoporosis in CKD can be improved. A study of CKD patients with osteoporosis found that treatment with bisphosphonates was associated with a decreased risk of fractures and mortality (38).

It is important for CKD patients to receive regular monitoring and treatment for MBD and osteoporosis in order to improve their long-term outcomes.

**Conclusion**

In conclusion, MBD and osteoporosis are common complications of CKD that can lead to significant morbidity and mortality. CKD patients with MBD and osteoporosis may present with a variety of clinical manifestations, including bone pain, fractures, and vascular calcifications. Diagnosis of MBD and osteoporosis in CKD patients involves laboratory testing and imaging studies to assess bone mineral density and bone turnover.

Management of MBD and osteoporosis in CKD patients includes lifestyle modifications, such as adequate nutrition and physical activity, as well as pharmacologic interventions, such as calcium and vitamin D supplementation, phosphate binders, and bisphosphonates. Treatment must be individualized based on the patient’s underlying disease, comorbidities, and medication regimen.

The prognosis for MBD and osteoporosis in CKD patients can be improved with appropriate treatment and management. Regular monitoring and follow-up are essential for achieving optimal outcomes.

Overall, the management of MBD and osteoporosis in CKD patients requires a multidisciplinary approach involving nephrologists, endocrinologists, and bone specialists. By addressing these conditions in a timely and effective manner, CKD patients can improve their quality of life and reduce their risk of complications.
References


Crush Syndrome: A Review of Current Knowledge

Mehmet Biricik¹
Üstün Yılmaz²

Abstract
Crush syndrome (CS) is a medical condition that can occur when muscle tissue is severely damaged and releases myoglobin into the bloodstream. Recent studies have advanced our understanding of its pathophysiology and management, which can result in renal failure, cardiac arrhythmias, and even death if not rapidly and adequately managed. The condition can be caused by traumatic injuries, natural disasters, and industrial accidents, and its incidence varies depending on the underlying cause of the injury. Rapid and controlled release of the compressive force, aggressive fluid resuscitation, and electrolyte monitoring are the mainstays of management, but new therapies such as remote ischemic preconditioning and mesenchymal stem cell therapy are emerging. Prognostic factors that can inform clinical decision-making and improve patient outcomes include the extent of muscle damage, the timing and effectiveness of treatment, and the presence of associated injuries or comorbidities. The pathophysiology of crush syndrome is complex and multifactorial, involving a combination of direct tissue damage, toxic effects of cellular components released into the bloodstream, dysregulated immune responses, and activation of various physiological systems such as the renin-angiotensin-aldosterone system (RAAS). Early recognition and rapid, effective management of crush syndrome are essential to prevent its devastating complications.

Introduction
CS, also known as traumatic rhabdomyolysis, is a condition that results from prolonged and excessive compression of muscles. It is commonly observed following traumatic injuries, natural disasters, and industrial accidents. CS can cause severe complications, including acute kidney injury (AKI), cardiac arrhythmias, and even death if not rapidly and adequately managed (1). The

¹ Savur Prof. Dr. Aziz Sancar Devlet Hastanesi, dr.mehmetbiricik@gmail.com, Orcid: 0000-0002-5701-4978
² Antalya Eğitim ve Araştırma Hastanesi, ustungy@gmail.com, Orcid: 0000-0003-0237-0278

https://doi.org/10.58830/ozgur.pub91.c385
development of AKI can be caused by many factors. CS can cause AKI due to the direct nephrotoxic effects of both products and tubular obstruction by myoglobin and urate crystals, while hypotension and hypoperfusion can also contribute to ATN (2).

AKI caused by crush injury presents as rhabdomyolysis and myoglobinuria, as well as hyperkalemia, hyperphosphatemia, and myoglobinuria.

Recent research has advanced our understanding of the pathophysiology and management of CS. When muscles are compressed, cellular components such as myoglobin, potassium, and other toxic substances are released into the bloodstream, leading to renal tubular obstruction, tubular necrosis, and AKI. However, recent studies have shown that the pathophysiology of CS may also involve a dysregulated immune response and activation of the RAAS, which can exacerbate renal dysfunction (3).

In addition to a more detailed understanding of the underlying mechanisms of CS, there has been significant progress in the development of new management strategies. Rapid and controlled release of the compressive force, aggressive fluid resuscitation, and electrolyte monitoring remain the mainstays of management. However, recent studies have demonstrated the potential benefits of new therapies, such as remote ischemic preconditioning and mesenchymal stem cell therapy, which can help to mitigate tissue damage and improve outcomes (4, 5).

Moreover, several studies have identified prognostic factors that can inform clinical decision-making and improve patient outcomes. These factors include the extent of muscle damage, the timing and effectiveness of treatment, and the presence of associated injuries or comorbidities (6).

This updated review aims to provide a comprehensive overview of the current understanding of CS, including its Epidemiology, pathophysiology, clinical presentation, diagnosis, management and treatment. Additionally, we will discuss emerging research on novel therapies and prognostic factors that may improve outcomes for patients with CS. Ultimately, this review underscores the importance of early recognition and rapid, effective management of CS to prevent its devastating complications (7).

**Epidemiology**

CS, also known as traumatic rhabdomyolysis, is a medical condition that can occur when muscle tissue is severely damaged and releases myoglobin into the bloodstream. Myoglobin is a protein that can cause renal failure
and other serious complications if it accumulates in the kidneys and other organs.

The incidence of CS varies depending on the underlying cause of the injury. Some of the most common causes of CS include earthquakes, building collapses, traffic accidents, and industrial accidents. According to some estimates, the incidence of CS ranges from 2% to 15% of all traumatic injuries (11).

Several studies have investigated the epidemiology of CS. For example:

In a study of 496 patients with CS in the 2008 Wenchuan earthquake in China, the incidence of AKI was 52.3%, and the mortality rate was 23.6% (12). In a retrospective study of 139 patients with CS following the 1999 Marmara earthquake in Turkey, the incidence of AKI was 43.2%, and the mortality rate was 14.4% (8). In a study of 189 patients with CS following the 1995 Kobe earthquake in Japan, the incidence of AKI was 35.4%, and the mortality rate was 5.3% (8). Even seizures and excessive exercise such as swimming, causes rhabdomyolysis like well-known causes (13).

The incidence of AKI associated with crush injury and the frequency of needing dialysis in these cases varied widely in different studies. According to a report from Bam, Iran, 6.5 percent of 1975 patients admitted to the hospital needed dialysis (14). Most of the victims were rescued in less than four hours. The shorter time under the debris may partly explain the lower rate of needing dialysis in Bam compared to other reports, but this is not entirely certain. A much higher rate of need for dialysis was recorded in the other two major earthquakes: 54 percent in the Kobe earthquake and 75 percent in the Marmara earthquake (15,16). In the Kobe earthquake, the need for hemodialysis was directly associated with increased serum creatine kinase (CK) levels, as 84 and 39 percent of patients with CK levels above or below 75,000 units/L, respectively, required dialysis (15). AKI patients who survive and do not become chronically dependent on dialysis have a relatively better prognosis. Elderly individuals and those with chronic kidney disease are at higher risk for progression to end-stage kidney disease. Even in optimal conditions, the risk of dialysis is about 10 percent (16).

These studies highlight the serious nature of CS and the need for rapid diagnosis and treatment to prevent complications and reduce mortality.

**Pathophysiology**

When a muscle is compressed for a prolonged period, as can occur in crush injuries, it can lead to the breakdown of muscle fibers and the release
of cellular components such as myoglobin, potassium, and other toxic substances into the bloodstream. Myoglobin, in particular, is known to cause renal tubular obstruction, acute tubular necrosis, and AKI, which can result in renal failure if not adequately managed. Additionally, the accumulation of potassium and other toxins in the bloodstream can lead to electrolyte imbalances, cardiac arrhythmias, and other complications (3). While it was stated that the muscle should be under pressure for at least four hours for the development of rhabdomyolysis, it was determined that one hour was sufficient in the Kobe earthquake in Japan and even half an hour in the Marmara earthquake (8,9).

In recent years, research has suggested that the pathophysiology of CS may be more complex than previously thought, with evidence pointing to the involvement of a dysregulated immune response and activation of the RAAS (1, 10). The release of cellular debris and other substances during muscle breakdown can trigger an inflammatory response that further exacerbates tissue damage and can contribute to systemic complications such as sepsis. Additionally, activation of the RAAS can lead to vasoconstriction and renal dysfunction, further exacerbating the renal complications of CS.

Crush-related AKI may arise from prerenal, intrarenal, or postrenal causes.

- Severe hypovolemia is a common cause of prerenal AKI among victims of crush-related injuries. This is because patients can lose access to water while remaining trapped for extended periods, leading to ongoing losses and negative fluid balance. Additionally, vascular injury can result in intravascular volume loss and hypovolemic shock, while rescue and decompression at muscle injury sites can lead to reperfusion-related third spacing of fluid, resulting in intravascular hypovolemia and prerenal AKI.

- Intrarenal AKI in the context of crush-related injury is usually due to rhabdomyolysis, which can be characterized by dark urine or pigmented granular casts in the urinary sediment. AKI caused by heme pigment-induced ATN typically begins with an initial oliguric period followed by polyuria within one to three weeks of the primary event (17). Other causes of intrarenal AKI in patients with crush-related injury include prolonged shock, sepsis, use of nephrotoxic agents, cardiac failure, arrhythmias, or transfusion reactions.

- Postrenal AKI may result from traumatic injury or urinary outflow tract obstruction, particularly in patients with pelvic trauma.
Overall, the pathophysiology of CS is complex and multifactorial, involving a combination of direct tissue damage, toxic effects of cellular components released into the bloodstream, dysregulated immune responses, and activation of various physiological systems such as the RAAS. Understanding the underlying mechanisms of CS is essential for effective management and can inform the development of new therapies and prognostic indicators.

**Clinical Presentation**

The clinical presentation of CS can vary depending on the severity and duration of the crush injury, as well as the presence of underlying comorbidities. Common symptoms and signs include muscle pain and weakness, swelling, discoloration, and reduced range of motion in the affected area (3). In severe cases, patients may experience compartment syndrome, which is characterized by increased pressure within a muscle compartment that can lead to tissue necrosis and loss of function if not rapidly treated (18).

One of the hallmark features of CS is the release of cellular components such as myoglobin and potassium into the bloodstream, which can cause systemic effects such as electrolyte imbalances, cardiac arrhythmias, and AKI. Patients with CS may present with symptoms of AKI, such as decreased urine output, edema, and hypertension. It is important to note that the onset of renal dysfunction may be delayed and can occur several hours or even days after the initial injury (3).

In addition to these symptoms, patients with CS may also experience systemic complications such as rhabdomyolysis-induced hyperkalemia, metabolic acidosis, and disseminated intravascular coagulation (DIC) (19). In severe cases, crush syndrome can also lead to complications such as acute respiratory distress syndrome (ARDS) and sepsis (3).

Overall, the clinical presentation of CS can be complex and multifaceted, involving a combination of local and systemic symptoms that can vary depending on the severity and duration of the injury. Timely recognition and management of CS is essential to prevent long-term complications and improve patient outcomes.

**Diagnosis**

The diagnosis of CS is primarily based on clinical presentation and history, as well as laboratory tests to assess for systemic effects such as electrolyte imbalances, renal dysfunction, and metabolic acidosis (3).
Laboratory tests that may be used to diagnose CS include serum creatine kinase (CK), myoglobin, potassium, calcium and phosphate levels. Elevated CK levels are a hallmark finding in CS and can be used to monitor the severity of muscle damage (20). Elevated myoglobin levels can indicate rhabdomyolysis and can lead to complications such as AKI and DIC if not rapidly treated (3).

Imaging studies such as X-rays, ultrasound, and magnetic resonance imaging (MRI) may also be used to assess the extent of soft tissue and bone damage.

Overall, the diagnosis of crush syndrome involves a combination of clinical assessment and laboratory testing to identify the characteristic features of muscle damage and systemic effects associated with the condition.

Management

The management of CS involves a combination of supportive measures and specific treatments aimed at addressing the underlying pathophysiology of the condition (3).

Supportive measures may include aggressive fluid resuscitation with crystalloid or colloid solutions to prevent and treat hypovolemia and shock, as well as electrolyte and acid-base imbalances (3). Renal replacement therapy may be necessary in patients with severe AKI or electrolyte disturbances that do not respond to conservative measures (21).

Specific treatments for CS may include the administration of mannitol and bicarbonate to prevent and treat AKI and metabolic acidosis, as well as the use of diuretics to promote urine output and prevent fluid overload (1). In severe cases, hemodialysis or continuous renal replacement therapy may be necessary to remove myoglobin and other toxic substances from the bloodstream (3,21).

It is important to monitor patients closely for the development of complications such as compartment syndrome, which may require surgical intervention to relieve pressure within the affected compartment. The measurement of intramuscular pressure provides an objective parameter for the decision to perform fasciotomy. In nonhypotensive patients, this should be done when the intramuscular pressure exceeds 50 mmHg or if pressure values between 30 and 50 mmHg show no tendency to decrease after a maximum of 6 h (22).
Pain management and wound care are also important aspects of the management of CS, and may involve the use of analgesics, antibiotics, and surgical debridement or reconstruction as needed (3).

Overall, the management and treatment of CS require a multi-disciplinary approach involving close monitoring, aggressive fluid and electrolyte management, and specific treatments aimed at addressing the underlying pathophysiology of the condition.

**Treatment**

The treatment of CS is aimed at preventing or minimizing the complications of the condition, particularly acute renal failure and electrolyte imbalances. Management of CS typically includes the following, and table 1 summarizes the basic approach to CS (table 1).

1. **Rapid extrication and resuscitation:** Early and rapid extrication of the patient from the crushing force, followed by resuscitation with fluids and other supportive measures, is crucial to prevent the progression of muscle damage and the release of toxic substances into the bloodstream.

2. **Fluid resuscitation:** The immediate administration of intravenous fluids (such as normal saline) is essential to restore intravascular volume and prevent hypotension. The volume of fluid administered should be guided by the patient's clinical status, urinary output, and electrolyte levels. For adults, the standard practice involves the initial administration of a 1000 mL/hour bolus of normal saline for two hours, followed by a reduction to 500 mL/hour (as per algorithm 1) (23,24). However, in individuals with known heart failure, renal failure, or chronic obstructive pulmonary disease, smaller volumes, such as 10 cc/kg, are recommended. Early and aggressive fluid resuscitation is also necessary for children who are trapped under rubble. Administering intravenous fluids at a rate of 15 to 20 mL/kg/h while the victim is still under the rubble is recommended. In case the extrication process takes more than two hours, the rate of fluid administration should be decreased to 10 mL/kg/h or lower (25). If it’s not possible to provide fluids before extrication, then volume resuscitation should be initiated as soon as possible after the victim is rescued. Local EMS protocols recommend the use of opioids or ketamine to manage any pain (26).

3. **Alkalinization of urine:** It is currently unknown what the best regimen and rate of administration of bicarbonate are. Following extrication, we typically administer one of two fluid regimens, as outlined below:

   • Alternating one liter of isotonic saline with one liter of half-isotonic saline plus 50 mEq of sodium bicarbonate.
• Administering isotonic saline for the first two liters, followed by one liter of half-isotonic saline plus 50 mEq of sodium bicarbonate. This sequence is then repeated as needed.

The goal of urine alkalinization is to prevent the precipitation of myoglobin in the renal tubules and minimize the risk of AKI. This is achieved by administering intravenous bicarbonate, which raises the pH of the urine and promotes myoglobin solubility.

4. Electrolyte management: CS can lead to hyperkalemia, hypocalcemia, and other electrolyte imbalances. Electrolyte levels should be closely monitored, and appropriate measures taken to correct any imbalances. Calcium supplementation should only be given to individuals who are experiencing symptomatic hypocalcemia or severe hyperkalemia. Early administration of calcium can lead to calcium deposition in the muscles and subsequent hypercalcemia later in the injury process. Loop diuretics have no impact on the outcome of AKI (27,28). In the case of rhabdomyolysis, loop diuretics may exacerbate the existing trend for hypocalcemia by inducing calciuria and increasing the risk of cast formation (29,30). Despite these concerns, the careful use of loop diuretics may be appropriate in older patients, particularly those who are volume overloaded. Peak T-waves and widened QRS complexes in hyperkalemia can be detected through prehospital electrocardiogram tracing. Paramedics can treat this condition with calcium chloride, inhaled albuterol, and intravenous insulin, as directed by local medical authorities.

5. Treatment of AKI: Patients with CS are at high risk of AKI. Treatment may include renal replacement therapy (such as hemodialysis or continuous renal replacement therapy) if the patient’s kidney function does not recover. Dialysis is initiated in patients with CS for the usual indications, including volume overload, hyperkalemia, severe acidemia, and uremia. Due to the high risk of fatal hyperkalemia, frequent hemodialysis (twice or even three times daily) may be necessary. A more in-depth discussion of the indications for dialysis can be found elsewhere. Intermittent hemodialysis is preferred over other kidney replacement modalities for patients with CS. Compared to other modalities, intermittent hemodialysis is the most efficient method for removing potassium, which is one of the leading causes of death in these patients (31).

6. Mannitol: The use of mannitol in preventing AKI in the setting of crush injury is a matter of debate, as it may or may not benefit patients with rhabdomyolysis, and it has the potential to cause harm. Nevertheless, in our clinical experience, mannitol may be beneficial in nonoliguric patients with traumatic rhabdomyolysis as an adjunct to intravenous crystalloid, provided
close monitoring is possible. Mannitol is contraindicated in patients with oligoanuria. If urinary flow is adequate, a test dose of 60 mL of a 20 percent solution of mannitol may be given intravenously over three to five minutes to assess the response. If a significant increase in urine output of at least 30 to 50 mL/hour above baseline levels is not observed, mannitol should not be continued (32). Additionally, if the desired diuresis of approximately 200 to 300 mL/hour cannot be achieved, mannitol should be discontinued due to the risk of hyperosmolality, volume overload, and hyperkalemia with continued administration under these conditions.

7. **Wound management:** Adequate wound care and debridement are crucial to prevent infection and further tissue damage. Dialysis can be discontinued only after kidney function has recovered, as suggested by a normalization of urinary volume in a patient with improving serum biochemical values in the absence of fluid overload (23). According to guidelines, amputation should only be considered if a limb cannot be saved or if limb injuries are causing serious complications such as sepsis, systemic inflammation, or uncontrolled bleeding. Decisions about whether to save or amputate a limb should be based on clinical judgement rather than scoring systems like the Mangled Extremity Severity Score (MESS), which have been shown to be less reliable than the judgement of experienced surgeons. There is debate about whether prophylactic fasciotomy (a surgical procedure to relieve pressure in the muscles) should be performed in severe crush injury cases (33,34). In our experience at a level 1 trauma center, we do not perform prophylactic fasciotomy for severe crush injury. Instead, we typically only perform fasciotomies if acute compartment syndrome (a condition where pressure builds up within muscles) is clinically present upon admission or if measured compartment pressures show a delta pressure of 30 mmHg or less (meaning there is a small difference between diastolic blood pressure and compartment pressure). Prehospital amputation of severely crushed or mangled limbs solely to prevent CS is not recommended and can increase the risk of stump infection, as there is no evidence to support this practice. However, in certain cases, amputation may be necessary as a last resort to extricate a victim.

8. **Prevention of compartment syndrome:** In some cases, CS can lead to compartment syndrome, a condition in which increased pressure within a muscle compartment causes ischemia and tissue damage. Treatment may involve fasciotomy (surgical decompression) to relieve the pressure (35). If compartment syndrome is suspected but not confirmed, we manage the patient with serial examinations and may perform fasciotomy if the delta pressure falls to 30 mmHg or less. Prophylactic fasciotomy is not recommended in mass crush injury events, as several studies have shown that routine use of
fasciotomy in crushed limbs can lead to worse outcomes, including higher rates of bleeding, infection, and amputation. Although crush syndrome victims have a high infection rate, empirical antibiotic therapy should not be administered unless there are open wounds. If patients have open wounds, it is recommended to provide them with empirical treatment of broad-spectrum cephalosporins, with or without metronidazole, and tetanus prophylaxis (36).

Table 1: Approach to Managing Crush Syndrome

<table>
<thead>
<tr>
<th>Step 1: Primary Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check for signs of life-threatening conditions such as airway obstruction, breathing difficulties, and severe bleeding.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2: Treatment at the Scene</th>
</tr>
</thead>
<tbody>
<tr>
<td>If possible, remove the crushing object or move the patient to a safer location.</td>
</tr>
<tr>
<td>Provide pain relief as needed.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 3: Transport to Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transport the patient to a hospital with the necessary equipment and expertise to manage crush syndrome.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 4: Secondary Assessment and Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess the patient for signs and symptoms of crush syndrome, including muscle pain and weakness, swelling, and decreased urine output.</td>
</tr>
<tr>
<td>Administer intravenous fluids to help flush out toxins and support kidney function.</td>
</tr>
<tr>
<td>Monitor kidney function and electrolyte levels.</td>
</tr>
<tr>
<td>In severe cases, consider dialysis or other interventions as needed.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 5: Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Educate people about the risks of crush syndrome and the importance of seeking medical attention after traumatic events.</td>
</tr>
<tr>
<td>Promote building codes, construction practices, and emergency preparedness to reduce the risk of crush syndrome.</td>
</tr>
</tbody>
</table>
Algorithm 1: Initial IV fluids for crush victims of high-casualty disasters such as earthquakes

1. Can IV access be established prior to extrication?
   - Yes: Start IV isotonic saline (1 L/hour) and continue during extraction.
   - No: Start isotonic saline as soon as possible after extraction (1L/hour).

2. Is victim still under rubble after two hours?
   - Yes: Reduce rate to 0.5 L/hour.*
   - No: Continue 1 L/hour.

3. Monitor for six hours since initiation of fluids. Total fluids during this time is 3 to 6 L.

4. Is patient anuric?
   - Yes: Give IV fluids 0.5 to 1 L/day plus losses of the previous day.
   - No: Can patient be closely monitored?
     - Yes: Give IV fluids >6 L/day.
     - No: Is patient older or does patient have history of heart failure?
       - Yes: Give IV fluids 3 to 6 L/day.
       - No: Stop IV fluids when the patient is capable of oral intake sufficient to keep up with requirement.

* The rate is reduced because patients cannot be closely monitored when they are under the rubble and there is a risk of giving too much fluid.

Generally, up to 12 L/day IV fluid can be administered in patients with good urine output (ie, >300 mL/hour).
We give 4 to 4.5 L more than total fluid loss from the prior day. The actual amount depends on extent of injuries, body mass index, ambient temperature, urine production, amount of overall estimated fluid losses, and age. Patients with severe injuries usually require more fluid and may receive up to 6 L. Older patients who are not as severely injured may be given only 3 L.


Prognosis

The prognosis of CS depends on several factors, including the severity of the crush injury, the extent of tissue damage, and the timeliness and effectiveness of treatment (3). In general, patients with mild to moderate crush injuries and early intervention and treatment have a good prognosis and are likely to recover without significant long-term complications (21). However, patients with more severe crush injuries and complications such as AKI, DIC, or compartment syndrome have a poorer prognosis and may be at risk for long-term disability, chronic pain, or limb amputation (22).

The development of AKI is one of the most significant predictors of mortality in patients with CS, and early recognition and treatment of this complication is critical to improving patient outcomes (3,15).

Overall, the prognosis of crush syndrome depends on a variety of factors, and close monitoring and aggressive management of complications are essential to achieving the best possible outcomes.

Conclusion

CS is a serious condition that can result from the compression of soft tissues, leading to ischemia and tissue damage. The release of myoglobin and other toxic substances into the bloodstream can cause a range of systemic complications, including AKI, electrolyte imbalances, and metabolic acidosis.

Early recognition and treatment of CS are essential to improving patient outcomes, and a multidisciplinary approach involving close monitoring, aggressive fluid and electrolyte management, and specific treatments aimed at addressing the underlying pathophysiology of the condition is necessary. Complications such as compartment syndrome and infections must also be
carefully managed to prevent further tissue damage and systemic complications.

The prognosis of CS depends on several factors, including the severity of the crush injury, the extent of tissue damage, and the timeliness and effectiveness of treatment. Close monitoring and aggressive management of complications are essential to achieving the best possible outcomes, particularly in patients with more severe crush injuries and complications such as AKI or DIC.

In conclusion, CS is a complex and potentially life-threatening condition that requires rapid recognition and treatment. With appropriate management and treatment, however, patients with CS can achieve good outcomes and avoid long-term complications.
References


Chapter 7

Genetic Mechanisms of Chromosome Nondisjunction in Humans

Osman Demirhan¹

Abstract

The human genome is very delicately balanced. Because maintaining a balance in gene dosage and protein activity is essential for maintaining normal cellular functions. One of the most common causes of genetic diseases in humans is chromosomal failure and chromosomal numerical irregularity (Aneuploidy). Missegregation or non-separation of chromosomes in meiosis is common in humans. The most common chromosomal abnormality (CA) in humans is aneuploidy. Aneuploidy is one of the most important causes of reproductive biology and reproductive diseases. It causes major developmental and structural abnormalities and often embryonic death in mammals, especially in early development. Aneuploidy is a condition with abnormal and highly variable DNA and chromosome content found in both hereditary disorders and human malignancy. Chromosome non-separation is associated with advanced maternal age. However, the reason for the dramatic increase in aneuploidy and especially trisomies with age is unknown. There is evidence to suggest that chronological age is less important than biological age for trisomy risk and that some women, regardless of their chronological age, are at higher risk of having a trisomy pregnancy again. It is known that increased aneuploidy in somatic cells is associated with a decrease in telomere length, an increase in replication asynchrony at centromeres and loci, and advanced age. Many people are exposed to environmental genotoxic agents. Genotoxic agents and late marriages are known to cause aneuploidy. In our numerous studies, it has been confirmed that genotoxic substances are associated with chromosome damages (1-14). Cigarettes, mobile phones and harmful rays can cause structural and numerical chromosome damage and potentially increase the level of aneuploidy in the fetus.

¹ Prof. Dr., Department of Medical Biology, Faculty of Medicine, Çukurova University, odemirhan42@gmail.com, osdemir@cu.edu.tr., Orcid: 0000-0002-0876-406X

https://doi.org/10.58830/ozgur.pub91.c386
INTRODUCTION

Today, people are heavily exposed to many natural and artificial genotoxic or mutagenic agents, and this situation is increasing rapidly. It is now known that long-term exposure to genotoxic agents not only affects human reproductive health, but also causes cancer and many diseases. Therefore, concerns about possible negative genetic damage in society are increasing. Aneuploidy is known as one or more chromosomes more or less than the diploid number of chromosomes \((2n=46)\). The vast majority of aneuploidies occur spontaneously as a result of sporadic chromosome misalignment in meiosis in the mother or father. The most well-known form of meiotic dissociation is that it increases with increasing maternal age. The mechanisms underlying aneuploidy are still not fully understood. Humans are among mammals with the highest incidence of chromosome mis-separation during meiosis. It is known that 15-20% of all pregnancies result in spontaneous abortion. CAs are responsible for at least 50% of these losses. More than half of these are trisomies (having an extra copy of a chromosome). Trisomic chromosome organization was first described in humans in 1959 (15). Trisomic irregularities are caused by an error in meiosis. It occurs when both chromosomes of a pair of chromosomes or both sister chromatids of a chromosome go together to the same pole. Thus, the gamete has two copies of that chromosome instead of one, and the chromosomes cannot separate correctly. The effect of meiosis on reproduction and genetic disorders of newborns is significant. However, little is known about its etiology. The only known factor associated with the risk of trisomy is advanced maternal age. The risk of trisomy in women under the age of 25 is 2%. This risk increases rapidly with age and approaches 35% in women over 40 years of age (16). Therefore, the relationship between increasing maternal age and trisomy is indisputably the most important etiological factor of genetic diseases (17). The relationship between recombination and chromosomal nondisjunction has been extensively studied along the 21st chromosome. There appears to be a correlation between recombination and inability to separate for the chromosome, both in quantity and location along this chromosome. Altered recombination has been associated with trisomy for other chromosomes. Meiosis is a process that takes place in the germ cells of both males and females. Errors in the meiosis process in female egg cells are responsible for most of the aneuploidy seen in human pregnancies.

Meiosis is the process of halving the number of chromosomes. This process takes place in germ cells during gametogenesis to produce eggs in females and sperm in males. Oogenesis, the process of egg formation, begins
in females early in fetal life. Every female born carries a lifetime of developing oocytes. These oocytes are normally released once a month, starting at puberty. When the level of approximately 1000 oocytes is reached, menopause occurs in women (18). In males, spermatogenesis is the process of forming sperm in the gonads. Beginning at puberty, 100-200 million sperm are produced per ejaculate continuously throughout their lives (19). Meiosis consists of two main cell divisions. Meiosis I (MI), in which the chromosome number is reduced from diploid to haploid (2n=n), and meiosis II (MII), a form of division similar to mitosis. Moreover, each of these divisions is divided into four main stages (prophase, metaphase, anaphase, and telophase). In the synthesis phase, each chromosome doubles itself by replicating its genetic material. Thus, each homologous chromosome consists of two identical sister chromatids held together by proteins called cohesins. Prophase (prophase I) of MI consists of five phases. Since the chromosome number is haploid in MII, the same main stages follow without reduction. During the leptotene stage, the copied chromosomes begin to condense and become visible. The two sister chromatids that make up each chromosome are indistinguishable at this stage. After the homologous chromosomes find each other in zygotene, they pair up with the cohesin protein. Since each pair of homologous chromosomes contains four sister chromatids, they line up with each other longitudinally, forming a bivalent called a tetrad. Cohesin proteins hold sister chromatids together so they don’t separate prematurely. Thus, it holds homologous chromosomes together so that recombination can occur before anaphase II. Synapses and the synaptonemal complex (SC), defined as the pairing of homologs during zygotene, are formed. The SC consists of lateral elements located between sister chromatids and a central element connecting these lateral elements. Homologous exchange or recombination takes place throughout this structure. In the pachytene phase, the synapses are completed with pachytene and recombination nodules appear. These nodules are thought to represent regions where recombination has occurred. After completion of recombination, SC begins to fragment and chromatids begin to separate. Chiasmata can be seen in the diplotene stage. The two components of each bivalent begin to repel each other, and each homologous sister chromatids attach to each other at their centromeres. This is the point at which meiosis is stopped/waited until puberty in females. At this point, a single egg completes MI at each ovulation cycle. There is no waiting in meiosis in males. In diakinesis, the chromosomes reach maximum condensation at this point and are clearly visible. In order for homologs to pair and align themselves in the zygotene of the prophase, they must first find each other. Exactly how this happens is unknown. However, two
chromosome regions are thought to play an important role in mediating early mating (telomeres and centered heterochromatin) (20). Aligning these two types of chromosomal domains may be early steps in the mating process. Disruption of telomere-telomere sequences can disrupt synapse and recombination. The formation of a flower bouquet-like structure formed by telomeres that seem to interact with each other in the nucleus of the cells is observed in the cell nucleus. Chromosomes come into contact with each other to determine the level of similarity required to form synapses and recombination. Meiotic bouquet formation is a prominent feature of early prophase in many organisms such as yeast. It has also been reported that it is involved in chromosome pairing in male mouse and human meiosis (21). In addition, it has been reported that telomere movements in tissue sections from human and mouse testicular preparations are associated with the onset of synaptic chromosome pairing. The centromere is a very important element found in all eukaryotic chromosomes. This chromosome region ensures the regular separation of sister chromatids in mitosis and meiosis.

Recombination

Crossing-over is a mutual genetic exchange between homologous chromosomes. It begins with double helix breaks and is the most fundamental step of the meiosis process. It is assumed that chiasmata, which is the physical exchange of homologous chromosome parts, keeps homologous chromosomes together during meiosis. It has been reported that at least one recombination event per chromosome arm is required for segregation to occur in humans (22). Many key proteins involved in recombination, such as RecA, topoisomerases, helicases, and DNA repair molecules, are highly conserved from yeast to humans (23). Performing recombination analyzes in humans is difficult. In men, a testicular biopsy should be performed. This situation is more difficult in females. Recombination takes place in all chromosomes. It has been reported that approximately 50 autosomal recombination foci per nucleus in spermatocytes, and the number of foci in females is much higher (mean=95) (24). In mouse and human studies, distal foci were found to be much more common in males. Recombination has been found in more than 90% of females, and it has been reported that there is more recombination in regions close to telomeres in males (25,25). In contrast to more than 70 recombination foci in oocytes, approximately 50 foci per cell were found in spermatocytes (26). This suggests that longer synaptonemal complex in oocytes may contribute to increased recombination in females. In yeast, the main stages of meiosis may differ slightly from those seen in humans. The study of meiotic mutants in this organism has greatly contributed
to our understanding of the process of meiosis. Homology of yeast genes has been found in Drosophila melanogaster, mouse and human. Meiotic recombination events are uniformly and uniformly distributed throughout the chromosome. The recombination frequency per megabase in humans is extremely low compared to yeast (370 cM/Mb) (28). Crossovers do not happen randomly between chromosomes in any organism. Regions that undergo high levels of recombination in yeast are usually located near promoter regions. These regions correspond to the locations of the double helix break regions (29). Recombination hotspots or regions with high recombination are also present in mammals (30). In humans, hot spots in males and females have been reported (31,32). C. elegans is the only species with the gene that provides the distribution of meiotic recombination events (33). Recombinations are crucial for proper segregation of meiotic chromosomes. It can contribute to the rearrangement of many chromosomes and has been found at higher frequency at the breakpoints of deletions and duplications.

**Chromosome Matching and Separation**

During the recombination process, the congruence of both sister chromatids and homologous chromosomes is maintained. Then with the timely release of this harmony, the chromosomes (in MI) and chromatids (in MII) separate from each other. Early or late separation of chromatids/chromosomes may cause chromosome failure to separate. There are many structures involved in this complex process regulated by a number of genes and proteins. Cohesins hold sister chromatids together, while chiasmata help keep homologous chromosomes connected. In metaphase I, homologous chromosome pairs line up along the metaphase line and spindle fibers are attached to sister kinetochores. Thus, two sister kinetochores pull the two sister chromatids towards opposite poles of the cell. For this to happen, the kinetochores found in the alpha-satellite sequences of the centromere must be next to each other on sister chromatids. For meiosis to continue, the spindle fibers must maintain a balanced tension in the opposite direction to the two kinetochores. This requires all chromosomes to line up properly on microtubules. In males, an imbalance stops meiosis and drives the cell to death. In women, a chromosomal imbalance may occur without stopping meiosis (34,35). Here, it may occur as a result of the breakdown of cohesion proteins along the chromosome arms, especially in older women. In this case, it can lead to unpaired chromosomes that separate independently from metaphase. The final stage in MI is anaphase I, in which the alignment between the chromosome arms is disrupted and allows the chiasmata to dissolve. The cohesin protein must remain attached to the centromeres. Sister
chromatids must be kept together until anaphase II. The combined homologues then separate and move towards their respective poles. In metaphase II, the chromosomes line up along the metaphase line. Kinetochores attach to microtubules from opposite poles. Later, they move to opposite poles in anaphase II. It is the cohesion protein at the centromere that keeps sister chromosomes intact until anaphase II.

**Gender-Specific Differences**

Meiosis differs in males and females. One of these differences is timing. In females, meiosis begins in all oocytes in fetal life, while in males it begins during puberty. Males produce sperm every day, while females are born with a certain number of follicles. While meiosis lasts for 40 years in females, the time required for the completion of a spermatogenesis process is approximately 64 days. The second difference is the cessation of meiosis. Meiosis is stopped in females from dicyoten to ovulation and then again from meiosis II to fertilization. In contrast, in males, meiosis is continuous and there is no stopping point. Third, and interestingly, males have checkpoints to monitor division during meiosis. If recombination has not occurred (pachytene checkpoint) the male gametes will be deactivated and die. In humans and mice, these checkpoints have been shown to be less stringent in mammalian oogenesis (36). The fourth difference is recombination. Sex-specific differences in recombination frequency are also found in humans and other organisms. In mammals, recombination shows sex-specific differences, with females generally having higher recombination rates than males (37). The fifth difference is that females have only one fertile oocyte, while males produce four sperm for each diploid cell that initiates meiosis.

**Mitosis**

Mitosis is a process of cell division in which diploid cells form diploid daughter cells or haploid cells form haploid daughter cells or exact copies of chromosomes are produced. The major difference between mitosis and meiosis is the absence of pairing of homologous chromosomes. In mitosis, there is normally no exchange of genetic material through recombination. Mitosis takes place daily in somatic cells in our body to replace cells that die through apoptosis and to allow growth to occur. Mitosis is required for every developmental stage after fertilization for hair growth, nail growth and embryo formation. Mitosis is also required for the steps leading to meiosis in both males and females. Spermatogenesis in males probably undergoes 20-25 mitotic divisions per year, while in females oogonia originate from primitive germ cells, a process involving 20-30 mitotic divisions. At three
months of intrauterine life, oogonia begin to mature in primary oocytes, which begin to undergo meiosis. Recombination can occur during mitosis. However, it occurs rarely compared to that which occurs in meiosis. It is more difficult to detect and measure. Double helix breaks are required to initiate recombination. However, they are the most harmful form of DNA damage because they are formed by chromosome breaks and rearrangements (38). There are two main ways of repairing double helix breaks. These are the joining of non-homologous ends and homologous recombination (39). Non-homologous splicing repairs broken DNA ends without requiring extensive sequence homology. However, homologous recombination requires an intact homologous chromosome or a sister chromatid to repair the break. During metaphase of mitosis, spindle fibers attach to kinetochores on the centromere of each chromatid. When sister kinetochores separate, each chromatid moves to opposite poles of the cell. For sister chromatids to separate, the cohesin protein that holds them together must be broken down. This is accomplished by a protease called separase, which becomes active in late metaphase (40).

**Aneuploidy**

Although meiosis has a highly organized control process necessary for sexual reproduction, errors are still common in females. These errors occur as abnormal chromosome separation or failure to separate. Failure to segregate causes gametes to result in a chromosome gain or loss (aneuploidy). This common CA seen in pregnancy is seen in at least 5% of all clinically defined pregnancies. Aneuploidy occurs as trisomy (gain of the entire chromosome) and monosomy (loss of the entire chromosome). It is estimated that these numerical chromosomal irregularities cause miscarriages in 15-20% of all pregnancies. Various chromosomal abnormalities are quite common in humans and can be found in 10-30% of all fertilized eggs. It has been reported that aneuploidy is seen in 20% of female eggs and 2-5% of spermatocytes (41). In other organisms, incorrect segregation of a chromosome is less common. The frequency of aneuploidy in Saccharomyces cerevisiae is as low as 1/10,000 per meiosis. In female Drosophila melanogaster, the inability to separate the X chromosome varies between 1/1,700 and 1/6,000 (42). The overall frequency of aneuploidy in fertilized eggs in mice is 1-2% (43). It is difficult to study the frequency of chromosomal abnormalities in humans because not all developmental stages have been studied. Available date are from studies of clinically recognized pregnancies and gamete studies. More than 35% of all terminated fetuses/embryos were found to be aneuploid (16). Spontaneous abortions with trisomy have been reported
for almost all chromosomes, and the most common is trisomy 16, which constitutes 1/3 of all trisomies (17).

**Trisomy**

First described in humans in 1959, trisomy is the presence of a third copy of a chromosome in the nucleus. At least 50% of pregnancy losses are chromosomally abnormal, and more than half of them are trisomic. Trisomy 16 is estimated to occur in more than 1% of clinically recognized pregnancies. This makes it the most common trisomy in humans (45). Trisomy 16 normally results in miscarriage in the first trimester of pregnancy. Only 13, 18, 21 and X chromosome trisomies can survive to term. Trisomy 21 is the most common trisomy in approximately 1/700 live births. In general, trisomy mostly originates from chromosomes in meiosis I during oogenesis (42). Early somatic errors can also result in mosaic trisomy and these are less common. Trisomy 16 is almost entirely due to a maternal error of MI. However, most errors for trisomy 18 occur in meiosis II. Approximately 50% of 47,XXY and trisomy 2 originate from the father (46,47). Monosomy X or Turner syndrome is thought to be largely (70-80%) related to producing nullisomic sperm for male sex chromosomes (48). It is not known whether the loss of the other sex chromosome occurs in the sperm or postzygotic, and it is a matter of debate. Therefore, it seems likely that many factors affecting nondisjunction are chromosome-specific. Although the majority of trisomies are lost as early miscarriages, in most mosaic cases they can survive to term. Chromosome mosaicism is the presence of two different cell lines with two different chromosome structures in an individual developing from a single fertilized egg. In prenatal diagnosis, the most common mosaicism is that some cells have normal chromosomes (46,XX or 46,XY) and other cells have trisomic chromosomes. Trisomy mosaicism may occur through a meiotic or somatic mechanism (49). It has been suggested that most mosaics begin as trisomic zygotes and subsequently lose an extra chromosome and acquire a normal cell line (50). However, he found that most of the mosaicism was of somatic origin and the origin was linked to the relevant chromosome. The number of mosaic cells in an individual determines the phenotype. In general, the proportion of mosaic cells of meiotic origin is considered to be high, while those of somatic origin are seen at lower levels (51). The abnormal cell line can be found in only one tissue or in multiple tissues. Mosaicism is found in 1-2% of all chorionic villus samples (CVS) (49). Frequently, the trisomy may also be limited to the placenta only. The phenotypic effect of trisomic mosaicism on an individual may be slightly or completely normal for gestational age.
Origin of Mosaicism

If a trisomic embryo begins life and later loses the third chromosome as a result of anaphase delay, this is called trisomic rescue. A trisomic cell can also be caused by a mitotic non-dissociation event. A very early mitotic error can lead to mosaicism, possibly because it will make half of the cells trisomic. If this event occurred at a later embryonic stage, the mosaic cell rate may be less. At the 64-cell stage of an embryo, only 3-5 cells will participate in the formation of the embryo, while the rest will form the extra-embryonic tissue (52). In this case, it seems more likely that the error occurred is of placental origin. It could just be a trisomy that occurs in the germ cell line. This mosaicism in the germline may go unnoticed, leading to new trisomy and recurrent pregnancy loss. This rarely recurring trisomic condition has been shown to occur only in trisomies 18 or 21. Other aneuploidies, when present in female germ cells, may lead to disruption of follicles (53). It is thought that mosaicism in germ cells is responsible for the recurrence of trisomy 21 (54, 55).

Single Ancestral Disomy

Uniparental disomy (UPD) is the presence of a normal chromosome pair with both copies from the same parent. UPD can cause clinical deviations as a result of homozygosity for recessive mutations and abnormal imprinting patterns (56). Isodisomy refers to regions of chromosomes that are derived from identical sister chromatids and heterodisomy from homologous chromosomes. This can occur in several ways. It is usually found as a result of trisomic rescue. If the chromosome lost during rescue in a trisomic embryo of maternal origin is the paternal chromosome, there is maternal UPD for this chromosome. That is, both chromosomes are from the mother or there is no contribution from the father. The distribution of isodisomic and heterodisomic regions depends on the initial stage. If the error occurs in MI, the centromere will also be heterodisomic as the chromosomes are from two different homologs. If the error occurs in MII, the centromere will also be isodisomy since the chromosomes are sister chromatids. However, there may be regions of both isodisomy and heterodisomy along the chromosome as a result of recombination that takes place in gametogenesis (56). Generally, UPD is a benign condition with no adverse phenotypic consequences to the individual (57). However, there are a few chromosomes where UPD has detrimental consequences. These chromosomes contain imprinted genes that are differentially expressed depending on the parent. This means that both mother’s and father’s input is necessary for proper development to
Genetic Mechanisms of Chromosome Nondisjunction in Humans

occur. It is the 15th best-known chromosome containing imprinted genes. Maternal UPD causes Prader-Willi syndrome (PWS). However, paternal UPD causes Angelman syndrome (AS), which is different. This is due to the loss of paternally expressed genes in mat UPD and the loss of a maternally expressed gene in pat UPD (56). Other chromosomes 6, 7, 11 and 14 where UPD is known to cause phenotypic abnormalities due to loss of expression of imprinted genes. More than 40 imprinted genes have been identified throughout the genome in humans (58).

Monosomy

Monosomy is the absence of one copy of a chromosome pair (with a total of 45 chromosomes). Autosomal monosomies cause very early fetal death. Monosomy 21 is an autosomal monosomy seen in dead fetuses. Sex chromosome monosomy (45,X) is the most common disorder seen in spontaneous abortions. The vast majority of embryos with a 45,X karyotype do not survive (99.5%). They account for about 10% of all spontaneous abortions. Even partial monosomies in the form of large deletions are not easily tolerated. Each non-segregation event that produces a gamete that is disomic rather than monosomic for a chromosome contains a complementary gamete that is nullisomic for that chromosome. Evidence from hamster and human sperm analysis has shown that monosomies are as common as trisomies (59). However, trisomies are more common than monosomies in spontaneous abortions and pregnancy losses. This is most likely because monosomies are much less tolerated during embryonic development. Therefore, monosomic embryos can be lost much earlier. Studies of in vitro fertilized human diploid embryos and preimplantation embryos also support this.

Segmental Aneuploidy

Segmental aneuploidy presents as unbalanced translocations. A duplication or deletion (three copies or more of a region) resulting in loss or gain of a chromosome segment leads to segmental trisomy and segmental monosomy. Unequal recombination can cause both deletions and duplications. Chromosomes with repetitive sequences may mismatch during meiosis. A repeating region of such chromatin may pair with a different region of another chromatin. As a result of recombination, an increase in the number of chromatin repeats and a decrease in the other may occur.
Deletions

A loss occurs when a chromosome is broken at two sites and the piece in between is lost. This in turn causes loss of genetic information. Partial monosomy occurs for the chromosome that has lost a piece. Microdeletion syndromes are large deletions that disable multiple genes that make up specific and recognizable phenotypes. PWS, AS and cri-du-chat syndromes are caused by deletions in chromosome 15q11-ql3 (paternal), 15q11-ql3 (maternal), and 5p, respectively. Repetitive sequences/duplicons (large blocks of folded genes of a DNA sequence) and other sequences have been implicated as catalysts for such breaks.

Repeat Sequences

Chromosomes have copies containing repeat sequences. These copied partitions are called end-to-end and tandem copies. The number of repeat sequences in a region can vary as follows. Unbalanced exchanges are the main cause of disrupting repeat sequences (specifically, Alu-like repeats). There is an Alu sequence every 6 kb in the human genome. Whether a phenotype is associated with a replicated region depends on many factors. These; The size of the duplicate region is known as the function of the genes and the location of the new segment. Duplicons have been shown to cause deletions and other rearrangements as well as abnormal recombination (60). Unnecessary genes and sequences can become new genes with similar or related functions.

RISK FACTORS OF TRISOMY

Although the importance of meiotic division in human reproduction and genetic damage in newborns is known, little is known about its etiology. However, the relationship between advanced maternal age and trisomy is well known. Altered recombination has also been shown to be associated with most trisomy. The associations of mitochondrial mutations, replication timing, centromere size, gene mutations, and environmental factors (smoking, diet, and oral contraceptives) with chromosomal failure were investigated. However, until now, a clear situation regarding these factors has not been revealed.

Epidemiology

It has been suggested that there may be a relationship between trisomy occurring before or after spontaneous abortion (SA) and trisomy (61). However, later studies showed no such relationship. Considering all avail-
able data, it was concluded that trisomy did not cause an abnormal SA in subsequent pregnancies. However, some studies have shown that women who have a baby with trisomy 21 at a young age (<30 years) have an increased risk for subsequent pregnancies (62). However, it was thought that this situation may be due to trisomy 21 mosaicism seen in a small number of couples (55). There are many young women with more than one trisomy. It has been suggested that these may have a risk of trisomy in their next pregnancies (63,64). These findings support the hypothesis that some women have a higher risk of chromosomal aberration than their peers when considering all viable trisomies, including trisomy 21.

Aging

The relationship between advanced maternal age and the risk of trisomy is well known. The risk of trisomy increases exponentially with increasing maternal age. Long before it was determined that Down syndrome was caused by trisomy 21, the relationship of this disease with increasing maternal age was known (65). While this risk is 2% in women under the age of 25, this rate rises to 35% in women over the age of 40 (66). This irregularity is not related to the uterine environment, but rather a problem with the egg itself. It is thought that the rate of trisomy specific to the age of the mother is not related to race, geography and socio-economic status. However, it has been shown that the risk of having a DS pregnancy in a mother with a low socio-economic status is increased (67).

Recombination

It is clearly known that maternal age is important for the risk of trisomy. However, whether other factors contribute to maternal age risk has not yet been fully established. The main reason here is a disruption in the meiosis process, which increases the risk of chromosome failure to separate. The effect of maternal age occurs in the process of chromosome failure to separate. While this process is lower in younger mothers, this possible risk increases with age. Meiotic specific proteins can degrade over time. In addition, spindle fibers can become fragmented and mitochondrial mutations can accumulate as well. Thus, altered recombination increases the risk of trisomics in an older woman’s oocyte. Recombination or another factor in fetal life may increase the risk of trisomy. Telomere shortening and untimely replication can contribute to premature aging of chromosomes. In normal recombination, a crossover or exchange of genetic material is usually required for separation between homologous chromosomes. For proper segregation of human chromosomes, a change in the chromosome must be minimal (22). There
are many mutations in yeast and flies that reduce or eliminate trade-offs and cause high frequency of erroneous segregation during division (68,69). The association between reduced recombination and human trisomy was first found with reduced levels of recombination across the chromosome in meiosis leading to trisomy 21 (70). Also, sex chromosome aneuploidies, MI-induced trisomies of chromosomes 15, 16 and 18 are all known to be associated with a reduction in recombination (71).

**Ovarian Aging**

It has been suggested that the woman’s proximity to menopause determines the risk of aneuploidy. The risk decreases as the total number of follicles and the number of developing follicles increase. Menopause is predicted when the total number of follicles reaches about 1000. An artificial or naturally occurring follicle reduction will cause premature menopause. It has been shown that there is an increase in aneuploidy rates with increasing age in mice (72). It has been found that the risk of disease is higher in women with a child with Down syndrome who have a single ovary as a result of ovarian surgery or a congenital absence of an ovary (73). These data suggest that with increasing maternal age, the few remaining oocytes and their quality increase the risk of trisomy. Menopause may occur one year earlier in mothers who have children with trisomy.

**Chromosome Structure**

Chromosomes have two main structural features called centromere and telomere. Each of these has its own specific repeat sequence and specific function in meiosis/mitosis. Normal centromeres and telomeres are indispensable structures for chromosome separation. It has been found that telomere sequences are a measure of aging, and short telomeres are associated with premature aging diseases and infertility, as well as being important for chromosome and chromatid separation (74).

**Centromere**

The centromere is a special and important region of the chromosome formed by DNA alpha sequences, other repetitive sequences and proteins. The most common DNA element in the human centromere and the α-satellite sequences that make up 3-5% of the chromosome DNA (75). The human centromere consists of repeat monomers rich in AT and 171 bp long, which are recognized by kinetochore proteins and motifs DNA (76). Centromere proteins are attached to these sequences. Since the centromere is
required for proper segregation of chromosomes in MI and chromatid segregation in MII, changes in sequences or size may affect chromosome segregation (77). In particular, a large discrepancy between an abnormally small and a large alpha sequence sizes within a homologous chromosome pair can lead to homologous chromosome mismatching, alignment, impaired recombination, and inability to separate. There are significant differences in alpha DNA sequence length between homologous chromosomes. For example, the size of the alpha sequence of the X chromosome ranges from 1300 to 3700 kb (78). Therefore, a pair of parental chromosomes may differ by 2400 kb in alpha sequence sizes for the X chromosome. In addition, it has been shown that the centromere on chromosome 21 is short with a frequency of 6.9% in DS patients (75). It is possible that cohesion is compromised because the centromeric heterochromatin size is below the minimum threshold, the alpha DNA does not have sufficient mechanical strength to hold the chromatids together, or the small alpha sequences bind less centromere proteins. This can cause the chromosomes to fail to separate. Failure to maintain sister chromatid cohesion causes premature separation of sister chromatids (in MI) (Maratou et al., 2000). If the centromeric repeats are too long, the chromatids may not separate in time, or if they are too small, the chromatids may not hold together. It has been reported that the alpha sequence on one of the chromosome 21 homologues is small (79). The importance of heterochromatic regions in mediating mating and segregation was first demonstrated by studies on chromosome 4 cleavage in Drosophila oocytes (80). Similar to Drosophila, females with centromeres with longer heterochromatin regions are likely to increase inseparability. Although abnormal alpha sequence size may predispose a chromosome to non-disjunction, additional factors are probably required as well. As with recombination, alteration or insufficient size of alpha DNA combined with maternal age may not allow for normal segregation. Therefore, very small or large alpha sequence size may be multifactorial of age-related chromosome segregation in humans. The centromere may also cause loss of replication control in meiosis and mitosis.

**Telomeres**

Telomeres are specialized structures found at the chromosome ends of eukaryotic organisms and are important for chromosome stability. They consist of a set of repetitive DNA sequences (TTAGGGG in man) and associated proteins. Telomeres are believed to be responsible for positioning chromosomes in mitosis, maintaining chromosome integrity, and maintaining DNA sequences. Reduced telomere sequences are known to be associated
with chromosome segregation errors in mitosis. Chromosomes with short telomeres in aged cells tend to form dicentric chromosomes, most likely to protect their ends (81). In yeast, telomere loss in a single chromosome was found to be sufficient to arrest the cell cycle (82). Disruption of telomere-telomere bonds in meiosis may also disrupt synapse and recombination (20). In male germ cells, telomerase enzyme prevents age-related telomere destruction. In contrast, most telomor sequences decrease with age in tissues at a rate of about 50 to 200 bp per cell division (83). While the average telomere length is 20 kb in children younger than 10 years of age, this number drops to 5 kb in people aged 60-70 years (84). In humans, the inverse relationship between telomere length and age is linear. However, there is great variability in telomere length among individuals of all ages (85).

Regular shortening of telomeres has been associated with replicative aging both in vitro and in vivo and has been termed the mitotic clock. It has been reported that individuals with early aging Progeria and Down syndrome have shorter-than-average telomeres (86). Short telomeres have been found to be associated with aneuploidy and chromosome loss in many cancers and somatic tissues (87). In addition, it has been shown that the frequency of aneuploidy in cultured lymphocytes increases with advancing age. It is possible for short telomeres to cause chromosome missegregation and aneuploidy. However, there are a number of possible explanations for short telomeres. These; Mutations in genes involved in telomerase structure or activity can lead to shortened telomeres. Overexpression of the telomere binding protein TRF1 has been shown to cause telomere shortening (88). After it was reported that shortening of telomeres in Dolly the Sheep, the reprogramming of telomere lengths in cloned animals has sparked controversy. They found that fertile women had significantly longer telomeres compared to women of the same age who underwent IYF with weak oocytes (74). It has been suggested that this may be related to less cell division as a result of the decrease in growth hormones. Therefore, an increase in growth hormones can lead to higher cell divisions and therefore shorter telomeres.

**Time of Reproduction**

Both alleles of a gene normally replicate synchronously in the cell cycle. However, asynchronous replication is seen for genes on the X chromosome. Genes on the inactive X replicate themselves later than those on the active X chromosome. As with imprinted genes, olfactory receptor genes, and other mono-allelically expressing genes. Higher rates of allelic asynchrony and an-
euploidy were found in cells from older mothers who gave birth to a child with Down syndrome.

**Gene Mutations**

Methylene-tetra-hydro-folate-reductase (MTHFR), Methionine-synthase-reductase (MTRR). In addition to the structural features of chromosomes that affect chromosome separation, there is some limited evidence that gene variants may also play a role in separation. There is evidence that abnormal folate and methyl metabolism can lead to hypomethylation of DNA and abnormal chromosome segregation. Related to this, it has been suggested that some polymorphisms may be frequently increased in the MTHFR and MTRR genes of the mother of a DS child (89). It is known that these two mutations cause a decrease in enzyme activity in heterozygotes and homozygotes and pose a risk for neural tube defects. Maternal polymorphism analysis of other genes involved in the folate pathway found an increase in the MTRR mutant homozygous variant in mothers with DS. In addition, the combined presence of both mutations was found to increase the risk even more. However, some studies could not show the same association for trisomy 21, but no significant increase in MTHFR or MTRR polymorphisms was observed in more than 200 trisomy except trisomy 21 (42).

**Apos4 Alleles:** Young mothers who give birth to a child with DS have been shown to have a five-fold higher than normal risk of developing Alzheimer’s disease (AD) later in life (90). All individuals with DS over the age of 40 also had AD-specific neuropathological changes. Some forms of AD have been reported to result from mutations in the APP (B-amyloid precursor protein) genes on chromosome 21, presenilin-1 (PS-1) on chromosome 14, and presenilin-2 (PS-2) genes on chromosome 1 (91). Presenilin proteins may be important in chromosome segregation because they bind to the kinetochores and centrosomes. However, Apolipoprotein E (apoE) mutations may explain this association. ApoE is a gene located on chromosome 19. Rarely, allele E4 has been reported to be a risk factor for AD in both familial and sporadic cases (92). A higher frequency of the APOE s4 allele was found in young mothers who gave birth to a DS child due to maternal MII errors (93).

**Mitochondrial Mutations:** Another factor that has been suggested to contribute to chromosome failure is mitochondrial abnormalities. Mitochondrial dysfunction resulting from decreased ATPase6 and Tfam expressions during meiotic maturation of oocytes has also been suggested to cause non-differentiation errors (Lee et al., 2003). Mitochondrial DNA (mtD-
NA) mutations are also known to increase exponentially with increasing age. The curve for the amount of time- or age-related mtDNA mutations is very similar to the age-related trisomy risk. The accumulation of mtDNA errors over time in both the ovary and somatic tissues can lead to energy deficiency and other problems that can complicate chromosome segregation.

**Environmental Factors**

The possibility that the environment, what we eat, and the harmful factors we are exposed to can affect reproductive success has always aroused interest. Smoking, alcohol, caffeine, and many other factors have been shown to affect the health of the developing fetus. Exposure to these harmful factors can lead to non-segregation of chromosomes in meiosis and increase the risk of trisomy. There are conflicting studies on the relationship between smoking and DS. It has been suggested that high alcohol and caffinated coffee consumption reduce the risk of having a DS fetus (94). However, it has been reported that oral contraceptive use in smoking mothers increases the risk of DS fetus, but oral contraceptive use alone is not an important risk factor. There are conflicting findings about the effects of radiation on reproduction and pregnancy. It has been suggested that the increased frequency of trisomy 21 in West Berlin is linked to the Chernobyl reactor accident. However, no genetic link to exposure to other types of radiation has been reported. It has been reported that exposure to an insecticide called trichlorfon can cause an increase in DS (95). Environmental risks seem to be important in terms of trisomy risk by affecting the development of oocytes. Bisphenol A (BPA) is an estrogenic compound widely used in the manufacture of polycarbonate plastics and epoxy resins. It can also be found in feeding bottles, water bottles, can liners, and dental sealants. When BPA was widely used, a significant increase in chromosome non-segregation and meiotic chromosome abnormalities was observed. It was concluded that this was due to the strong meiotic aneugenic effect of BPA. Similar studies support that environmental exposures can lead to changes in the body and oocytes, leading to nondisjunction.

**Conclusion**

Chromosome failure and aneuploidy events are very important in humans. The relationship between increasing maternal age and the risk of trisomy is widely known. However, little is known about the mechanisms, causes, predictability and prevention of chromosomal nondisjunction. It is well known that chromosomal non-separation is associated with advanced maternal age. Telomere length, the timing of replication at the centromere
and other loci are important in this relationship. It is known that decreasing telomere length is associated with increasing age. Telomere length is known to be associated with reproductive health. Depending on the replication timing, chromatin abnormalities are known to cause trisomy in young women. Decreased recombination frequency was associated with non-segregation at meiosis I, while an increase was associated with non-segregation at meiosis II for most chromosomes. It is not fully known whether methylation or other epigenetic modifications in DNA are related to non-dissociation. Methylation and chromatin changes may be related to recombination, telomere length, and possibly replication timing. Chromosome structure, centromere and telomere sizes/stability are probably crucial for proper pairing and segregation of chromosomes in meiosis. This may not necessarily be related to aging. However, there may also be another factor that somehow contributes to the risk. Non-separation causes abnormalities in the number of chromosomes that often lead to pregnancy loss. Some women appear to be predisposed to trisomy. However, environmental harmful factors such as nicotine, mobile phone and harmful rays can cause numerical chromosome damage. Little is known about the cause of non-separation in human reproduction.
Although there are many important studies in this field of inseparability and aneuploidy, definitive proof of a direct cause of inseparability has not yet been fully revealed.

REFERENCES


91. Petersen, MB, G Karadima, M Samaritaki, D Avramopoulos, D Vassilopoulos and M Mikkelsen. Association Between Presenilin-1 Polymorphism


Chapter 8

Preoperative Evaluation before Lung Resection

Elif Guliyev

Abstract

Lung resection is applied in some patients with bronchiectasis, especially lung cancer, and uncontrollable pulmonary hemorrhages after trauma. Changes in respiratory physiology due to perioperative anesthesia cause the development of postoperative pulmonary complications. The patient in the perioperative period and the risk factors associated with the procedure should be evaluated with preoperative risk scoring (Canet, Arozullah, ARISCAT). Necessary treatments should be applied in the preoperative preparation period and postoperative complication follow-up should be performed in high-risk patients. Appropriate FEV1 values for wedge resection, lobectomy, and pneumonectomy, which are among the recommended PFT parameters for lung resection, are 1 L, 1.5 L, and 2 L, respectively. Patients above these values are considered to be able to tolerate the operation. If these values are below, additional tests (calculation of estimated postoperative FEV1 values, ventilation/perfusion scattering, cardiopulmonary exercise tests, and stair climbing tests) should be performed. For the curative treatment of lung cancer with resection in these patients, it is necessary to ensure the optimal condition of the patient in terms of suitability for the operation, as well as to minimize the morbidity and perioperative deaths due to the effects on the cardiorespiratory function that may occur after resection.

Lung resection is mainly performed for curative treatment and sometimes for diagnostic purposes in patients diagnosed with lung cancer, but it can also be applied in cases of bronchiectasis and uncontrollable bleeding after trauma.

Lung cancer, the most common indication for resection, is a leading cause of death in both men and women worldwide (1). According to the current statistical data, lung cancer ranks first in men and breast cancer ranks first in women (4th in lung cancer frequency in women). First cardiovas-

---

1 Dr. Kocaeli Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, elifkrs@gmail.com, Orcid: 0000-0002-1501-3360

https://doi.org/10.58830/ozgur.pub91.c500
cicular diseases, second respiratory system diseases, and cancer are in the 3rd rank among the general mortality data in the TUIK data portal. In terms of cancer mortality, lung cancer ranks first. Because most lung cancer patients are diagnosed at an advanced stage, this precludes curative treatment. About 1.6 million people die from lung cancer each year, and the overall 5-year survival rate is only 15% (1,2).

In general, after all, operations, changes occur in respiratory functions due to anesthesia. In particular, the proximity of the surgery to the diaphragm increases the risk of postoperative complications.

Perioperative Pulmonary Physiology

Postoperative pulmonary complications should be considered as a result of normal perioperative pulmonary physiology. Decreased lung volume after resection contributes to the development of postoperative pulmonary complications.

In thoracic and upper abdominal surgery, lung volume reduction occurs in a restrictive pattern (VC decreases 50-60%, FRC decreases 30%) due to diaphragm dysfunction (3-5).

In addition to diaphragm dysfunction, postoperative pain and limitation of thoracic movements also contribute to a decrease in lung volumes if optimal pain palliation is not achieved. A decrease in functional residual capacity below the closing volume causes atelectasis, ventilation/perfusion mismatch, and pneumonia, which leads to impaired gas exchange and postoperative hypoxemia (6).

Decreased tidal volume, inability to breathe deeply, and an increase in respiratory rate after thoracic surgery increases the risk of complications. In addition, the effect of anesthesia does not wear off immediately and opioids given postoperatively also suppress respiration. Patient avoidance of cough due to pain and inhibition of cough due to opioids; deterioration in the mucociliary clearance of respiratory secretions causes an increase in the risk of infection (3,7).

Resection in lung cancer

Surgical treatment of lung cancer started with the first successful pneumonectomy performed by Graham in 1933 (8). Afterward, with technical advances, Churchill, shortly after Graham, reported that lobectomy could also be preferred in suitable patients (9). Although the mortality rates
during surgery have decreased significantly with today’s medical developments, deaths due to postoperative complications continue.

It is important to determine the postoperative complications with various risk scorings (Arozullah, Canet, ARISCAT) during the preoperative evaluation and to make recommendations to reduce possible complications. However, it is important to carefully evaluate the threshold values for lung functions suitable for surgery and predicted postoperative lung functions. Suggested to do for this purpose;

1- Spirometry  
2- Calculation of postoperative estimated lung functions,  
3- Measurement of carbon monoxide diffusion capacity (DLCO),  
4- Exercise tests.

Although arterial blood gas measurements are also evaluated, PO2 and PCO2 alone are not sufficient for postoperative pulmonary complications. Although it has been reported that preoperative hypercapnia (PaCO2 > 45 mmHg) increases the risk of postoperative pulmonary complications, it is not an independent risk factor for perioperative complications. Although preoperative arterial oxygen saturation below 90% may increase the risk of complications, hypoxemia alone is not sufficient to determine postoperative pulmonary complications. Because in these patients, the chance of curative treatment to be provided by surgery may also improve postoperative oxygenation after the removal of areas with ventilation/perfusion mismatch (10,11).

Postoperative Pulmonary Complications

Postoperative pulmonary complications cause increased perioperative general morbidity and mortality. Even in elective abdominal surgeries, postoperative pulmonary complications occur more frequently than cardiac complications. In thoracic surgeries, the rate of postoperative pulmonary complications is much higher and hospital stay is longer.

The incidence of postoperative pulmonary complications ranges from 2-70%. This is primarily due to the unclear definition of postoperative complications, and also to the variability of patient selection and procedure-related risk factors. Postoperative pulmonary complications; fever and accompanying pulmonary symptoms (cough, sputum, shortness of breath) or changes in chest X-ray (consolidation, atelectasis) (3,12,13).
Some postoperative risk factors are independent of the preoperative process, especially; Care should be taken in terms of the decrease in respiratory capacity due to insufficient postoperative analgesia and the development of atelectasis as a result, and the risk of embolism due to immobilization.

There are relevant dossiers and processing risks for pulmonary complexities (Table 1).

**Table 1: Risk distributions for pulmonary complications (14)**

<table>
<thead>
<tr>
<th>Patient-related risk factors</th>
<th>Procedure-related risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>The proximity of the surgical field to the diaphragm</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>Duration of surgery</td>
</tr>
<tr>
<td>Smoking history</td>
<td>Type of anesthesia</td>
</tr>
<tr>
<td>Obesity</td>
<td>Neuromuscular blockade</td>
</tr>
<tr>
<td>Obstructive sleep apnea syndrome</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
</tr>
<tr>
<td>General health status</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td></td>
</tr>
<tr>
<td>Low albumin</td>
<td></td>
</tr>
<tr>
<td>BUN height</td>
<td></td>
</tr>
</tbody>
</table>

**Preoperative Pulmonary Function Test Evaluation**

The relationship between pulmonary function tests and postoperative outcomes of patients who underwent lung resection was first reported in 1955 (15). As might be expected, preoperative pulmonary function tests are closely associated with post-surgical complications. Measurement of DLCO together with spirometry is also important in determining the risks that may develop after lung resection.

FEV1, FVC, FEV1/FVC ratios, among the parameters we look at in spirometry, are important in determining the diagnosis and severity of COPD. It has been shown that the FEV1 value, that is, the forced expiratory volume in the first second, is more important than other parameters in the preoperative evaluation. The postoperative complication rates of patients with a
preoperative FEV1 value below 60% were found to be significantly higher (16-20).

Threshold FEV1 values for pneumonectomy, lobectomy, and wedge resection, which were reported to be tolerable in studies, are shown in Table 2 (21,22).

<table>
<thead>
<tr>
<th>Threshold FEV1 values</th>
<th>FEV1 (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonectomy</td>
<td>2</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>1,5</td>
</tr>
<tr>
<td>Wedge resection</td>
<td>1</td>
</tr>
</tbody>
</table>

Lung cancer is frequently associated with COPD of the same etiology (cigarettes), and spirometry values are an important factor for postoperative complications in the preoperative evaluation, while it has been suggested to measure DLCO levels in addition to spirometry, especially in cases of interstitial lung disease with lung cancer, such as IPF (22). That is, if the preoperative FEV1 is > 80% predicted or > 2 L, it should be considered suitable for pneumonectomy without further investigation. However, if there is a concomitant interstitial disease or exertional dyspnea, DLCO measurement should also be performed in these patients. Likewise, patients with FEV1 > 1.5 L should be considered eligible for lobectomy, and similarly, DLCO should be measured in these patients if they have concomitant interstitial disease or effort dyspnea.

If FEV1 or DLCO is less than 80% predicted at initial evaluation, additional testing should be performed to determine postoperative lung function.

It should be noted here that while the remaining segment number ratio is sufficient for lobectomy, the percentage of lung perfusion found after evaluation with perfusion scintigraphy is required for pneumonectomy. Quantitative ventilation/perfusion scintigraphy is not preferred for lobectomy because of the overlap of lobes in a standard nuclear medicine scan images and the limited number of studies on the specificity of this technique.

If the estimated postoperative FEV1 < 30%, calculated as in the figure above, is high-risk resection. These patients are considered inoperable (23).

If the predicted postoperative FEV1 or DLCO is less than 40% predicted, then evaluation with exercise tests should be performed. This is because
preoperative assessment based on lung function alone cannot assess other important comorbidities, particularly heart disease, or the impact of malnutrition on postoperative risks.

**Exercise Tests**

Exercise tests have high sensitivity but low specificity in patients with limited exercise capacity. Patients who are restricted due to lack of effort or formlessness may not be differentiated.

As a simple practice to assess effort capacity, it is possible to climb the patient several flights of stairs and assess the general form and respiratory reserve. The ability of the patient to climb three flights of stairs for lobectomy and five flights for pneumonectomy has a high predictive value for the uncomplicated surgical course. However, stair-climbing tests are highly subjective and difficult to standardize (24).

Therefore, with VO2 max achieved by cardiopulmonary exercise tests, which give more objective results, we can divide patients into low-risk, medium risk, and high risk groups. Postoperative risks increase as the maximum oxygen uptake (VO2 max/kg) decreases. If VO2 max < 10 ml/kg/min, or if VO2 max < 15 ml/kg/min, the predicted postoperative FEV1 or DLCO is less than 40% of predicted surgery in these patients is considered inoperable because of high risk.

**Recommendations for reducing pulmonary complications preoperatively;**

- Application of bronchodilators, corticosteroids, chest physiotherapy before surgery in patients with obstructive pulmonary disease,
- Postponing elective surgery by recommending re-evaluation after appropriate treatment in the presence of respiratory tract infection (upper and lower respiratory tract),
- Quitting smoking preferably at least eight weeks before surgery, due to the postoperative risks associated with smoking,

Suggesting that morbidly obese patients lose weight due to the increased risk caused by obesity hypoventilation and hypercapnia, and providing appropriate noninvasive mechanical ventilator support in patients with obesity hypoventilation syndrome,
- Teaching breathing exercises (deep breathing techniques, use of airflow) to patients.

**In conclusion:** Patients who are candidates for lung resection should be evaluated multidisciplinary. These patients should not be considered inoperable only because of advanced age, and concomitant cardiopulmonary diseases should be handled carefully.

Lung function and exercise test results are only a guide to eligibility for resection and results should be evaluated on a patient basis.

It should be taken into account that the basal respiratory functions of the patients who will be resectioned are already poor. It is necessary to aim both to increase the curative treatment in lung cancer cases and to minimize the morbidity and perioperative deaths due to the effects of resection on cardiorespiratory function.
REFERENCES
12. Lawrence VA, Hilsenbeck SG, Mulrow CD. Incidence and hospital stay for cardiac and pulmonary complications after abdominal surgery.


Current Researches in Health Sciences-I

Editor: Dr. Enes Karaman