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Abstract
Since the last months of 2019, the COVID-19 pandemic caused by SARS-CoV-2, a brand new coronavirus, catches our attention on our agenda as it harms economic and socio-cultural structures almost all around the world. For the elimination of SARS-CoV-2, there has to be an effective and sufficient immune response that includes innate and adaptive immunity against the virus. Also, this immunity should help us to prevent and control the infection. However, there are some complications about our body’s response to this virus: Hyperactivation of the immune response can cause tissue damage and organ failures. On the other hand, immunodeficiency is one of the major obstacles to the elimination of the virus. Type I IFN response is essential for COVID-19 disease. Some of the SARS-CoV-2 infection pathogenesis is caused by delay, deficiency, or inhibition of IFN release. The infection can be limited if type I IFN is secreted early and adequately. The overproduction of pro-inflammatory cytokines (such as IL-1, IL-6, and TNFα), neutrophilia, and lymphopenia is associated with COVID-19 disease severity and mortality in patients. Our current understanding of SARS-CoV-2 immunity is still limited. Further clarification of the immunopathogenesis of COVID-19 disease will guide us in both diagnosis and treatment. It will also shed light on new drugs and vaccine studies. Therefore, extensive researches on the host immune response against SARS-CoV-2 are still necessary.

Key words: COVID-19, Immunity, SARS-CoV-2 Vaccine.

INTRODUCTION
Coronaviruses (CoV) are zoonotic agents that can infect many animals and humans in nature. They are common viruses that usually cause respiratory tract infections. Although human coronaviruses (HCoV)-NL63, HCoV-229E, HCoV-HKU1 and HCoV-OC43 mostly cause self-limiting upper respiratory tract infections, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) can cause fatal respiratory disease in humans. They may also cause various clinical diseases with gastrointestinal, hepatic, and neurological involvement (1-3).

Although the diseases caused by coronaviruses in humans did not attract much attention before, they have become quite popular in the last two decades. Outbreaks caused
by SARS-CoV in 2002 and MERS-CoV in 2012 have attracted considerable attention due to the high mortality rates (3). The first SARS case was reported in China in November 2002. SARS affected 26 more countries, causing a total of 8096 cases and 774 deaths. As of July 2003, the World Health Organization (WHO) declared the end of the SARS outbreak, and no human SARS cases have been identified since then. MERS-CoV was first reported from Saudi Arabia in 2012; it had a high mortality rate (34%), mostly caused by acute pneumonia and renal failure. MERS-CoV caused 2562 cases and 881 deaths worldwide at the end of December 2020 (4, 5). A brand new coronavirus with a mortality rate of 2% has been on our agenda because it has damaged economic and socio-cultural structures almost everywhere in the world by causing a pandemic at the beginning of 2020 (3, 6).

In December 2019, cases of pneumonia of unknown cause were detected in people who had a connection with the seafood and livestock market in the Wuhan province of China. The authorities reported that the authorities in China to WHO, on December 31, 2019, that the agent causing the disease may be a new virus epidemic factor. With the full genome analysis of the virus, it was found on January 7, 2020, that the agent was a new coronavirus, and it was very similar to SARS-CoV (80%). The new virus was named SARS-CoV-2, and the disease it causes was named COVID-19. Due to the rapid spread of the disease worldwide, WHO declared a pandemic on March 11, 2020 (7). Despite many measures taken, by the end of 2020, more than 75 million people worldwide were diagnosed with COVID-19, and around 1.7 million people died due to COVID-19 (8). According to Turkey’s Ministry of Health data, approximately 2.2 million people were infected with SARS-CoV-2, and 19371 people lost their lives due to COVID-19 on December 25, 2020 (9). These numbers are increasing day by day.

Antiviral drug and vaccination studies are continuing in almost all countries against SARS-CoV-2. An antiviral with a curative effect against COVID-19 has not been found yet. However, some vaccines that have completed the pre-clinical phase or phases 1-3 are ongoing, and they are promising for the future (2, 10-12). There are currently 61 vaccine candidates in the clinical phase 1-3 and 172 in the pre-clinical phase (13).

VIROLOGICAL FEATURES OF CORONAVIRUSES

Coronaviruses (CoV) are enveloped, positive-sense single-stranded RNA viruses that belong to the Coronavirinae subfamily in the Coronaviridae family in the Nidovirales order. The Coronavirinae subfamily includes four genera: alpha-CoV (αCoV), beta-CoV (βCoV), gamma-CoV (γCoV) and delta-CoV (δCoV). According to evolutionary analysis, it has been shown that αCoV and βCoV are of bat and rodent origin, and γCoV and δCoV are of bird origin. Among these four genera, only the αCoV and βCoV strains are known to infect humans. There are seven coronaviruses known to cause infections in humans. Among these, HCoV-229E (229E) and HCoV-NL63 (NL63) belong to the αCoV genus; HCoV-HKU1 (HKU1), HCoV-OC43 (OC43), SARS-CoV, MERS-CoV, and SARS-CoV-2 belong to the βCoV genus(1, 2).

1. Structural features of SARS-CoV-2

   a. Genome

   The genome of coronaviruses is approximately 30 kb and is the most extensive known RNA among viruses (4, 5). The SARS-CoV-2 genome ranges from 29.8 kb to 29.9 kb and has 11 open reading regions (ORF). The ORF lab gene region at the 5′ end, which makes up approximately 66% of the genome, encodes 16 non-structural proteins (nsp). The rest of the genome, the 3′ end, contains genes encoding four structural (S, E, M, and N) proteins and contains ORF3a, ORF6, ORF7a, ORF7b, and ORF8 genes that encode six accessory proteins. (2, 14).

   b. Envelope

   The envelope is comprised of; spike (S) protein, membrane (M) protein, and envelope (E) protein.

   Spike proteins protrude out of the envelope, and this structure has given its name to coronaviruses because it resembles a crown (corona) structure. The virus acts by binding to host cells with its homotrimeric pointed glycoprotein structure, making this protein a crucial target for potential diagnosis and treatment. SARS-CoV-2 attaches to the host cell’s ACE-2 (Angiotensin-converting enzyme-2) receptor with its S proteins to enter the host cell. Meanwhile, transmembrane serine protease-2 (TMPRSS2) is involved in preparing the S protein (2, 15). S protein has two subunits: S1 and S2. The primary function of the S1 protein is to bind to
the host cell receptor. This binding also triggers the fusion of the viral membrane and the host cell membrane. S2 protein is mainly responsible for the fusion of membranes. There is a furin cleavage region (PRRAR) on the border between S1 and S2 subunits. Furin is an enzyme mostly expressed in the lungs that play a role in viral infections. Furin has the potential to increase the fusion between the viral membrane and the host cell membrane by cleaving envelope glycoproteins (2, 16).

The S protein binds to ACE-2 via its receptor-binding domain (RBD) (2). It is known that with the D614G mutation, amino acids on RBD are altered (glycine instead of aspartic acid), and this polymorphic virus has been reported to become dominant in the world. It has been suggested that this D614 mutated variant causes an excessive viral load in the upper respiratory tract and increases the virus’s contagiousness; however, it does not aggravate the presentation of the disease. Nevertheless, the clinical significance of this variant is not fully known(17). On December 14, 2020, authorities from the United Kingdom of Great Britain and Northern Ireland reported that a new SARS-CoV-2 variant was identified with viral genomic sequencing. This new variant was referred to as SARS-CoV-2 VUI 202012/01 (Variant Under Investigation, the year 2020, month 12, variant 01). Initial analysis was reported to indicate that this new variant may spread easier than its predecessor among humans. The variant is defined by the presence of a range of 14 mutations that resulted in some amino acid changes and three deletions. It is thought that some of these mutations may alter the transmissibility of the virus in humans. Two of the identified mutations are N501Y and P681H mutations in the RBD. Research is ongoing in order to determine whether this variant is associated with any changes in symptom severity, antibody response, or vaccine efficacy (18).

The M protein has three transmembrane domains. It gives shape to virions, enhances the curvature of the membrane, and binds to the nucleocapsid. The E functions in both virus assembly and secretion, and it plays a role in the pathogenesis of the virus (19).

3. Nucleocapsid (N) protein

N protein is associated with the RNA genome of SARS-CoV-2. It protects the genome and preserves the viral RNA stability by shaping its structure(2). N protein has two domains, which has the ability to bind the viral RNA genome through various mechanisms. It has been reported that N protein can attach to nsp3 protein to help bind the virus genome to RTC, and package the encapsidated genome into virions. It also inhibits host cell interferon (IFN) synthesis and secretion during viral replication(19).

PATHOGENESIS

The characteristics of the virus and the host play a significant role in developing the COVID-19 disease and determining the clinical severity of the disease. The viral load, the characteristics of the virus mutation, the viral escape mechanism of the virus, and the age, gender, neuroendocrine-immune regulation, and HLA genes of the host affect the disease’s course (20).

SARS-CoV-2 is mainly transmitted through respiratory droplets and various contact routes. Therefore, the virus spreads easily in overcrowded areas. The virus first begins to replicate in the nasal cavity and pharynx, then progresses to the lower respiratory tract. Binding of the virus to a host cell by the target ACE-2 receptor is the first step of SARS-CoV-2 infection. ACE-2 is a carboxypeptidase that converts angiotensin I to angiotensin II. It is expressed in many places in the body, such as the nose, lung, ileum, heart, eye, liver, bladder, kidney, pancreas, brain, prostate, testis, and placenta. Thus it causes many different clinical situations and multiple organ dysfunction. SARS-CoV-2 is inclined to infect airway and alveolar epithelial cells, vascular endothelial cells, macrophages, and type 2 pneumocytes by binding to the ACE-2 receptor (3, 20). Especially binding of SARS-CoV-2 to receptors in type II pneumocytes (ACE-2) in the lungs triggers an inflammatory cascade in the lower respiratory tract, which is among the cornerstones of the pathogenesis (21).

While the S1 subunit binds to ACE-2 with its RBD, furin protease catalyzes the cleavage formation between the spike proteins (S1 / S2), and S2 subunit binds to TMPRSS2 of the host cell for the virus to fuse to the host cell membrane (22). The virus then enters the host cell, and the genome of the virus is released into the host cell cytoplasm. The replicase transcriptase complex is formed directly from the positive RNA genome, and the
RNA replication begins. In coronaviruses, this complex is only responsible for viral RNA synthesis; thus, it is able to escape the immune system response. After translation of structural and accessory proteins, the M, S, and E proteins attach onto the endoplasmic reticulum membrane. The mature virion is formed when the nucleocapsid and viral genome reach the Endoplasmic Reticulum - Golgi intermediate compartment (ERGIC). After the assembly, virions are transported to the surface of the cell in vesicles and released by exocytosis (3, 23).

Recently, many studies also indicate that SARS-CoV-2 penetrates host cells using CD147-spike protein. It was mentioned that this novel invasion route for SARS-CoV-2 could provide a new target for antiviral drug development. However, as these results are controversial, further research is needed (24-26).

COVID-19 infection becomes symptomatic after an incubation period of approximately 5.2 days. The most common symptoms are fever, dry cough, weakness, and dyspnea because the virus primarily targets the airways. Other symptoms of the disease include sputum production, headache, diarrhea, and lymphopenia. The patients' clinical situation is asymptomatic or mild in most patients. The disease progression worsens in about 10-20% of the patients, which have to be followed up in the hospital service or an intensive care unit. Among the risk factors for poor prognosis, comorbidities such as advanced age, male gender, obesity, hypertension, cardiovascular disease, diabetes, and respiratory system disease may be listed (3, 27).

COVID-19 pneumonia is atypical viral pneumonia. Although histopathological findings are non-specific, they are important. Pathological changes associated with COVID-19 are usually encountered in the lungs. These changes generally include bilateral edema, protein or fibrin-rich alveolar exudate, diffuse reactive hyperplasia of type II pneumocytes with widespread alveolar damage, desquamation of pneumocytes, and hyaline membrane formation (21, 28).

The pandemic still continues, and more information is needed on the virus's life cycle and host's immune response to find effective treatment options and vaccines for the COVID-19 disease (3).

### IMMUNE RESPONSE TO SARS-COV-2

SARS-CoV-2 has been shown to disrupt normal immune system responses, causing uncontrolled inflammatory reactions in severe and critical COVID-19 patients. It is known that these patients have lymphocyte activation, lymphopenia, lymphocyte dysfunction, granulocyte and monocyte abnormalities, high cytokine levels, and an increase in total antibodies (29).

**Innate Immune Response**

The innate immune response constitutes the first line of host defense against the coronavirus infection and is important in immunity against viruses. It consists mainly of macrophages, dendritic cells, natural killer (NK) cells, and molecules such as type I interferon (IFN), cytokines, and chemokines (30).

In RNA viruses such as SARS-CoV-2, this immune response begins with the recognition of single and double-stranded viral RNA (ssRNA, dsRNA, respectively) by pattern recognition receptors (PRRs). Phagocyte cells with PRRs on their surfaces become activated when pathogen-associated molecular patterns (PAMPs) expressed by pathogens are recognized. PRRs important for coronavirus are toll-like receptor (TLR) 3 and TLR7, which are activated by RNA in endosomes; RIG-I (retinoid-inducible gene) / MDA-5 (melanoma differentiation-associated gene 5) and the cGAS-STING pathway, which recognize cytosolic RNA (31, 32). This recognition event leads to the synthesis of cytokines via Nuclear Factor kappa B (NF-kB) and interferon regulatory transcription factor (IRF3) pathways (32). Among these cytokines, there are type I (IFN-α, β, ω) and type III (IFN-λ) interferons, which are the most critical elements of the antiviral response. There are also pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF -α), interleukin-1 (IL-1), IL-6, and IL-8. These induce the antiviral immune response in target cells and enhance the acquired antibody response. Type I IFN response is particularly important. The fundamental pathology in SARS-CoV-2 is a delay, deficiency, or inhibition in IFN release. SARS-CoV-2 infection can be limited if type I IFN is secreted early and properly. Type I IFN triggers an antiviral effect by inducing interferon-stimulated genes (ISGs), which have the ability to inhibit viral replication to an extent.
through various mechanisms. Suppose there is a delay in IFN production. In that case, viral replication cannot be controlled; cellular damage occurs in the airway epithelium and lung parenchyma, resulting in the formation of a lethal inflammatory cytokine storm. These cases are generally more common in older people (31).

The data obtained from various studies suggest that a myeloid response disorder may contribute to acute respiratory distress syndrome (ARDS), cytokine storm, and lymphopenia development in patients with severe COVID-19. It has been shown that monocyte-derived inflammatory macrophages (FCN1 + macrophages) were increased in bronchoalveolar lavage (BAL) samples in severe COVID-19. FCN1 + macrophages have an inflammatory and cause excessive chemokine production seen in the cytokine storm (33).

It is thought that the dysregulated macrophage activation observed during a coronavirus infection, parallel to the significant macrophage infiltration to the lungs, plays a part in the pathogenesis of severe COVID-19 cases. According to RNA sequence analysis, 80% of the total cells in bronchoalveolar lavage fluid (BALF) of severely ill patients are mononuclear phagocytes (MNPs), and it is known that most of the MNPs in BALF are monocyte-derived macrophages rather than alveolar macrophages (30).

Neutrophils are the first line of cells that reach the site of infection and destroy pathogens through oxidative burst, phagocytosis, cytokines, proteases, and neutrophil extracellular traps (NETs). NETs are web-like DNA structures and proteins that are secreted from neutrophils. NETs are useful in host defense against pathogens; however, the continuous formation of NETs causes damage to epithelium, endothelium and acts as a stimulating factor for many diseases. Neutrophilia occurs in severe COVID-19 patients. It is argued that the increase in NETs formation may be related to some genes. The excessive NETs formation may induce consecutive inflammatory reactions that destroy the surrounding tissues, cause micro thromboses and result in permanent organ damage to the pulmonary, cardiovascular, and renal systems (34, 35). Besides, an increased neutrophil/lymphocyte ratio has been determined to be an independent risk factor for severe disease (35).

The complement system plays an important part in the immune reaction against viral infections. It participates in acute lung injury whilst the coronavirus infection. A recent study examining the histology of pulmonary and cutaneous biopsies and autopsy samples from five critical patients infected with SARS-CoV 2 revealed complement-mediated micro thrombotic disease, including c5b-9, c4d, and Mannan-binding lectin serine protease 2 (MASP2) deposits. The use of an anti-C5a antibody in a mouse model of MERS-CoV infection resulted in the recovery of the respiratory symptoms without an increase in the viral load (3).

There are studies reporting a decrease in NK cell count in peripheral blood in patients with severe COVID-19. CXCR3 is a chemokine receptor that mediates NK cell infiltration. In vitro, CXCR3 ligand (CXCL9-11) has been observed to increase in the lung tissue of patients infected with SARS-CoV-2 and the proliferation of monocytes producing CXCR3 ligand in the lung of COVID-19 patients. The CXCR3 pathway is thought to facilitate the uptake of NK cells from the peripheral blood into the lungs in COVID-19 patients. Besides, impaired production of chemokine, IFN-γ, and TNF-α was detected in these cells. Significant increases in NK cell inhibitory receptor NKG2A expression were observed in patients infected with SARS-CoV-2. NKG2A expression induced by SARS-CoV-2 may be associated with early functional depletion of cytotoxic lymphocytes such as cytotoxic T lymphocytes and NK cells, leading to disease progression (30, 31).

Adaptive Immunity

1. Cellular Immune Response

Lymphopenia is a key feature of COVID-19 patients, and it happens mainly in severe cases. Significant decreases in CD4+ T cell, CD8+ T cell, NK cell, and B cell numbers are observed. It is known that lymphocyte percentages are below 20% in severe cases. Previous research has revealed a notable reduction in T cell counts, specifically CD8+ T cells, in severe cases compared to mild cases. It has been reported that the lymphopenia level, especially T lymphocyte levels, can be a predictor for the severity and prognosis of the disease and risk of death (29). The mechanism of lymphopenia in COVID-19 infection is
still unknown; however, some possible explanations for this finding have been provided, including chemokine-mediated redistribution, virus-induced destruction, bone marrow suppression, and apoptosis (30).

Lymphocytes are activated but dysfunctional in COVID-19. In a study of 128 patients who recovered, CD8+ T cell response was observed more frequently than the CD4+ T cell response. Zhou et al. reported that CD69, CD38, and CD44 surface receptors on CD4+ and CD8+ T cells were highly expressed in SARS-CoV-2 infected patient group in contrast to the healthy control group. OX40 and 41BB are critical molecules in the clonal expansion and stimulation of the immune response. These molecules were significantly increased, indicating T cell activation, especially in severe COVID-19 patients. Besides, T cells in COVID-19 patients indicate depletion of phenotypes, highly elevated exhaustion levels, and decreased functional diversity of T cells, which may be considered a marker for severe disease progression in COVID-19 patients (29).

2. Humoral Immune Response

It is believed that SARS-CoV-2 creates a potent B cell response, which is dependent on detection of virus-specific IgM, IgG, and IgA and neutralizing IgG (nAb) after a patient has been infected (36). After the onset of symptoms, IgM and IgA can be detected on 5-7th days, and IgG on 7-10th days in blood. Mostly serum IgM and IgA titers begin to decrease at nearly 28 days, and IgG titers peak at approximately 49 days (37). It is still not fully understood exactly how long IgG titers remain high in the blood; thus, further studies are needed to enlighten this subject.

The most commonly detected antibodies are the ones that bind to S and N proteins. However, among the four structural proteins of coronavirus, S protein is believed to be the only active antigen that triggers the production of neutralizing antibodies (30). The primary target of neutralizing antibodies (nAb) in SARS-CoV is the receptor-binding domain (RBD) of the S protein, which binds to the ACE-2 receptor. This region is highly immunogenic. Antibodies that bind to this domain neutralize and block the virus interaction with the host entry receptor ACE2 (31).

It is believed that the antibody-dependent enhancement (ADE) phenomenon may cause severe clinical COVID-19 cases. It has been documented that ADE occurs in viral infections by two different mechanisms. The first mechanism increases antibody-mediated virus uptake into phagocytic cells by Fc gamma receptor IIA (FcRIIA); thus, viral replication also increases. The second mechanism increases inflammation through excessive amounts of antibodies that form an immune complex. Both mechanisms function through non-neutralizing antibodies and/or antibodies at sub-neutralizing levels that bind to viral antigens without directly inhibiting or removing the infection (38). Clinical deterioration associated with ADE is well described in some viral infections such as Dengue, Zika, Ebola, and MERS. A neutralizing monoclonal antibody targeting the RBD of the S protein of the MERS virus has been proven to promote virus entry into cells via the Fc portion of the antibody that binds to the Fc receptor (FcR) on cells. This information supports the relationship between antibody upregulation and the poor prognosis of patients infected with the SARS-CoV-2 virus. However, the ADE-mediated inflammatory response and the association of preexisting antibodies with disease progression and severity in COVID-19 patients require further research (29, 36).

VACCINES FOR COVID-19

A strong consensus worldwide that a COVID-19 vaccine will probably be the most effective way to control the COVID-19 pandemic (39) sustainably. Vaccine development fit for human use may take years, mainly if new technologies that have not been broadly tested for safety or scaled up for mass production are being used (40). Nevertheless, a remarkable research effort and global coordination have resulted in the fast development of vaccine candidates and initiated various trials (39).

Moreover, previous research on SARS-CoV and the related MERS-CoV vaccines have shown that the S protein on the virus surface is an ideal target for a vaccine. In both viruses, SARS-CoV and SARS-CoV-2, the S protein interacts with the ACE2 receptor, and antibodies that target the S protein may interfere with this attachment, thus neutralizing the virus. Therefore, the S protein has been the major target for vaccine development (40). The advantages and disadvantages of the different strategies vaccines are summarized in Table 1.
Licensed vaccines used in humans are traditionally live attenuated viruses, inactivated viruses, protein or polysaccharide conjugated subunit, and virus-like particles vaccines. Several new technologies have been introduced in vaccine development in recent years, such as nucleic acid (DNA and RNA), viral vector, and recombinant protein-based vaccines (39).

The classical inactivated viral vaccine could be produced with chemical and physical agents such as formaldehyde, UV light, and β-propiolactone. Whole virus vaccines have a significant advantage compared to other vaccines because they have the ability to induce more effective than the different vaccine types. However, live virus vaccines should be investigated more carefully because of the safety issues (41).

Vector vaccines are usually constructed with a carrier virus such as an adenovirus or smallpox virus. The virus used is non-replicative. The carrier virus is designed to carry the S gene of SARS-CoV-2. The main advantage of vector vaccines; it has the ability to induce potent T cell responses without the need for an adjuvant (42, 43).

Different types of subunit vaccines are developed and studied, such as recombinant production of the S protein. One vaccine consists of a trimmerized SARS-CoV-2 S protein, and another one only contains the receptor-binding domain (RBD) (41). Subunit vaccines in which the proteins of the virus are injected into the host have the potential to exhibit efficacy in protecting humans from viral infection. However, given that only a few viral components of the virus are included in the vaccine, their protective efficacy

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Target</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Live attenuated</td>
<td>Whole virion</td>
<td>Existing infrastructure can be used, induce immunity higher</td>
<td>Production infectious material, takes time because of large genome size, inappropriate for highly immunosuppressed patients</td>
</tr>
<tr>
<td>Inactivated</td>
<td>Whole virion</td>
<td>Existing infrastructure can be used, safety, adjuvants can be used to increase immunogenicity</td>
<td>The need for large amounts of infection virus, antigen and/or epitope integrity needs to be confirmed</td>
</tr>
<tr>
<td>Subunit</td>
<td>S protein</td>
<td>High safety, adjuvants can be used to increase immunogenicity</td>
<td>Global production capacity might be limited, antigen and/or epitope integrity needs to be confirmed, high price, lower immunogenicity, require adjuvants and several doses</td>
</tr>
<tr>
<td>Viral vector-based</td>
<td>S protein</td>
<td>Safety, induces high titer immunoglobulins, excellent pre-clinical and clinical data for many emerging viruses, including MERS-CoV</td>
<td>Vector immunity may affect vaccine effectiveness conversely</td>
</tr>
<tr>
<td>RNA</td>
<td>S protein</td>
<td>No infectious virus needs to be handled, vaccines are usually immunogenic, rapid manufacturing possible</td>
<td>Safety issues with reactogenicity have been reported</td>
</tr>
<tr>
<td>DNA</td>
<td>S protein</td>
<td>No infectious virus needs to be handled, low production costs, high heat stability, tested in humans for SARS-CoV, rapid manufacturing possible</td>
<td>The vaccine needs specific delivery devices to reach good immunogenicity</td>
</tr>
</tbody>
</table>
may be limited, and in some cases, they can cause unstable immune responses (43). Also, unlike viral vector vaccines or nucleic acid based, recombinant S proteins in subunit vaccines may have an appropriate epitope structure unless they are produced in mammalian cells (42). Virus-like particles (VLP) vaccines have viral capsid proteins but do not have a genome. Therefore, it is safe and causes a high immune response (43).

The traditional vaccine production process is very time-consuming for responding to an outbreak. In contrast to traditional vaccines, nucleic acid vaccines may shorten the response time. Different DNA or RNA vaccines are currently under evaluation. The mRNA vaccine consists of an mRNA molecule of the virus that has been synthesized using laboratory techniques. After mRNA vaccine implementation, mRNA enters the cells, and spike protein is synthesized in the human body, so this type of vaccine saves months in the manufacturing process (41). mRNA vaccines are a good alternative to traditional vaccines with low cost, rapid production, and high potency. However, the RNA vaccine’s safety and effectiveness in humans are unknown (43).

DNA vaccines are similar to mRNA vaccines in terms of safety and ease of production. However, they are poorly immunogenic, so they require multiple doses and the addition of an adjuvant (42).

According to the WHO report, 61 vaccine candidates are in clinical evaluation and 172 vaccine candidates in the pre-clinical assessment as of December 22, 2020 (13).

As a result, our current understanding of SARS-CoV-2 immunity is still limited. Further clarification of the immunopathogenesis of COVID-19 disease will guide us in both diagnosis and treatment. It will also shed light on novel drugs and vaccine studies. Therefore, extensive research is still necessary on the host immune response against SARS-CoV-2.

Declarations
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References


Real Life Data for Glecaprevir/Pibrentasvir: A Single-Center Study

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Abstract

Background: Licensing of next-generation direct-acting antiviral agents (DAA) has revolutionized the treatment of Hepatitis C Virus (HCV) infection. These agents are important due to their high virological efficacy, high resistance barrier, short duration of treatment, and rare serious side effects. The purpose of our study was to present real-life data of chronic hepatitis C (CHC) infected patients with genotypes 2 and 3 who were treated with glecaprevir/pibrentasvir regimen.

Methods: Glecaprevir/pibrentasvir treatment was initiated in 127 patients infected with CHC genotype 2 and 3. Patients received glecaprevir/pibrentasvir (100 mg/40 mg) orally in the form of three tablets once a day as per recommendations of the Republic of Turkey, Ministry of Health. In the assessments of patients at the time of diagnosis and following DAA use, virological response criteria HCV-RNA value was <25 IU/ml.

Results: 127 patients were included in the study. The mean age of the patients was 27 ± 6, and 125 patients (98.4%) were male. 118 patients (92.9%) had a history of intravenous drug use, and 78 patients (61.4%) were convicts. 83.6% (n:106) of the patients were genotype 3, 15% (n:19) genotype 2, 0.7% (n:1) genotype 1+3, and 0.7% (n:1) genotype 3+4. The mean liver fibrosis stage was 1.7±0.8 and histological activity index was 7.9±2.7. 99.2% (n:126) of the patients achieved virological response and sustained virological response (SVR)-12, and only 1 patient did not achieve end-of-treatment response and SVR-12.

Conclusion: An effective, well-tolerated, oral and short-term treatment for patients infected with CHC genotypes 2 and 3 is currently possible with glecaprevir/pibrentasvir.

Key words: Chronic Hepatitis C, Direct-Acting Antiviral Agent, Glecaprevir, Pibrentasvir.

INTRODUCTION

Chronic hepatitis C (CHC) infection is one of the main causes of chronic liver diseases across the world. Liver damage may vary from minimal histological changes to severe fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Approximately 71 million people are infected with CHC infection worldwide (1, 2). In the studies conducted on blood donors in Turkey, HCV prevalence was 0.3-1.8%. It is estimated that there are 350000-700000 patients infected with Hepatitis C Virus (HCV) in Turkey (3). All patients with CHC are potential candidates for antiviral therapy (4). The primary objective in the treatment of CHC is to achieve sustained virological response (SVR), which is also expressed as a cure, and to prevent mortality and morbidity due to complications (5).
The first treatment in CHC started with standard alpha interferon (IFN) monotherapy in 1991, and with the addition of ribavirin (RBV) to this monotherapy in 1997. SVR rates increased from 6% to 34% in 24 weeks of treatment, and from 16% to 42% in 48 weeks of treatment (6). In 2001, it was attempted to extend the half-life with pegylation of IFN in order to increase virological response rates. Even though 48 weeks of treatment with Peg-IFN+RBV, SVR rates increased to 56%, adequate treatment rate was not reached and side effects rates were not reduced (7). Over time, HCV’s life cycle and pathogenesis were better understood, and treatments that directly targeted the virus were developed. Licensing of next-generation direct-acting antiviral agents (DAA) has revolutionized the treatment of HCV infection. These agents are important due to their high virological efficacy, high resistance barrier, short duration of treatment and rare serious side effects (8).

Glecaprevir/pibrentasvir (MAVIRET TM) is a fixed-dose combination tablet of glecaprevir, a NS3/4A prosthesis inhibitor, and pibrentasvir, a NS5A inhibitor, and has been developed by Abbvie for the treatment of CHC (9). Glecaprevir/pibrentasvir was formulated as a single tablet at a fixed dose (100 mg/40 mg, respectively). The recommended daily dose is three tablets taken orally once a day including 300 mg of glecaprevir and 120 mg of pibrentasvir. This fixed-dose oral combination of glecaprevir/pibrentasvir was approved by the Food and Drug Administration (FDA) in August 2017 in non-cirrhotic or compensated cirrhotic genotype 1, 2, 3, 4, 5 or 6 CHC patients. In March 2019, it was included into the reimbursement plan within the scope of Health Implementation Communique. The purpose of our study was to present real-life data of CHC-infected patients with genotypes 2 and 3 who were treated with glecaprevir/pibrentasvir regimen.

**MATERIALS AND METHODS**

**Study Design**

Between March 2019 and January 2020, patients who were followed up with the diagnosis of CHC at the infectious diseases and clinical microbiology clinic of the Health Sciences University of Konya Training and Research Hospital were included in the study. The inclusion criteria were: 1- Patients who were >18 years old; 2- Patients whose HCV-RNA values have been detectable for ≥6 months (CHC diagnostic criteria); 3- Patients who were infected with CHC genotype 2 or 3. 137 patients who met these criteria were included in the study. 10 patients who did not complete the 8-week glecaprevir/pibrentasvir treatment were excluded from the study.

**Data Collection**

Clinical, demographic and laboratory data of the patients were retrieved from the hospital database. Liver biopsies were performed percutaneously and evaluated based on the Ishak scoring system. According to this system, 0-2 points were classified as “no fibrosis or minimal fibrosis”, 3 points as “portal fibrosis”, 4 points as “bridging fibrosis” and 5-6 points as “cirrhosis”.

**Laboratory Tests**

Real-time polymerase chain reaction (Anatolia Geneworks HCV, Turkey) was used to detect HCV RNA and HCV genotype. Hemogram analysis was performed with Sysmex XN-1000 (Sysmex, Kobe, Japan). HCV RNA measurements and other tests were performed at weeks 0, 4, 8 and 12.

**Management of Glecaprevir/Pibrentasvir Treatment in Patients with Chronic Hepatitis C**

The administered treatment and the duration of treatment was determined according to the National Healthcare Practice Communique of the Republic of Turkey Ministry of Health. Based on this guideline, glecaprevir/pibrentasvir is used for a total of 8 weeks in treatment-naive, non-cirrhotic patients with CHC genotype 2 and 3 and for a total of 12 weeks for cirrhotic patients. For non-cirrhotic patients with CHC genotype 2 who have received prior treatment, the duration of therapy with glecaprevir/pibrentasvir for NS5A-inhibitor-naive patients is 8 weeks in total, and it is 16 weeks in total for patients who have received a NS5A inhibitor previously. The duration of treatment with glecaprevir/pibrentasvir in non-cirrhotic patients with genotype 3 who have received any prior treatment is 16 weeks, while it is 16 weeks in total for cirrhotic (Child-Pugh A) patients. Patients received glecaprevir/pibrentasvir (100 mg/40 mg) (Maviret; Abbvie) orally in the form of three tablets once a day as per the recommendations of the Republic of Turkey Ministry of Health. In the assessment of the data of patients at the time of diagnosis and following DAA use, <25 IU/ml HCV-RNA value was accepted as virological response criteria.
Ethical Approval

This study was approved by the local ethics committee of University of Health Sciences, Konya Training and Research Hospital, with the 08/03/2020/36-15 ID number, and the study was conducted according to the Declaration of Helsinki 1975.

Statistical Analysis

SPSS version 20.0 (IBM SPSS Statistics 20.0) was used for data evaluation and analysis. Continuous variables were expressed as median (minimum-maximum) and mean ± standard deviation values. Categorical variables were expressed as n (%).

Table 1. Demographic Data of Patients

<table>
<thead>
<tr>
<th>Gender</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.6% (2/127)</td>
</tr>
<tr>
<td>Male</td>
<td>98.4% (125/127)</td>
</tr>
<tr>
<td>Age</td>
<td>27 ± 6 (19-69)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-Naive</td>
</tr>
<tr>
<td>Received Prior Treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 3</td>
</tr>
<tr>
<td>Genotype 2</td>
</tr>
<tr>
<td>Genotype 1+3</td>
</tr>
<tr>
<td>Genotype 3+4</td>
</tr>
</tbody>
</table>

Table 2. Laboratory Parameters Prior to Treatment of Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV RNA</td>
<td>3149060 IU/ml (1333-58490000 IU/ml)</td>
</tr>
<tr>
<td>Fibrosis stage</td>
<td>1.7±0.8</td>
</tr>
<tr>
<td>Histological Activity Index</td>
<td>7.9±2.7</td>
</tr>
<tr>
<td>ALT</td>
<td>93.5 u/L (10-591 u/L)</td>
</tr>
<tr>
<td>AST</td>
<td>53.2 u/L (16-289 u/L)</td>
</tr>
</tbody>
</table>

RESULTS

127 patients who completed the eight weeks of treatment were included in the study. The mean age of the patients was 27 ± 6, and 125 (98.4%) were male. Four (3.1%) patients received prior treatment, and 123 (96.9%) patients were treatment-naïve. Three patients who received prior treatment had relapsed after one year of peg-IFN+ribavirin treatment, while one patient discontinued sofosbuvir therapy. All patients were non-cirrhotic. Four patients had asthma, one had chronic renal failure (CRF), and one had hypogonadotrophic hypogonadism. 118 (92.9%) patients had a history of intravenous drug use. 78 (61.4%) patients were convicts. Genotype distributions were as follows: 83.6% (n:106) of the patients were genotype 3, 15% (n:19) were genotype 2, 0.7% (n:1) was genotype 1+3, 0.7% (n:1) was genotype 3+4. 28 (20.4%) patients had a liver biopsy before treatment was initiated. The mean stage of fibrosis was 1.7±0.8, and the mean histological activity index (HAI) was 7.9±2.7. Patients who completed 8 weeks of treatment achieved a virological response; however, only one patient did not achieve end-of-treatment response. All 126 patients who achieved a treatment response and completed a 12-week follow-up achieved SVR-12; however, SVR-12 rate was 99.2% due to the one patient who did not develop a response at the end of treatment. As adverse events, four patients had weakness, one patient had change in taste sensation, one patient had diarrhea, one patient had nosebleed, one patient had bleeding in gums, one patient had constipation and one patient had stomach complaints. All complaints occurred in the first weeks of treatment and resolved spontaneously in the next weeks. There were no serious adverse events that resulted in interruption of treatment or discontinuation of treatment.

DISCUSSION

Glecaprevir/pibrentasvir has shown great improvement in real-life data regardless of baseline patient characteristics such as gender, age, fibrosis stage, kidney function and past HCC therapy (10). In our study, SVR-12 rate was 99.2% in genotype 2 and 3 patients, only one patient did not achieve end-of-treatment response and SVR-12. This patient was a convicted patient infected with genotype 3 and had no other known chronic disease. HCV RNA result was negative at the end of the fourth week; however, at the end of the eighth week, it was positive again. It is believed that the patient did not use
the drug or used it irregularly; however, the patient could not be reached again, as the patient was a convict and the pandemic had started. The efficacy of glecaprevir/pibrentasvir in non-cirrhotic or compensated cirrhotic patients infected with CHC genotype 3 was investigated in studies ENDURANCE-3 and SURVEYOR-2 (Section 3). ENDURANCE-3 is a partially randomized, actively controlled and open-label study in treatment-naïve patients. In this study, SVR-12 rates were 94.9% (149/157) and 95.3% (222/233), respectively in 8-week and 12-week glecaprevir/pibrentasvir treatment groups (11). SURVEYOR-2 is an open-label study in which 12 or 16 weeks of glecaprevir/pibrentasvir treatment was randomized in patients with non-cirrhotic or compensated cirrhosis. In this study, SVR-12 rate was 98% (39/40) with 12-week treatment in treatment-naïve cirrhotic patients, and SVR-12 rate was 96% (66/99) with 16-week treatment in cirrhotic patients who received prior treatment (12). In the study which presented real-life data of patients with genotype 1-4 CHC in Italy, SVR rates were 99.2% and 100%, respectively, for 8 weeks and 12-16 weeks of glecaprevir/pibrentasvir treatment (13).

There are studies that show that glecaprevir/pibrentasvir is also effective in specific patient populations. EXPEDITION-4 is a single-arm and open-label study. In this study, SVR rate was 98% in non-cirrhotic and compensated cirrhotic patients with chronic renal failure (CRF) stage 4 and 5 (82% was undergoing hemodialysis) and genotype 1-6 infection. It has been emphasized that renal failure does not affect the effectiveness of glecaprevir/pibrentasvir and that dose adjustment is not required in these patients (14). MAGELLAN-2 is an open-label, single-arm study that evaluated patients with liver and kidney transplants and CHC genotype 1-6 infection. Patients were receiving cyclosporine ≤100 mg, sirolimus, tacrolimus, everolimus, mycophenolate, azathioprine and prednisolone, and the SVR-12 rate was 98% (15). In a study conducted in non-cirrhotic patients with CHC, genotype 1-6 co-infected with human immunodeficiency virus (HIV), SVR-12 rate was 98% with glecaprevir/pibrentasvir treatment. Glecaprevir/pibrentasvir was also found to be effective in HIV-infected patients (16).

Severe side effects were observed with telaprevir, another DAA, which was previously used. These side effects led to a treatment discontinuation rate of 8-12% (17, 18). In several studies, very few side effects associated with glecaprevir/pibrentasvir were reported (13, 19). The most common complaints in our study were weakness, gastrointestinal tract complaints, nose bleeds and bleeding in gums. However, these side effects were not very severe and occurred at the beginning of treatment and then resolved. No patient discontinued treatment due to side effects. In a combined analysis of tolerability data of 8, 12 and 16 weeks of treatment with glecaprevir/pibrentasvir, the most commonly reported side effects were headache (13%), fatigue (11%) and nausea (8%) (20).

In another study, there was a high discontinuation rate in treatment with glecaprevir/pibrentasvir among patients over the age of 75 years, and it was recommended that adequate care be provided for elderly patients (10).

This study has some limitations. Most of the patients included in the study were convicts, which reduced treatment compliance, and there were patients who discontinued the treatment. Moreover, this was a descriptive study, and there was no comparison between the subgroups. The main reason for the inability to compare is that the distribution of subgroups were uneven. Another limitation is that the cause of the lack of response in one patient was not clarified as the only patient who was not able to receive an end-of-treatment response and SVR did not attend the follow-up.

In conclusion, there are currently effective, well tolerated, oral and interferon-free treatment regimens involving direct-acting antiviral agents for almost all patients infected with genotypes 2 and 3. In this study, our treatment experience with the glecaprevir/pibrentasvir regimen is presented. It has been determined that this regime is safe, well tolerated and has high efficiency in the treatment of CHC.

Declarations
The authors received no financial sport for the research and/or authorship of this article. There is no conflict of interest.

References


Intra-Articular Methylprednisolone Injection for Advanced Osteoarthritis in Geriatric Patient Population

Ali Yüce¹, Niyazi İğde², Tahsin Olgun Bayraktar³, Mustafa Yerli³, Ali Çağrı Tekin³, Mehmet Kürşad Bayraktar³, Hakan Gürbüz³

Abstract

Background: We aimed to investigate the effect of intra-articular methylprednisolone injection on pain and functional outcomes and the number of outpatient clinic admissions in patients with advanced knee osteoarthritis in the geriatric age group.

Methods: The files of 78 patients over the age of 65 who were administered intra-articular methylprednisolone injection with the diagnosis of primary gonarthrosis between 2018 and 2020 were analyzed retrospectively. Age, gender, and affected side of the patients were recorded. The number of outpatient clinic admissions, VAS and WOMAC scores before and after injection were evaluated statistically.

Results: 18 of the patients were male (24.7%) and 55 were female (75.3%). The mean age was 74.95±7.11 years. WOMAC and VAS score values of the patients at the first and third months were significantly lower than the pre-injection period. The decrease in the number of outpatient visits in the 6-month period after the injection compared to the number of outpatient visits in the 6-month period before the injection was statistically significant. A strong positive correlation was found between the number of outpatient visits before injection and the first VAS score.

Conclusions: In geriatric patients with advanced-stage knee osteoarthritis who do not accept total knee arthroplasty, intra-articular methylprednisolone injection may be a feasible method that reduces pain and the number of outpatient clinic visits in the short term.

Key words: Knee Osteoarthritis, Steroids, Injection, Gonarthrosis, Geriatric Patient.
INTRODUCTION

Osteoarthritis (OA) is the most common joint disease in the world and is the leading cause of chronic musculoskeletal pain. In general, symptomatic OA can be seen in up to 40% of individuals over the age of 65 in the general population (1). Approximately 10% of men and 13% of women over the age of 60 are affected by osteoarthritic knee (2).

Surgical treatment is preferred in patients with advanced-stage degeneration (3). Although arthroplasty is an effective treatment option for pain and dysfunction associated with late stage osteoarthritis, this procedure may not be suitable for all patients due to comorbidities, lack of social support, or other factors (4).

The goals of conservative treatment of this disease are: slowing the progression of the disease, increasing functional capacity, and relieving symptoms (5). Conservative methods are generally preferred in the early stages of OA. Intra-articular injections are one of the conservative methods that can positively affect pain and functional status in gonarthrosis (3,6). On the other hand, long-term injections may cause cartilage damage and worsening of gonarthrosis (7). For this reason, although the clinical benefits of corticosteroids are not clear, methylprednisolone may be the most effective molecule among corticosteroids in symptomatic relief of knee osteoarthritis (8).

Our hypothesis is that in patients with advanced knee osteoarthritis in the geriatric age group, intra-articular methylprednisolone injection is an effective treatment method that reduces pain and the number of outpatient clinic visits. Therefore, we aimed to investigate the effect of intra-articular steroid injection on pain and functional outcomes and the number of outpatient clinic admissions in patients over 65 years of age with advanced-stage OA who do not accept arthroplasty treatment.

MATERIALS AND METHODS

This study was approved by the local ethics committee of University of Health Sciences, Okmeydani Training and Research Hospital, with the 24.09.2019/1439 ID number, and the study was conducted according to the Declaration of Helsinki 1975.

The files of 78 patients who received intra-articular methylprednisolone injection with the diagnosis of gonarthrosis between 2018 and 2020 were retrospectively analyzed. Patients under 65 years of age, those with a history of surgery in the injected knee, those with rheumatic diseases, isolated patellofemoral pain, a history of injection in the last 6 months, osteoarthritis after a fracture, infection at the injection site, and systemic infection were excluded from the study. Four patients without follow-up and one patient who developed osteoarthritis after a fracture were excluded and 73 patients over 65 years of age with a diagnosis of primary gonarthrosis were included in the study.

Anteroposterior and lateral knee radiographs and patella tangential radiographs of the cases were evaluated. Patients with stage 4 OA according to the Kellgren-Lawrence classification on radiographs were included in the study (Table 1) (5, 9). All of the cases were patients who did not accept total knee arthroplasty due to comorbidities or social reasons.

Table 1: The stages of radiological arthrosis according to the Kellgren-Lawrence classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Degree of osteoarthritis</th>
<th>Radiographic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Suspicious</td>
<td>Minimal osteophyte, significance uncertain</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Minimal</td>
<td>Prominent osteophyte, joint space intact</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Moderate</td>
<td>Moderate narrowing of the joint space</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Severe</td>
<td>Severe narrowing of the joint space, sclerosis in subchondral bones</td>
</tr>
</tbody>
</table>

With the assistance of a physician, all patients were asked to fill the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale and the visual analogue scale (VAS) before intra-articular injection and at 4, 8 and 12th weeks of follow-up (10,11). The visual analog scale value was recorded by the patients as the amount of knee pain during walking and resting on a 10-mm-sized 1 to 10 scale (5). While calculating the WOMAC score, patients were asked to fill in three subscales (1-severity of pain during various positions or movements, 2-severity of joint stiffness, and 3-difficulty in performing daily functional...
activities). The total WOMAC score was then calculated using the formula (total score x100)/96.

Intra-articular knee injections were done by the same orthopedist. After the patients were seated on a stretcher, the feet were dropped down and the knee was sterilized. When the knee joint was at 90 degrees, 1 ml of 2% prilocaine HCL with 1 ml 40 mg/mL methylprednisolone acetate combination was applied into the knee through the patella and the lateral of the patellar tendon junction under sterile conditions. Immobilization was not recommended after the injection, and patients were followed up with the recommendation of nonsteroidal anti-inflammatory drugs.

Patients’ age, gender, affected side, pre-injection VAS and WOMAC scores, VAS and WOMAC scores at 1, 3 and 6 months after the injection, and the number of referrals to the outpatient clinic with complaints of gonarthrosis in the 6 months before and after the injection were recorded. The data obtained were evaluated statistically.

### Statistical Analysis

Normality of the data was tested with the Shapire-Wilk test. Student t test was used to compare normally distributed variables between two independent groups, and Mann Whitney U test was used to compare non-normally distributed variables between two independent groups. Normally distributed variables in two dependent groups were examined with the paired t test. Normally distributed variables in repeated measurements were examined with repeated-measures ANOVA test and Bonferroni correction test was used as the post hoc test. Numerical variables were expressed as mean ± standard deviation and categorical variables were expressed as number and % values. SPSS Windows version 23.0 package program was used for statistical analysis and p < 0.05 was considered statistically significant in all analyses.

### RESULTS

18 of the patients were male (24.7%) and 55 were female (75.3%). The mean age was 74.95 ± 7.11 years. 37 injections were done on the right knee (50.7%), and 36 on the left knee (49.3%). WOMAC and VAS scores at the 1st and 3rd months of follow-up were significantly lower compared to the pre-injection values (Table 2).

**Table 2: VAS and WOMAC scores of the patients before injection and at 1st, 3rd, and 6th months after injection**

<table>
<thead>
<tr>
<th></th>
<th>median</th>
<th>mean±sd</th>
<th>min-max</th>
<th>tp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial VAS</td>
<td>6</td>
<td>6.00±1.72</td>
<td>3-10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Month 1 VAS</td>
<td>3</td>
<td>2.93±1.99</td>
<td>0-9</td>
<td></td>
</tr>
<tr>
<td>Month 3 VAS</td>
<td>5</td>
<td>4.52±1.72</td>
<td>0-8</td>
<td></td>
</tr>
<tr>
<td>Month 6 VAS</td>
<td>6</td>
<td>6.11±1.78</td>
<td>3-10</td>
<td></td>
</tr>
<tr>
<td>Initial-month 1</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial-month 3</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial-month 6</td>
<td>0.999</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial WOMAC</td>
<td>64</td>
<td>65.70±9.13</td>
<td>48-88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Month 1 WOMAC</td>
<td>33</td>
<td>33.45±8.93</td>
<td>17-53</td>
<td></td>
</tr>
<tr>
<td>Month 3 WOMAC</td>
<td>50</td>
<td>49.53±10.04</td>
<td>31-72</td>
<td></td>
</tr>
<tr>
<td>Month 6 WOMAC</td>
<td>65</td>
<td>65.48±8.05</td>
<td>50-85</td>
<td></td>
</tr>
<tr>
<td>Initial-month 1</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial-month 3</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial-month 6</td>
<td>0.983</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†p Repeated measures ANOVA test, ‡p post hoc test, *p Paired t test

The decrease in the number of outpatient visits in the 6-month period after the injection compared to the number of outpatient visits in the 6-month period before the injection was statistically significant (p <0.001) (Table 3).
Table 3: Number of outpatient clinic visits before and after injection

<table>
<thead>
<tr>
<th></th>
<th>median</th>
<th>mean±sd</th>
<th>min-max</th>
<th>†p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of outpatient clinic visits before injection</td>
<td>5</td>
<td>5.34±1.77</td>
<td>1-9</td>
<td></td>
</tr>
<tr>
<td>Number of outpatient clinic visits after injection</td>
<td>3</td>
<td>3.12±1.76</td>
<td>0-7</td>
<td></td>
</tr>
</tbody>
</table>

†p Repeated measures ANOVA test ‡p:post hoc test, *p:Paired t test

An analysis was carried out with the hypothesis that gender may have an effect on pain perception and thus on the results of the scores. No statistically significant relationship was found between gender and pre-injection VAS score, pre-injection WOMAC score, and the number of outpatient clinic visits before and after the injection (Table 4).

Table 4: Relationship between gender, VAS and WOMAC scores, and number of outpatient clinic visits

<table>
<thead>
<tr>
<th>Variables</th>
<th>Male (n=18) M (mean±sd)</th>
<th>Female (n=55) M (mean±sd)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial VAS score</td>
<td>5 (5.39 ± 1.33)</td>
<td>6 (6.2 ± 1.79)</td>
<td>0.082</td>
</tr>
<tr>
<td>Initial WOMAC score</td>
<td>66 (65.83 ± 8.38)</td>
<td>64 (65.65 ± 9.44)</td>
<td>0.943</td>
</tr>
<tr>
<td>Number of outpatient clinic visits before injection</td>
<td>4.5 (4.89 ± 1.78)</td>
<td>6 (5.49 ± 1.75)</td>
<td>0.211</td>
</tr>
<tr>
<td>Number of outpatient clinic visits after injection</td>
<td>3 (2.61 ± 1.5)</td>
<td>3 (3.29 ± 1.81)</td>
<td>0.155</td>
</tr>
</tbody>
</table>

*p* value was obtained from student t test

A strong positive correlation was found between the initial WOMAC score and the initial VAS score (r = 0.678, P = 0.001). A strong positive correlation was found between the number of outpatient visits before injection and the initial VAS score (r = 0.633, P = 0.001) (Table 5). One patient with diabetes mellitus was admitted to the emergency room at the night of the injection due to high blood glucose levels.

Table 5: Correlation between number of outpatient visits, pre-injection VAS score and pre-injection WOMAC score

<table>
<thead>
<tr>
<th>Initial WOMAC score</th>
<th>Initial VAS score</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>0.678**</td>
<td>0.01</td>
</tr>
<tr>
<td>p</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of outpatient clinic visits before injection</th>
<th>r</th>
<th>0.633**</th>
<th>0.378**</th>
<th>p</th>
<th>0.001</th>
<th>0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of outpatient clinic visits after injection</td>
<td>r</td>
<td>0.337**</td>
<td>0.325**</td>
<td>p</td>
<td>0.004</td>
<td>0.005</td>
</tr>
</tbody>
</table>

r: Pearson’s correlation coefficient, (n=73), ** The correlation coefficient is significant at p < 0.01, * The correlation coefficient is significant at p < 0.05.

DISCUSSION

Primary OA is a common disease of the knee with unknown cause, unpredictable prognosis and a high morbidity rate and that may lead to disability (5). It causes chronic pain, limitation of movement, and angular deformities in the knee joint and depresses the patient functionally and mentally (5). Treatment methods in gonarthrosis are various, and patient education, rest, preventive measures, pharmacological treatment, physical therapy and surgical treatment methods can be used alone or together according to the stages of the disease (3). While surgical treatment is preferred in patients with advanced-stage degeneration, conservative methods are preferred in the early stages. Intra-articular injections positively affect pain and functional status in gonarthrosis (3). The median age of our patient group was older compared to the
general OA population (12). This population constitutes the different aspect of our study. At the same time, intra-articular steroid injection may be an effective treatment method for short-term follow-up in geriatric cases with advanced OA.

Uğur et al. compared intra-articular hyaluronic acid and methyl prednisolone injections in patients with gonarthrosis and reported that the functional results of methylprednisolone applications were better in the short-term, but further long-term studies were required. In the same study, they observed more significant improvements in 1st and 3rd month WOMAC scores in the steroid administered group. They attributed this observation to the effectiveness of intra-articularly administered steroid in suppressing inflammation (13). A meta-analysis confirmed the short-term pain relief effect of intra-articular corticosteroid therapy in knee OA patients. The study noted short-term benefits for up to 2 weeks after injection, and also reported some long-term benefits for up to 16-24 weeks (14,15). Our study may support the findings indicating that intra-articular corticosteroid injection provides similar effects in the elderly population with advanced-stage OA.

In general, conservative treatments for knee OA are largely ineffective; only a minority of eligible patients considers arthroplasty and high tibial osteotomy in the long term (16). Practically, this suggests that a patient with moderate or severe knee OA pain or disability who fails to respond to conservative treatment may choose to delay arthroplasty for decades (16). Recently, the search for new treatment modalities in patients that do not respond to conventional treatment methods, who do not accept surgery or has comorbidities has begun to gain traction in the literature (17). Intra-articular steroid use creates cost efficiency in the short term (18). Moreover, intra-articular steroid injections may cause a decrease in the number of outpatient clinic visits in patients with advanced knee OA. We believe that this may be beneficial in reducing the workload of outpatient clinics caused by geriatric OA patients in institutions that provide healthcare services based on a social state policy as in Turkey.

Intraarticular injections are available for the elderly and advanced gonarthrosis groups. Although the expectation of functional recovery is limited in patients who do not accept surgical treatment, these injections can be safely applied as a palliative treatment in terms of pain (5). In the present study, there was a correlation between pre-injection WOMAC scores and the number of outpatient clinic visits and pre-injection VAS scores. We believe that this may be the direct outcome of pain. There is a pain component in WOMAC scoring, and at the same time, the number of outpatient clinic visits may be related to ongoing pain complaints. The significant reduction in pain caused by intra-articular methylprednisolone injection may have led to a decrease in both scorings and the need for hospital admission.

In the present study, methylprednisolone acetate and prilocaine HCL were used in combination. Methylprednisolone acetate (MP) has a long-lasting effect and has been recommended for intra-articular injections (8). Prilocaine is a fast and short-acting local anesthetic drug, and it facilitates pain reduction and spread of the steroid agent into the joint via the volume effect (3).

Clinical and epidemiological studies have found that inflammation in the knee joints of people with knee osteoarthritis is common and is associated with the progression of cartilage damage (7). This suggests that suppression of inflammatory processes by corticosteroids (already in widespread clinical use for knee osteoarthritis) may reduce the progression of knee osteoarthritis (7). However, repeated intra-articular injections of corticosteroids may also be associated with progressive cartilage damage, and injections are not recommended to be made with intervals of less than 3 months (19). On the other hand, in the advanced age group with end stage OA, advanced cartilage damage has already occurred and we believe that intra-articular corticosteroid injections may be applied within 3-month periods in this age group.

Although complications of intraarticular corticosteroid therapy are rare, the most frequently reported adverse effects include skin atrophy at the injection site, facial flushing, and post-injection exacerbation. Systemic side effects such as infection, increased blood glucose, hypercortisolism, and others are rarely seen, but precautions such as careful planning and wearing gloves should be taken to avoid them (15). In the present study, the procedure caused an increase in blood glucose level in only one patient. However, it should be kept in mind that intra-articular injections are invasive procedures, and the possibility of complications will increase with repeated injections.
There are certain limitations of the present study. The retrospective design of the study is one of the limitations. Furthermore, the efficacy of the procedure could not be revealed by comparing the study group with patients who underwent arthroplasty and/or received other intra-articular injection agents. The data obtained included a single injection and short follow-up period, and the long-term cost-effectiveness and complication rates were unknown. In addition, the patients used non-steroid anti-inflammatory drugs during follow-up (as it may have affected the results in the short-term follow-up).

In geriatric patients with advanced-stage knee osteoarthritis who do not accept total knee arthroplasty, intra-articular methylprednisolone injection may be a feasible method that reduces pain and the number of outpatient clinic visits in the short term.

Declarations
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Suzuki Frame Results in the Treatment of Comminuted Phalanx Fractures

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2 Ağrı Training and Research Hospital, Department of Orthopedics and Traumatology, Ağrı, Turkey

Abstract

Background: Comminuted fracture of the PIP joint is one of the most challenging fractures to be treated in hand surgery practice. The pins and rubber traction frame is an easy method to perform for these fractures. This study aimed to present the treatment stages of patients who had PIP joint fractures-dislocations with the pins and rubber traction frame and the functional results of patients.

Methods: The results of eight patients with fracture-dislocations of the PIP joint between 2016 and 2019 were retrospectively analyzed. Age and gender of patients, time between trauma and surgery, postoperative follow-up periods, affected area on the joint surface, postoperative complications, range of motion of PIP and DIP joints, affected finger, and the causes of the trauma were recorded.

Results: Five (62.5%) patients were male, and three (37.5%) patients were female in this study. The mean age of the patients was 28.50 ± 3.42 years. The mean range of motion of the PIP joint examined in the postoperative 12th month was 4.88° to 86.25°. In the same period, the mean range of motion of the DIP joint of the patients was 4.38° to 86.25°. We obtained union in all patients. Malunion or nonunion and osteomyelitis were not seen in any patients.

Conclusions: The pins and rubber traction frame is a method that can be used safely and effectively in fractures of the phalanx joints that are difficult, comminuted, and involving the joint.

Key words: Proximal Interphalangeal Joint, Fracture, Dislocation, Dynamic Fixation, Frame.

INTRODUCTION

Metacarpal and phalanx fractures are amongst the most frequently encountered orthopedic injuries (1). These fractures account for 10% of all fractures or 1/3 of all hand injuries (2). The proximal interphalangeal joint (PIP) is a hinge-style joint. It contributes to the grip dynamics of the hand with movements in the direction of flexion-extension and little rotational movement. The middle phalanx is subject to frequent injuries due to its weakness in soft tissue support. Some injuries only concern soft tissue, while others may be comminuted fractures (3). In these...
fractures, the fragments will shift according to the pulling directions of the flexor and extensor tendons. While phalanx shaft fractures are generally stable, oblique and spiral fractures tend to slip and require close follow-up in conservative treatments. In these fractures with difficult closed reductions, if the fracture line concerns more than 30% of the middle phalanx joint surface or if flexion of more than 30 degrees is required for the continuation of reduction, it is considered unstable and requires surgical intervention. Kirschner wire fixation, traction systems, static or dynamic external fixators, volar plate arthroplasty, and open reduction internal fixation (ORIF) are the surgical options of choice for these fractures (4, 5).

Comminuted fractures of the PIP joint are rare. These fractures are often accompanied by subluxation. Open reduction internal fixation or external fixation application and early motion protocol are valid treatment methods. Joint stiffness, degenerative arthritis, swelling, and pain are the most common complications (6). It is one of the most challenging fracture types to be treated in hand surgery practice.

Many techniques have been described in PIP joint fracture-dislocations (7-9). The pins and rubber traction frame described by Suzuki et al. (10) is an easy method to perform for the fracture-dislocations of the PIP joint. This method does not require unique materials. This method allows for early joint motion.

In this study, we aim to present the treatment stages of eight patients who had PIP joint fractures-dislocations with the pins and rubber traction frame and the functional results of patients.

**MATERIALS AND METHODS**

In our study, the results of eight patients with fracture-dislocations of the PIP joint (Figure 1) between 2016 and 2019 were retrospectively analyzed. The pins and rubber traction frames were performed on patients with fracture-dislocations of the PIP joints in our study. Eight patients (five men, three women) were included in our study. Patients were followed postoperatively for at least 12 months. Patients’ age, gender, time between trauma and surgery, postoperative follow-up periods, affected area on the joint surface, postoperative complications, range of motion of PIP and DIP joints, affected finger, and causes of the trauma were recorded.

FIGURE 1: A 27-year-old male patient had left-hand ring finger PIP joint comminuted fracture-dislocation after a motorcycle accident (A, B). The anteroposterior and lateral radiographs of the patient (C, D).

**Figure 1: A**

**Figure 1: B**

**Figure 1: C**
Regional anesthesia was applied to all patients as a standard procedure. Under fluoroscopy control, a long Kirschner wire (1.2 mm) was passed transversely just proximal to the joint-related fracture (this wire was the axial pull pin). This wire was bent 90 degrees, approximately 5 mm close to the skin, and its ends were made into hooks. A second Kirschner wire of the same size was passed through the middle of the intact fragment distal to the fracture transversely, parallel to the first wire. As previously described, it was bent 90 degrees to be close to the skin, and the ends were made into hooks again (this wire was the hook pin). Rubbers were used to pull both Kirschner wires whose ends were made into hooks. The traction force between the fracture fragments, the thickness and the number of rubbers were adjusted accordingly under fluoroscopic control (Figure 2). If there was luxation within the fracture, a third Kirschner wire was used to correct the subluxation. Our entire surgical procedure was performed, as described by Suzuki (10). All of our patients received one dose of antibiotics, preoperatively and postoperatively, and nonsteroid analgesic drugs were prescribed to all patients postoperatively.
Postoperative Care

Anteroposterior and lateral hand radiographs of all patients were seen one day after the operation. Weekly controls were made for four weeks, and radiographs were checked for any deterioration in the fracture line. The patients were given new dressings every three days and were advised to keep their bandages clean. At the end of the third week, a strict physical therapy program that would last about 8-12 weeks was prepared for the patients. The pins of all patients were removed at the end of four weeks in the outpatient clinic without anesthesia, except for one patient with a pin-track infection. All patients received physiotherapy afterwards.

RESULTS

We obtained union in all patients. Malunion or nonunion and osteomyelitis were not seen in any patients.

In our study, five (62.5%) patients were male, and three (37.5%) patients were female. The mean age of the patients was 28.50 ± 3.42 (range: 24-34) years. The mean time between trauma and surgery was 3.88 ± 2.29 (range: 1-7) days. The mean postoperative follow-up period of the patients was 14.88 ± 2.74 (range: 12-20) months. The average percentage of the affected joints of the fractured-dislocated phalanges was found to be 47.25% (range: 35%-62%) (Table 1).
Table 1. Summary of the results

<table>
<thead>
<tr>
<th>Patients</th>
<th>Gender</th>
<th>Age</th>
<th>Delay (day)</th>
<th>Follow-up (month)</th>
<th>Joint Fracture %</th>
<th>Complication</th>
<th>PIP ROM-Flex</th>
<th>PIP ROM-Ext</th>
<th>DIP ROM-Flex</th>
<th>DIP ROM-Ext</th>
<th>Injured Finger</th>
<th>Cause of Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>24</td>
<td>2</td>
<td>12</td>
<td>54</td>
<td>None</td>
<td>0</td>
<td>85</td>
<td>0</td>
<td>100</td>
<td>Middle</td>
<td>Sport</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>27</td>
<td>1</td>
<td>12</td>
<td>40</td>
<td>Some stiffness in the DIP joint</td>
<td>7</td>
<td>90</td>
<td>10</td>
<td>85</td>
<td>Ring</td>
<td>Traffic accident</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>27</td>
<td>4</td>
<td>14</td>
<td>45</td>
<td>Pain</td>
<td>5</td>
<td>90</td>
<td>5</td>
<td>80</td>
<td>Ring</td>
<td>Fall</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>34</td>
<td>6</td>
<td>15</td>
<td>62</td>
<td>None</td>
<td>0</td>
<td>85</td>
<td>0</td>
<td>90</td>
<td>Middle</td>
<td>Sport</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>32</td>
<td>7</td>
<td>16</td>
<td>45</td>
<td>Pin-track infection</td>
<td>5</td>
<td>80</td>
<td>0</td>
<td>90</td>
<td>Small</td>
<td>Sport</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>25</td>
<td>5</td>
<td>13</td>
<td>35</td>
<td>Some stiffness in the DIP joint</td>
<td>10</td>
<td>90</td>
<td>15</td>
<td>70</td>
<td>Middle</td>
<td>Sport</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>29</td>
<td>1</td>
<td>17</td>
<td>42</td>
<td>Pain</td>
<td>5</td>
<td>90</td>
<td>5</td>
<td>85</td>
<td>Index</td>
<td>Traffic accident</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>30</td>
<td>5</td>
<td>20</td>
<td>55</td>
<td>None</td>
<td>7</td>
<td>80</td>
<td>0</td>
<td>90</td>
<td>Small</td>
<td>Fall</td>
</tr>
</tbody>
</table>

Considering the cause of injury, four (50%) patients developed fracture-dislocations in the PIP joint during sports activities, two (25%) patients due to traffic accidents, and two (25%) of them as a result of falling. Complications that develop during the postoperative follow-up of the patients are moderate pain in two patients (25%), limitation of movement in the DIP and PIP joints in two (25%) patients, and pin-track infection in one (12.5%) of them.

The mean range of motion of the PIP joint of patients examined in the postoperative 12th month was 4.88° to 86.25° (range: 0-10° and 80-90°) (Figure 3). In the same time period, the mean range of motion of the DIP joint of the patients was 4.38° to 86.25° (range: 0-15° and 70-100°) (Figure 3).

Figure 3: The final follow-up evaluation of the patient (A, B). The anteroposterior and lateral radiographs of the patient (C, D)
DISCUSSION

This study discussed the results of the operations performed with pins and rubber traction frame in a total of 8 patients with fractures in their phalanges with comminuted fracture-dislocations. Patients could use their fingers with pins and rubber traction frame functionally after the follow-up period. The functional and clinical results of patients obtained in our study were excellent and good, except for two patients with limitation of movement in the DIP and PIP joints.

It is necessary to carefully evaluate whether there are rotational deformity and angulation in the comminuted fracture-dislocations of the phalangeal joints. The fingers are flexed to assess the rotational deformity. Overlapping or rotational asymmetry of nails is also investigated. The full lateral radiograph is examined to evaluate the angulation. If there is excessive angulation, tendon injury should be considered (11).

The aim of treatment in the comminuted fracture-dislocations of the phalangeal joints is to provide stable reduction that allows early motion. In addition, joint cartilage integrity should be ensured in these fractures, and arthritis development should be prevented. Moreover, conservative methods are insufficient to provide stability in these fractures.

ORIF should be considered in unstable PIP joint fracture-dislocations if the displacement in the fracture fragment is more than 2 mm or if the piece is large enough to carry the mini-screw (12). However, open reduction is challenging in some fractures that may be difficult to fix with open surgery. They should be securely treated; for this purpose, it would be wiser to maintain the length by applying external fixators.

More popular among percutaneous applications are external fixators prepared with Kirschner wires. Different application methods have been described in the literature (10, 13-15). Inanami et al.(16) described a small dynamic external fixator consisting of two parallel apparatuses with two pulleys at both ends and a center pulley. They reported that they obtain optimal results with no complications. They stated that the final PIP joint range of motion was 88°. Bain et al. (17) and Krakauer and Stern.(18) reported that the hinge was able to restore range of motion almost fully. However, they stated that many complications were encountered.
Skoff (19) described a device composed of two K-wires. He reported that the patient achieved a final range of motion of 115° with this device. Agee (20, 21) described a new technique using three K-wires and was activated by a single rubber band. The pins and rubber traction frame have a significant contribution to stability and are simple to use. The traction frame used in this study is prepared using K-wires and rubber bands (10). Other advantages are that it can be easily applied under fluoroscopy, does not interfere with control graphs, and allows early active movement.

Badia et al. (22) treated six patients with fracture-dislocations of the PIP joint with a simple dynamic fixator method. They stated that they achieved the reduction in all patients and that the mean range of motion of the PIP joint at the concluding follow-up evaluation was 5° to 89° (range, 0° to 100°). Cardoso and Li (23) operated on two patients with comminuted proximal phalanx fractures and achieved excellent results. Kiral et al. (24) performed on 33 patients with the pins and rubber traction frame in their study. They stated that they achieved satisfactory results. Nanno et al. (25) operated on 39 patients with this technique in their research. They reported that they achieved good results in their study. In our study, we obtained satisfactory results clinically and functionally.

Suzuki et al. (10) treated seven patients for phalangeal fractures. They reported that the final active motion of the injured DIP joint in one patient was from 0 to 40° of flexion. Badia et al. (22) said that one of the six patients had some stiffness in the DIP joint. Cardoso et al. (23) operated on a 50-year-old right-hand dominant female patient. They stated that she showed a pain-free active range of motion of 0 to 75 and 0 to 68 degrees in the MP and PIP joints postoperatively. In our study, two patients had some stiffness in the DIP and PIP joints after the follow-up period.

Our study has some limitations. These limitations are a relatively small sample size, a retrospective design study, and a relatively short follow-up period. Studies with a larger sample size and long-term follow-up period are required to obtain detailed findings.

In conclusion, our study demonstrated promising clinical results with the pins and rubber traction frame for fracture-dislocations and comminuted intraarticular fractures of the PIP joint. This study has demonstrated that the pins and rubber traction frame successfully treated various complicated intra-articular fractures. This technique provided both anatomical reduction and stable fixation. It also prevented joint stiffness by allowing early motion. The pins and rubber traction frame is a method that can be used safely and effectively in fractures of the phalanx joints that are difficult, comminuted, and involving the joint.

Declarations
The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

A written informed consent was obtained from each patient. The study protocol was approved by the Erzurum BEAH KAEK Ethics Committee (No: 2021/01-15 Date: 04.01.2021). The study was conducted in accordance with the principles of the Declaration of Helsinki.

References
Antioxidant Efficacy of Hypericum Perforatum L. on 7,12-Dimethylbenzanthracene-Applied Rat Tongue Tissues

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Abstract

Background: Hypericum species have chemopreventive and antioxidant effects which have been described in the past. However, Hypericum perforatum L. extract has not been the subject of any in vivo chemoprevention studies. The purpose of this study was to investigate the effects of H. perforatum L. extract on the oxidant-antioxidant system in 7,12-dimethylbenzanthracene applied tongue tissues of rats.

Methods: Thirty male Wistar rats were divided into four groups. Control group: only paraffin, DMBA group: only 7,12-dimethylbenzanthracene, HP+DMBA group: 7,12-dimethylbenzanthracene and H. perforatum L. extract and HP group: only H. perforatum L. extract application to the oral mucosa. After a 16-week study period, animals were sacrificed and tongue samples were taken. Superoxide dismutase, catalase, glutathione peroxidase enzyme activities, and malondialdehyde and total antioxidant status levels were measured.

Results: HP+DMBA group revealed significant differences with regard to catalase and superoxide dismutase enzymes compared to control, DMBA and HP groups (Catalase: p = 0.019, 0.019, 0.000, respectively; Superoxide dismutase: p = 0.001, 0.012, 0.009, respectively). Parallel to this data, total antioxidant status value in the same group was decreased with regard to other groups. Glutathione peroxidase enzyme activity and malondialdehyde levels did not demonstrate any significant differences among groups.

Conclusions: H. perforatum L. extract did not reveal any significant evidence that indicates an antioxidant effect. Moreover, antioxidant enzymes (catalase and superoxide dismutase) were believed to be suppressed by a by-product of H. perforatum L. and 7,12-dimethylbenzanthracene reaction in the HP+DMBA group.

Key words: Antioxidants, Carcinogen, Hypericum.

INTRODUCTION

Free radicals are highly reactive and unstable molecules that have unpaired electrons. Reactive oxygen species (ROS) are by-products of the mitochondrial electron transport chain. Under normal circumstances, hazardous effects of ROS are balanced with non-enzymatic and enzymatic antioxidants in the human body. However, excessive production of ROS or any kind of defect affecting the antioxidant defense mechanisms result in oxidative stress increase in tissues and cells. It is widely known that the oxidative stress caused by free radicals and ROS plays an important role in many pathophysiological conditions including cancer (1-3).

Oral cancer is the eighth most commonly encountered cancer around the world and it may be considered a serious public health problem due to its high morbidity and mortality rates (3, 4). Recently, antioxidant agents such as natural products, herbs and medical supplements have been subject to many studies in order to discover alternative solutions to various health problems. It has been reported that plant-derived chemical compounds and products may be used as chemopreventive agents by inhibiting the initiation and progression phases of carcinogenesis. Chemopreventive agents are believed to suppress cancer formation through inhibition of ROS formation and strengthening the antioxidant defense mechanisms (4-6).

Hypericum perforatum L., also known as St. John’s Wort, has been used in different cultures as traditional medicine for decades against various health conditions. It has been reported to have wound healing, anti-inflammatory, antibacterial, antimicrobial, antiviral, antifungal, anti-proliferative, antioxidant, antidepressant, antimalarial, antineoplastic and analgesic properties (7-13). It contains various compounds including flavonoids and proanthocyanidins, which are believed to be responsible for its antioxidant effects (8, 9).

7,12-dimethylbenzanthracene (DMBA) is a procarcinogen that exerts its effect by causing excess production of ROS and damaging the antioxidant defense mechanisms. It has been used in many animal studies in order to evaluate the chemopreventive potential of natural and synthetic products (6, 14-16).

The purpose of this study was to determine the effects of H. perforatum L. on the oxidant-antioxidant system in tongue tissues of rats that have been exposed to DMBA through oral mucosa.

MATERIALS AND METHODS

This study was approved by Gazi University Local Ethics Committee for Animal Experiments (G.Ü.ET-17.033).

Plant Material

The aerial parts of H. perforatum L. was collected in May-June 2017 during the blossoming period of plants. The plant samples were dried in room temperature and minced. The air-dried powdered plant samples were used to obtain an ethanolic extract of H. perforatum L. The crude extracts were diluted with glycerol to obtain 10 mg/ml H. perforatum L. extract. The extract solutions were stored in dark glass bottles at +4°C.

Carcinogenic material

DMBA (Sigma-Aldrich, Milwaukee, WI, USA) was used in order to induce oxidative stress in the tissues. It was prepared according to previous research protocols and diluted with liquid paraffin to 0.5% (w/v). The solution was stored in dark glass bottles at room temperature.

Animals and Experimental Design

Thirty male Wistar rats were used for the experiment. All rats were randomly divided into four groups as 6 rats in the control group and 8 rats in each of the other three groups. Liquid paraffin was applied to oral mucosa of the control group animals three days of the week (Monday, Wednesday, Friday). DMBA group received 0.5% DMBA in liquid paraffin application to the oral mucosa three times a week (Monday, Wednesday, Friday). HP+DMBA group received H. perforatum L. extract application twice a week (Tuesday, Thursday) and 0.5% DMBA in liquid paraffin application three times a week (Monday, Wednesday, Friday). HP group only received H. perforatum L. extract application twice a week (Tuesday, Thursday).

The animals were housed in propylene cages under controlled conditions of room temperature, humidity and a 12h light/dark cycle. All animals were provided with standard pellet diet and water ad libitum. All groups received 16 weeks of treatment and were sacrificed at the end of the experimental period. Tongue tissues were excised totally and stored at -80°C until used for analyses.

Biochemical analyses

All tissue samples were homogenized in physiological saline solution (20% w/v). After centrifugation of the homogenate at 5000 rpm for 30 minutes, upper clear supernatants were collected to be used in the analyses. All samples were analyzed in order to measure superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) enzyme activities and malondialdehyde (MDA) and total antioxidant status (TAS) levels.

SOD activity was measured with a method based on nitro blue tetrazolium (NBT) reduction rate. SOD activity was expressed as the amount of enzyme protein causing 50% inhibition in the reduction rate of NBT (17, 18). CAT activity was determined by measuring the absorbance of H$_2$O$_2$.
decrease at 240 nm (19). GSH-Px activity was measured by monitoring changes in NADPH absorbance at 340 nm (20). SOD activity was expressed in U/mg protein, and CAT and GSH-Px activities were expressed in IU/mg protein. MDA method is based on the absorbance measurement of thiobarbituric acid–malondialdehyde complex formation (21). TAS levels were measured with Rel Assay Total Antioxidant Status Test Kit (Mega Tıp San. ve Tic. Ltd. Şti., Gaziantep, Turkey) according to the manufacturer’s instructions. Protein amount was measured according to the Lowry method (22).

**Statistical analyses**

Data were analyzed using SPSS 11.5 software. Normally distributed values were expressed as mean ± standard deviation (SD), if not normally distributed, as median (min-max). In order to determine whether there was a statistically significant difference between the categories of a qualitative variable with three or more categories in terms of quantitative variables, one way Analysis of Variance (ANOVA) was used if normal distribution assumptions were met; if not, Kruskall-Wallis test was used. Post-hoc Tukey test was used with ANOVA in order to determine which group causes the significant difference. Bonferroni adjusted Mann-Whitney U test was used with Kruskall-Wallis variance analysis when determining which group causes the difference. The significance level was determined as p<0.05.

**RESULTS**

CAT, SOD and GSH-Px enzyme activities and MDA and TAS levels were measured in the tongue tissue samples. All measurement values are as shown in Table 1. CAT and SOD enzyme activities were found to be significantly lower in HP+DMBA group compared to the control, DMBA and HP groups (CAT: p = 0.019, 0.019, 0.000, respectively; SOD: p = 0.001, 0.012, 0.009, respectively). GSH-Px enzyme activity was also lower than all the other groups in the HP+DMBA group; however, the difference was not statistically significant. MDA levels also revealed lower values in the HP+DMBA group with respect to all the other groups, which was not statistically significant. HP+DMBA group demonstrated significantly lower TAS levels in comparison to the control group (p = 0.004).

**Table 1: CAT (IU/mg), SOD (U/mg), GSH-Px (mIU/mg) enzyme activities and MDA (nmol/mg) and TAS (µmol Trolox eq/L) levels for rat tongue tissue samples**

<table>
<thead>
<tr>
<th></th>
<th>CAT Median (min-max)</th>
<th>SOD Median (min-max)</th>
<th>GSH-Px Mean±SD</th>
<th>MDA Mean±SD</th>
<th>TAS Median (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=6)</td>
<td>12.17 (11.04-23.04)</td>
<td>3.76 (3.17-4.96)</td>
<td>36.83±12.91</td>
<td>1.42±0.53</td>
<td>0.27 (0.22-0.32)</td>
</tr>
<tr>
<td>DMBA (n=8)</td>
<td>12.47 (10.77-16.89)</td>
<td>3.37 (2.77-3.79)</td>
<td>32.13±2.10</td>
<td>1.18±0.15</td>
<td>0.23 (0.21-0.28)</td>
</tr>
<tr>
<td>HP+DMBA (n=8)</td>
<td>5.00 (4.05-7.14)</td>
<td>2.42 (2.14-2.65)</td>
<td>28.87±4.64</td>
<td>0.96±0.13</td>
<td>0.18 (0.15-0.24)</td>
</tr>
<tr>
<td>HP (n=8)</td>
<td>13.92 (11.51-24.09)</td>
<td>3.23 (2.85-4.93)</td>
<td>34.25±8.48</td>
<td>1.36±0.47</td>
<td>0.21 (0.19-0.37)</td>
</tr>
</tbody>
</table>

Statistical analysis

Multiple comparison (p values)  <0.001  <0.001  0.272  0.077  0.006

Bonferroni adjusted Mann-Whitney U test

<table>
<thead>
<tr>
<th></th>
<th>P</th>
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<tbody>
<tr>
<td>Control vs DMBA</td>
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<td>1.0</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control vs HP+DMBA</td>
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<td>0.001</td>
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<tr>
<td>Control vs HP</td>
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<tr>
<td>DMBA vs HP+DMBA</td>
<td>0.019</td>
<td>0.012</td>
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<tr>
<td>DMBA vs HP</td>
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<td>1.0</td>
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<tr>
<td>HP+DMBA vs HP</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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Statistical analysis

Multiple comparison (p values)  <0.001  <0.001  0.272  0.077  0.006

Bonferroni adjusted Mann-Whitney U test

<table>
<thead>
<tr>
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</tr>
</thead>
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<tr>
<td>Control vs DMBA</td>
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<td>1.0</td>
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<tr>
<td>Control vs HP+DMBA</td>
<td>0.019</td>
<td>0.001</td>
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<td></td>
</tr>
<tr>
<td>Control vs HP</td>
<td>1.0</td>
<td>1.0</td>
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</tr>
<tr>
<td>DMBA vs HP+DMBA</td>
<td>0.019</td>
<td>0.012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMBA vs HP</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HP+DMBA vs HP</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
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</tbody>
</table>
DISCUSSION

Recently, many researchers have focused on prevention of cancer, natural product and plant or herb usage in order to provide alternative management strategies against various diseases and the biological properties (antioxidant, antibacterial, antiviral, antineoplastic etc.) of various plants (3, 10, 11, 23). Chemoprevention is a novel and promising method used in experimental oncology in order to interfere with the cancer formation process using non-cytotoxic natural or synthetic agents. Chemopreventive agents are believed to function by either inhibiting the metabolic activation of carcinogens or increasing the detoxification of the metabolic residue during cancer formation, which may eventually suppress, inhibit, suspend or reverse the cancer formation process. Moreover, they may also inhibit excessive production of ROS and support the antioxidant defense mechanisms (6).

Increase in ROS production and thus oxidative stress is known to have negative effects on the endogenous antioxidants. In order to support the radical scavenging activity against oxidative stress exogenous antioxidants have been subject to many studies (24-26). Various plant-derived chemicals such as polyphenols, flavonoids and terpenes are known to have antioxidant properties (7, 27, 28). H. perforatum L. extract used in this study contains various compounds that exert in vitro antioxidant activity (29, 30).

DMBA is a carcinogen that promotes cancer formation through ROS production (14). MDA (or TBARS) is a lipid peroxidation marker used as an indicator of oxidation or oxidative stress (31). MDA level was lower in the HP+DMBA group compared to the other groups; however, the difference was not significant.

This study did not reveal any significant data with regard to the antioxidant activity of H. perforatum L. in rat tongue tissues. Inhibition of antioxidant enzyme activities (CAT, SOD) was observed when H. perforatum L. was applied together with DMBA. Further studies are needed in order to clarify the mechanism behind the inhibition of enzyme activities and the in vivo antioxidant potential of H. perforatum L.

Acknowledgements

We acknowledge Prof. Aysel Uğur and Assoc. Prof. Nurdan Saraç for their contributions about extract preparation.

Declarations

This study was funded by Gazi University, Projects of Scientific Investigation Unit (03/2017-15). There is no conflict of interest.

References


Are Patients With Diabetes Mellitus at Increased Risk of COVID-19 Infection?

Mehmet Sözen1* Fatma Çölkesen2* Melia Karaköse4 İbrahim Erayman5 Soner Demirbaş6 Turgut Teke6

Abstract

Background: The aim of this study was to examine the clinical course and outcomes of patients with diabetes mellitus (DM) with coronavirus disease-2019 (COVID-19).

Methods: This retrospective, single-center study included 185 adult patients diagnosed with COVID-19. All patients were separated into 4 groups. Group 1 (n=79): patients with no accompanying disease, Group 2 (n=14): patients with only DM, Group 3 (n=31): patients with comorbid disease(s) including DM, Group 4 (n=61): patients with comorbid disease(s) without DM. Data about COVID-19 management and outcome were obtained from the medical records of the patients. COVID-19 was confirmed by real-time polymerase chain reaction (RT-PCR) from throat swab samples. All patients underwent chest x-rays or chest computed tomography.

Results: 185 patients diagnosed with COVID-19 were evaluated. The COVID-19 prognoses of the patients were classified as good, moderate and poor. No statistically significant difference was determined between the groups in terms of COVID-19 prognosis (p>0.05). While the rate of DM patients with a good prognosis was 20.4%, the DM patient rate increased up to 40% among moderate or poor prognosis patients. A statistically significant difference was observed between blood glucose levels and mortality (p: 0.008). Mortality due to COVID-19 pneumonia developed in 15 (8.1%) patients. Mortality increase was mostly encountered in the group with DM and accompanying comorbidities. It was observed that ACEI / ARB use had no effect on mortality.

Conclusions: Although the study results do not show a statistically significant effect of DM on the prognosis of COVID-19 patients, the higher rate of DM patients in the group with poor prognosis suggests that it may affect the severity of COVID-19. These results may be useful for clinicians in the management of DM patients with COVID-19.

Key words: Diabetes Mellitus, Coronavirus, COVID-19, Prognosis, Mortality.

*Mehmet Sözen and Fatma Çölkesen contributed equally to this work

INTRODUCTION

Coronaviruses (CoV) are single-stranded, enveloped ribonucleic acid viruses that cause respiratory infections in humans (1). The coronavirus disease-2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus spread rapidly worldwide and was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 (2).

Diabetes mellitus (DM) is becoming an increasing health problem worldwide and is recognized as one of the major risk factors for various infections and serious infection-related deaths. DM worsens the prognosis of infectious diseases, and these patients show increased morbidity and mortality rates for infection-related sepsis compared to the general population (3). Moreover, DM has recently been reported to be an important risk factor for mortality in patients infected with influenza A (H1N1) and coronavirus-associated Middle East respiratory syndrome (MERS-CoV) (4,5).

Evidence from epidemiological studies in areas severely affected by SARS-CoV-2 and data from the Centers for Disease Control and Prevention (CDC) and other national health centers and hospitals suggest that death rates from COVID-19 are up to 50% higher in individuals with DM than those who do not have DM (6). There are several hypotheses that explain the higher incidence of COVID-19 infection in people with DM. In general, people with DM are at an increased risk of infection due to innate phagocytosis, neutrophil chemotaxis, and defects affecting cell-mediated immunity. However, the high prevalence of DM in severe cases of COVID-19 could probably be associated with higher prevalence of DM in the elderly. Moreover, advanced age DM is associated with cardiovascular disease, which may also help explain the association with the fatal consequences of COVID-19 (7).

In this context, it has been suggested by many health authorities that DM should be in the group of high-risk diseases for COVID-19. However, there is still insufficient reliable data on DM characteristics in patients hospitalized due to COVID-19 (8). In this single-center retrospective study of 185 confirmed COVID-19 cases, the relationship between DM and clinical outcomes and mortality in COVID-19 patients were evaluated.

MATERIALS AND METHODS

This retrospective, single-center study included patients who presented at Necmettin Erbakan University, Meram Faculty of Medicine Hospital, Konya, Turkey, between March 15, 2020 and July 15, 2020, and were diagnosed with COVID-19 according to the WHO interim guidance. According to the pandemic measures implemented by the Turkish Government, adult patients were admitted centrally to the hospital from the whole province of Konya without selectivity. All patients included in the study were hospitalized and treated. All the data regarding the patients in this study have been shared with the Ministry of Health. The epidemiological, demographic, clinical, laboratory, management, and outcome data were obtained from the patient medical records. If data were missing from the records or clarification was needed, the attending doctors and other healthcare providers were contacted directly.

Nasal and throat swab specimens from the upper respiratory tract were obtained from all patients on admission and maintained in viral-transport medium. COVID-19 was confirmed with real-time polymerase chain reaction (RT-PCR). Sputum or endotracheal aspirates were obtained on admission for the identification of possible causative bacteria or fungi. All patients were applied with chest x-rays or chest computed tomography (CT). According to the United States National Institutes of Health COVID-19 Treatment Guidelines, the prognosis of COVID-19 disease is divided into three groups as mild, moderate, or severe (9).

Ethical Approval: The study was approved by the Local Ethics Committee of Necmettin Erbakan University, Meram Faculty of Medicine (decision no: 2020/2664) and the study was conducted according to the Declaration of Helsinki, 1975.

Statistical analysis

Statistical evaluations were made using IBM SPSS 20.0 software (IBM Corp., Armonk, NY, USA). Conformity of the data to normal distribution was evaluated with the Shapiro Wilk Test. Normally distributed numerical variables were stated as mean ± standard deviation, non-normally distributed numerical variables as median (25th-75th percentile) values, and categorical variables as frequency (%). Differences between groups were
determined using t-test for numerical variables with normal distribution, Mann Whitney U test for numerical variables without normal distribution, Kruskal Wallis test, One-Way Variance analysis and Dunn’s multiple comparison test, and Fisher chi-square test for categorical variables, together with Yates chi-square, Pearson Chi-square and the Monte Carlo chi-square test. Relationships between variables were determined using Spearman Correlation Analysis. For testing two-sided hypotheses, a value of p<0.05 was considered statistically significant.

RESULTS

185 patients with COVID-19 were evaluated. The patients were divided into 4 groups; Group 1 (n=79): patients with no accompanying disease, Group 2 (n=14): patients with only DM, Group 3 (n=31): patients with comorbid disease(s) including DM; Group 4 (n=61): patients with comorbid disease(s) without DM. None of the patients were medical staff. The chronic diseases of patients in Group 4 included cardiovascular, cerebrovascular, endocrine system, digestive system, respiratory system and nervous system diseases, and malignant tumours (Table 1).

Table 1: Numerical data of the patients enrolled in the study.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>Count</td>
<td>Count</td>
<td>Count</td>
<td>Count</td>
</tr>
<tr>
<td>Female</td>
<td>36</td>
<td>5</td>
<td>20</td>
<td>36</td>
<td>97</td>
</tr>
<tr>
<td>%</td>
<td>45.6%</td>
<td>35.7%</td>
<td>64.5%</td>
<td>59.7%</td>
<td>52.7%</td>
</tr>
<tr>
<td>Male</td>
<td>43</td>
<td>9</td>
<td>11</td>
<td>25</td>
<td>88</td>
</tr>
<tr>
<td>%</td>
<td>54.4%</td>
<td>64.3%</td>
<td>35.5%</td>
<td>40.3%</td>
<td>47.3%</td>
</tr>
<tr>
<td>Total</td>
<td>79</td>
<td>14</td>
<td>31</td>
<td>61</td>
<td>185</td>
</tr>
<tr>
<td>%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

The median (25th-75th percentile) age of the groups was; Group 1: 57 years (39.00-66.00), Group 2: 54.50 years (49.00-66.75), Group 3: 65 years (59-75), Group 4: 62.50 years (54.75-59.00). A statistically significant difference was observed between Group 1 and Group 3 considering median age (p<0.001) and there was no difference between the other groups.

When the HbA1c and fasting plasma glucose (FPG) levels of the patients with DM (Groups 2 and 3) were compared with each other, no statistically significant difference was found between the two groups (p>0.05). All patients’ DM was similarly regulated. All patients included in the study were hospitalized and followed up. The COVID-19 prognosis of the patients was classified as mild, moderate, or severe. There was no statistical difference between the four groups in terms of COVID-19 prognosis (Table 2).

Table 2: COVID-19 prognosis of the patients.

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total</th>
<th>pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>63 (79.7%)</td>
<td>11 (78.6%)</td>
<td>18 (58.1%)</td>
<td>50 (82.0%)</td>
<td>142 (76.8%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Moderate</td>
<td>4 (5.1%)</td>
<td>1 (7.1%)</td>
<td>1 (3.2%)</td>
<td>2 (3.3%)</td>
<td>8 (4.3%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Severe</td>
<td>12 (15.2%)</td>
<td>2 (14.3%)</td>
<td>12 (38.7%)</td>
<td>9 (14.8%)</td>
<td>35 (18.9%)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

When all the DM patients (Groups 2 and 3) were compared with other COVID-19 positive patients (Groups 1 and 4) in terms of prognosis, there was no statistically significant difference between the groups (p=0.064). In the subgroup analyses, the majority of patients with a good prognosis (79.6%) were non-DM patients. While the rate of DM patients with a good prognosis was 20.4%, the DM patient rate increased up to 40% among moderate or poor prognosis patients (Table 3).
Of all the patients included in the study, 167 were discharged from the hospital. Of these, 75 had a negative COVID-19 PCR result at the time of discharge, and the remaining patients were discharged with instructions to continue isolation at home. Hospitalization of 3 patients continued, and mortality developed in 15 (8.1%) due to COVID-19 pneumonia. Only 3 of the patients who died had no history of chronic disease. The remaining 12 patients had at least one chronic disease. Mortality was mostly observed in the group including patients with DM and comorbid diseases (Group 3). Mortality did not occur in any of the 14 patients (Group 2) with only DM (Table 4).

### Table 3: COVID-19 prognosis of the DM and non-DM patients.

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Group 2+3</th>
<th>Group 1+4</th>
<th>Total</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>29 (20.4%)</td>
<td>113 (79.6%)</td>
<td>142 (100.0%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (25.0%)</td>
<td>6 (75.0%)</td>
<td>8 (100.0%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Severe</td>
<td>14 (40.0%)</td>
<td>21 (60.0%)</td>
<td>35 (100.0%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total</td>
<td>45 (24.3%)</td>
<td>140 (75.7%)</td>
<td>185 (100.0%)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Considering the final status of the patients, a statistically significant difference was observed between blood glucose levels and mortality. The median blood glucose level of the patients who died was statistically significantly higher than that of patients who were discharged (p=0.008).

When the effect of angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) on COVID-19 prognosis was evaluated, no significant negative effect was observed (p>0.05) (Table 5). No significant difference was observed between surviving and exitus patients considering the ACEI/ARB usage rate (p=0.102) (Table 6).

### Table 4: The condition of the patients enrolled in the study after treatment.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged</td>
<td>1 (1.3%)</td>
<td>1 (7.1%)</td>
<td>1 (3.2%)</td>
<td>0 (0.0%)</td>
<td>3 (1.6%)</td>
</tr>
<tr>
<td>PCR (-) discharge</td>
<td>38 (48.1%)</td>
<td>8 (57.1%)</td>
<td>14 (45.2%)</td>
<td>32 (53.2%)</td>
<td>92 (50.0%)</td>
</tr>
<tr>
<td>Exitus</td>
<td>3 (3.8%)</td>
<td>0 (0.0%)</td>
<td>8 (25.8%)</td>
<td>4 (6.5%)</td>
<td>15 (8.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>79 (100.0%)</td>
<td>14 (100.0%)</td>
<td>31 (100.0%)</td>
<td>61 (100.0%)</td>
<td>185 (100.0%)</td>
</tr>
</tbody>
</table>

### Table 5: The effect of drug use on disease prognosis.

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI / ARB users</td>
<td>31 (77.5%)</td>
<td>1 (2.5%)</td>
<td>8 (20.0%)</td>
<td>40 (100.0%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Drug free</td>
<td>68 (78.2%)</td>
<td>5 (5.7%)</td>
<td>14 (16.1%)</td>
<td>87 (100.0%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Other drugs</td>
<td>43 (74.1%)</td>
<td>2 (3.4%)</td>
<td>13 (22.4%)</td>
<td>58 (100.0%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total</td>
<td>142 (76.7%)</td>
<td>8 (4.3%)</td>
<td>35 (18.9%)</td>
<td>185 (100.0%)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>
DISCUSSION

Diabetes mellitus (DM) is one of the leading causes of mortality and morbidity worldwide and is expected to increase significantly in the coming years. DM is associated with a variety of vascular, cardiac, and renal complications that affect the overall survival of patients, and patients with DM are generally more susceptible to infections (10). Infectious diseases such as influenza and pneumonia are very common among elderly diabetic patients. In previous studies, DM has been shown to be a risk factor for the mortality and morbidity of many viral infections, including H1N1, MERS-CoV and SARS-CoV (10,11).

In this retrospective cohort study, data from 185 patients with COVID-19 were analyzed, including 45 patients with DM and 140 patients without DM. Age distribution of the patients was compared among the four groups. It was observed that patients with comorbid diseases were older than others. Patients with DM and comorbidity in particular constituted the oldest population. It is well known that the incidence of DM increases with aging, and some studies have shown that old age is one of the most important risk factors affecting the prognosis of COVID-19 (12). Therefore, a poor clinical outcome may be predicted for a large proportion of diabetic elderly patients.

In a study evaluating the severity of COVID-19 in DM patients, Wu et al. found a higher rate of diabetes in severe cases of COVID-19 compared to mild cases (13). Similarly, in another study, COVID-19 patients with DM were more likely to develop severe or critical illnesses. In addition, these patients had a greater need for invasive or non-invasive mechanical ventilation and higher mortality rates (14). In a study by Liu et al., the percentage of patients with diabetes among the severe and critical COVID-19 cases among 1880 COVID-19 patients was higher than mild or moderate cases. However, there was no difference between the patients with and without DM during the follow-up period. Similar mortality rates were found in patients with or without DM (2.9% (n = 4) and 1.1% (n = 9), respectively (p=0.114)) (15). In the current study, no statistically significant difference was determined between the four groups in terms of COVID-19 prognosis, which is consistent with some data in the literature. However, when all DM patients were compared to those without DM, worse prognoses were mostly encountered in DM patients. This may partly explain the higher proportion of severe or critical COVID-19 cases in the groups with DM than in the groups without DM.

Recent studies have revealed that DM is one of the most common comorbidities in COVID-19 infection (16). Furthermore, some studies have suggested that COVID-19 patients with DM have a higher risk of death during infection (16,17). In a study of 1382 patients by Roncon et al., higher rates of intensive care unit admission and a higher risk of mortality were reported in DM COVID-19 patients (18). In another study reporting 1880 COVID-19 patients, the mortality rate of patients with and without DM was 2.9% (n = 4) and 1.1% (n = 9), respectively (p=0.114) (15). The mortality rates in the current study were found to increase with accompanying comorbid diseases. The highest mortality rate was observed in the patient group with comorbid disease(s) including DM. These data support many studies in the literature reporting increase in severity and mortality rates for COVID-19 patients who have DM.

ACEI and ARB drugs are recommended by the National Institute for Health and Care Excellence as first-line treatment for patients under 55 years of age with hypertension, as second-line treatment for those over 55 years of age and for those of African descent (19). However, the use of ACEI and ARB in COVID-19 patients has caused great debate because ACE-2 is a surface receptor

### Table 6: The effect of drug use on mortality.

<table>
<thead>
<tr>
<th></th>
<th>Exitus</th>
<th>Surviving</th>
<th>Total</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI / ARB users</td>
<td>6 (15%)</td>
<td>34 (75%)</td>
<td>40 (100.0%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Other drugs</td>
<td>9 (6.2%)</td>
<td>136 (93.8%)</td>
<td>145 (100.0%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total</td>
<td>15 (8.1%)</td>
<td>170 (91.9%)</td>
<td>185 (100.0%)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>
for SARS-CoV-2 (20). Previous research has shown that SARS-CoV-2 binds to ACE-2 enzyme at low cytosolic pH values, entering the cell and causing infection (21). Angiotensin II has a strong pH alkaline effect, which causes alkalinization in the environment pH even after strong acid loading (22). ACEIs and ARBs lead to a reduction in angiotensin II level by increasing the ACE2 level, thereby causing a low cytosolic pH (21). The presence of ACE2 in many organs such as the cardiovascular system, lungs, kidneys and brain may explain why some COVID-19 patients die from multiple organ failure (23). It has been suggested that the mortality and morbidity rates would be higher in COVID-19 patients with DM if they were using ACEI and ARB (21).

In a cohort study including 19486 patients with COVID-19 disease in the United Kingdom, ACEI were associated with a significantly reduced risk of COVID-19 disease. In the same study, no increase was found in the risk of intensive care unit hospitalization. There were significant interactions between ethnicity and ACEI and ARB use for risk of COVID-19 disease. The risk of COVID-19 disease associated with ACEI use was higher in Caribbean and Black African groups than the white group. A higher risk of COVID-19 associated with ARB was observed for Black African group compared to the white group (24). In a multicenter retrospective study of 1128 adult patients with hypertension diagnosed with COVID-19, the results consistently demonstrated a lower risk of COVID-19 mortality in patients who received ACEI/ARB than those who did not receive ACEI/ARB (25). Conversely, in another study there was no evidence of a reduced risk of results in patients taking ACEI and ARB medications (26). In the current study, the prescription of ACEI and ARB drugs was not determined to have a significant effect on mortality. However, the prognosis for COVID-19 was significantly better in ACEI/ARB users.

A few limitations of this study should be addressed. First, the retrospective, non-randomized design led to sample heterogeneity. Second, although maintaining blood glucose regulation can affect the clinical course and outcome of COVID-19, there was insufficient analysis of the data on anti-DM treatment. Third, the relative mechanism behind the impact of diabetes on COVID-19 was not examined in this study. Fourth, the clinical outcome data includes data of patients within a specified period after hospitalization. The absence of data of the hospitalized patients at the end of the pre-defined study period may have affected the findings, including mortality rates. Finally, the difference in disease progression and prognosis between COVID-19 patients with or without DM may change with a longer follow-up period.

In conclusion, whether DM significantly affects the prognosis of COVID-19 is still a matter of debate. The results of this study showed that DM had no significant effect on the prognosis of COVID-19, but the increased rate of DM patients in the poor prognosis group suggests that it may be related to the severity of the disease. This study may assist clinicians in managing COVID-19 patients with DM. However, prospective studies with larger patient populations will more clearly reveal the impact of DM on COVID-19 prognosis.

Declarations
The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

References


The Predictive Role of the CHADS-VASc Score on Reduced Left Ventricular Ejection Fraction in Patients with Acute Coronary Syndrome

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Abstract

**Background:** Reduced left ventricular systolic function is associated with significant mortality and morbidity in patients with the acute coronary syndrome (ACS). Predicting which patients may go on to develop heart failure (HF) with optimal treatment is thus likely to be effective in reducing mortality and morbidity. This study aims to evaluate the role of the CHA2DS2-VASc score in predicting reduced left ventricular ejection fraction (LVEF) in patients with ACS.

**Methods:** 202 patients diagnosed with the ACS participated in the study. Coronary angiography (CAG) was performed on all patients. The LVEF values of the patients before and three months after discharge were evaluated by transthoracic echocardiogram (TTE). Group 1 consisted of patients with LVEF values below 50% at the third month, while Group 2 consisted of those with LVEF values of 50% and above.

**Results:** The mean age of the patients was 62 ± 12 years, and 142 of the patients were male. The LVEF values in the third month were 55.58 ± 0.24 in Group 1 and 42.07 ± 0.86 in Group 2 (p<0.001). While the mean CHA2DS2-VASc score was 0.86 ± 0.78 in Group 1, it was 1.78 ± 0.87 in Group 2 (p<0.001). Multiple regression analysis showed that the CHA2DS2-VASc score had an independent relationship in predicting the LVEF values in patients with ACS (Odds ratio [OR] 3.179, 95% CI 1.972-5.124, p<0.001). CHA2DS2-VASc scores above 1.5 can be used as a predictor for decreased left ventricular systolic function in patients with ACS with 53% sensitivity and 80% specificity.

**Conclusion:** The CHA2DS2-VASc score is a simple and easy parameter that can be used to predict decreased and preserved left ventricular systolic functions in patients with ACS.

**Key words:** CHA2DS2-VASc Score, Ejection Fraction, Acute Coronary Syndrome.
INTRODUCTION

Cardiovascular disease is the leading cause of death in the elderly population worldwide. According to statistics from the American Heart Association (AHA) for 2015, approximately 300,000 recurrent ACS attacks occur annually (1).

The growing prevalences of hypertension (HT), kidney diseases and coronary artery disease (CAD) as age increases are risk factors for ACS and its complications (2). Although the frequency of complications such as free wall rupture, arrhythmias and pericarditis can be reduced with early diagnosis and treatment, congestive heart failure (CHF) is still accepted as an important complication. CHF developing as a result of ACS is associated with high mortality, and clinical pictures with edema, pulmonary congestion, and ventricular arrhythmias in both acute and chronic stages impair the quality of life (3).

Predicting the potential complications after ACS is likely to contribute greatly to the reduction of mortality rates. Although the CHA2DS2-VASc score was developed to predict cerebrovascular events in patients with atrial fibrillation, recent studies have shown that it can also be used in the evaluation of high-risk ACS patients (4). Impaired heart functions are associated with poor prognoses in patients with ACS (5). This study thus aimed to investigate the relationship between the left ventricular systolic function and CHA2DS2-VASc scores in patients with ACS.

MATERIALS AND METHODS

Study Population and Data Collection

This retrospective study examined data from 202 consecutive patients who were admitted to a single cardiology center with a diagnosis of ACS between January 2017 and December 2019. The diagnosis and treatment of ACS in the patients were made according to current guidelines (6). Coronary angiography (CAG) was performed in all patients. Before the procedure, transthoracic echocardiogram (TTE) and CHA2DS2-VASc scores were calculated.

Three months after discharge, control TTE was performed and LVEF values were calculated. Patients with LVEF values below 50% were designated as “Group 1”, while those with LVEF values of 50% and above were designated as “Group 2”.

Patients who were younger than 18 years of age, those with chronic renal failure, HF, previous CAD, active infections, malignant diseases, as well as those who had undergone coronary artery bypass surgery (CABG), who were scheduled for valve surgery, who had contraindications for coronary angiography, and who did not agree to participate in the study, were not included. The hemogram, CRP, whole blood, lipid panel, and kidney function tests of all patients were obtained from the patient files.

This study was approved by the local ethics committee of the hospital in which it took place in line with the recommendations of the Declaration of Helsinki (Decision no: 2020-14).

Definitions

Patients who were using antihypertensive drugs, and who had a systolic blood pressure equal to 140 mmHg or above and a diastolic blood pressure equal to 90 mmHg or above, were defined as high-blood-pressure patients. Patients who had fasting blood glucose levels equal to 126 mg/dL or above or who were using a drug for glucose regulation were defined as diabetes mellitus.

Coronary Angiography and Calculation of CHA2DS2-VASc Score

CAG was performed using the Judkins technique through the femoral or radial arteries. Coronary arteries were evaluated by analyzing images obtained from at least two different angles. Percutaneous coronary intervention (PCI) was performed using the standard technique. All of the PCIs were performed successfully. Points were allocated for each item specified for calculating the CHA2DS2-VASc score as follows: CHF (ejection fraction <40%) (1 point), HT (1 point), age ≥75 years (2 points), diabetes mellitus (1 point), stroke (2 points), vascular disease (peripheral artery disease or myocardial infarction) (1 point), age 65-74 (1 point) and gender (female) (1 point).
Echocardiographic examination

Echocardiography of the patients was performed by an independent cardiologist who did not have any information about the clinical characteristics of the patients. All the echocardiographic examinations were performed using a Philips EPIQ 7 Ultrasound Machine (Philips EPIQ 7 Cardiac Ultrasound, Bothell, WA, USA) and a 2.5 MHz probe. The LVEF values were calculated using the modified Simpson method as pre-discharge and third-month controls. TTE examinations were performed in accordance with the imaging guidelines recommended by the American and European Societies (8).

Statistical Analysis

The SPSS 21.0 (SPSS Inc, Chicago, IL, USA) program was used for statistical analysis. Whether the variables fitted normal or non-normal distribution was evaluated using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as percentages and numbers. The one-way ANOVA test was used for analysis of the normal distribution of parametric values between groups. The chi-square test was used to compare the odds ratios of categorical variables. Logistic regression analysis was performed to determine the effect of variables. 95% confidence intervals were calculated with standardized beta coefficients. The ROC curve was used to predict the CHA2DS2-VASc score for the left ventricular systolic function in patients with ACS. p<0.05 was considered statistically significant.

RESULTS

The basic clinical, echocardiographic, and laboratory values of the 202 patients are shown in Table 1. A total of 130 patients were diagnosed with ST-segment elevation myocardial infarction (STEMI), and 72 patients were diagnosed with non-ST segment elevation myocardial infarction (NSTEMI). According to the CAG results, 165 patients had single vessel disease, 30 patients had double vessel disease, and 7 patients had triple vessel disease. In addition, the culprit lesions were identified in the left anterior descending artery (LAD) in 69 patients, in the circumflex artery (Cx) in 78 patients, and in the right coronary artery (RCA) in 65 patients (Table 1).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n=157)</th>
<th>Group 2 (n=45)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.2±1</td>
<td>69±1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>38(24.2)</td>
<td>22(48.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>HT n (%)</td>
<td>78(49.7)</td>
<td>24(53.3)</td>
<td>0.666</td>
</tr>
<tr>
<td>DM n (%)</td>
<td>18(11.5)</td>
<td>12(26.7)</td>
<td>0.022</td>
</tr>
<tr>
<td>LVEF at admission %</td>
<td>55.58±0.24</td>
<td>42.07±0.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF at third month %</td>
<td>45.95±0.39</td>
<td>35.16±0.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker n (%)</td>
<td>104(66.2)</td>
<td>25(56.2)</td>
<td>0.254</td>
</tr>
<tr>
<td>Serum glucose mg/dL</td>
<td>136.66±1.70</td>
<td>176.07±14.42</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.88±0.01</td>
<td>0.95±0.02</td>
<td>0.010</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>138.87±0.22</td>
<td>139.93±0.57</td>
<td>0.045</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.28±0.03</td>
<td>4.78±0.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GFR, mL/min, median (IQR)</td>
<td>68(40)</td>
<td>94(34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>STEMI, n (%)</td>
<td>102(65)</td>
<td>28(62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NSTEMI, n (%)</td>
<td>55(35)</td>
<td>17(38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of coronary arteries narrowed, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>124(79)</td>
<td>41(91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>26(17)</td>
<td>4(9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>7(5)</td>
<td>0(0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Culprit lesion, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>58(84)</td>
<td>11(16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cx</td>
<td>59(76)</td>
<td>19(24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RCA</td>
<td>40(73)</td>
<td>15(42)</td>
<td>0.001</td>
</tr>
<tr>
<td>CHA2DS2-VASc score, median (IQR)</td>
<td>0.86±0.78</td>
<td>1.78±0.87</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

DM: Diabetes mellitus; HT: Hypertension; LVEF: Left ventricular ejection fraction; GFR: Glomerular filtration rate; STEMI: ST elevation myocardial infarction; NSTEMI: non-ST elevation myocardial infarction; LAD: Left anterior descending; Cx: Circumflex; RCA: Right coronary artery; CHA2DS2-VASc: Congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), and vascular disease, age 65-74 years, and sex category (female).
There was no statistically significant difference between the groups in terms of HT. In the group with LVEF values below 50%, more patients were diabetic or smokers. The CHA2DS2-VASc score values showed a statistically significant difference between the groups (p<0.001). While the mean LVEF value at the third month was 55.58 ± 0.24 in Group 1, it was 42.07 ± 0.86 in Group 2 (Table 1). In the univariate logistic regression analysis, a significant correlation was found between the CHA2DS2-VASc score and glucose values for the LVEF values below 50%. The results of the multivariate logistic regression analysis showed that there was a significant independent correlation between the CHA2DS2-VASc score and LVEF scores below 50% in the patients with ACS, unlike other parameters. (odds ratio: 3.179, 95% CI: 1.972-5.124, p<0.001; Table 2). The receiver operating characteristic (ROC) curve analysis revealed that when the CHA2DS2-VASc scores are higher than 1.5, LVEF values below 50% can be predicted in patients with ACS (p<0.001) (with 53% sensitivity and 80% specificity, 0.764 are under the curve 95% CI: 0.689-0.839) (Fig.1).

**Table 2. Univariate and multivariate regression analysis of predictors of reduced left ventricular ejection fraction**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p</td>
<td>OR</td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td>&lt;0.001</td>
<td>3.469</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>0.240</td>
<td>1.038</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.002</td>
<td>1.007</td>
</tr>
<tr>
<td>STEMI</td>
<td>0.735</td>
<td>0.888</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>0.735</td>
<td>1.126</td>
</tr>
<tr>
<td>1 vessel</td>
<td>0.062</td>
<td>2.833</td>
</tr>
<tr>
<td>2 ≥ vessels</td>
<td>0.099</td>
<td>0.397</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The most important result of the current study was that the CHA2DS2-VASc score was found to be associated with the LVEF values in patients with ACS, and was a strong indicator for LVEF. CHA2DS2-VASc scores above 1.5 were found to be an independent predictor for decreased LVEF values.

ACS is still the most important cause of mortality and morbidity globally, and there is a strong increase in mortality rates due to HF that develops as a result of a decrease in LVEF values after ACS (9). It is thus important to predetermine the high-risk patients.

Although the CHA2DS2-VASc score is used to detect a stroke in patients with nonvalvular atrial fibrillation who require treatment at an early stage (10), Mony et al. showed that it is also associated with the follow-up results of patients with HF (11). Fernando et al. showed that the severity of CAD in patients with ACS was correlated with...
the CHA2DS2-VASc score (12). The current study found a correlation between the CHA2DS2-VASc score and left ventricular systolic function in the follow-up of patients who had undergone PCI due to the diagnosis of ACS.

The LVEF value is an important prognosis criterion in patients with CAD (13). While advances in treatments and its effective administration improve survival, individuals with reduced ejection fraction still have higher mortality than individuals with preserved ejection fraction (14).

Hyperglycemia, an increased CRP value and the neutrophil-to-lymphocyte ratio are associated with many adverse clinical scenarios (15). Silvia et al. showed that hyperglycemia is a strong predictor of short and long-term mortality in diabetic and non-diabetic patients with ACS (16). In the current study, higher glucose levels were observed in the group with low LVEF values, which is an effective and useful predictor for the prognosis of ACS in patients. Zhang et al. conducted a meta-analysis with 10,245 patients with acute myocardial infarction with ST segment elevation and found a significant relationship between NLR and clinical conditions such as HF and major adverse cardiovascular events (17). Similarly, higher NLR values were observed in the group with LVEF values below 50% in the current study.

The CHA2DS2-VASc score has been shown to be a strong predictor of mortality in patients with low ejection fraction (18). The relationship between the CHA2DS2-VASc score and left ventricular systolic function has not been investigated in the follow-up of ACS patients (19). According to the results of this study, the CHA2DS2-VASc score can be used to predict preserved and decreased left ventricular systolic functions in the follow-up of patients with ACS.

The main limitation of this study is its retrospective design and monocentricity. Data on adverse cardiovascular events could not be obtained in the follow-up of the patients. Since the study was carried out over a relatively short period of time, no data could be obtained about the usability of the CHA2DS2-VASc score to predict decreased LVEF values when the maximal treatment that patients can tolerate in the long term is reached. Also, since patients with a history of CABG with preserved LVEF values were not included in the study, data regarding the usability of the CHA2DS2-VASc score after CAG in these patients could not be obtained. The results of the current study need to be further confirmed by prospective and multi-center studies.

The CHA2DS2-VASc score is an easy-to-calculate measurement that can be used to predict preserved and reduced left ventricular systolic functions in patients with ACS.

Declarations
The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

References


Use of Vitamin, Mineral and Supporting Products in Children in Adana

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2 Çukurova University Medical Faculty, Department of Social Pediatrics, Adana, Turkey.

Abstract

Background: To determine the frequency, methods and families’ knowledge about vitamins, minerals and supplementary products in children.

Methods: A questionnaire form was applied by face-to-face interviews with a total of 300 parents with children under the age of 5 who applied to the University Hospital, Training and Research Hospital and randomly selected family health centers in Adana. The demographic characteristics of the participants, their level of knowledge about preventive medication and supportive products, how they used them, and who suggested starting them were evaluated.

Results: The mean age of the children included in the study was 24.3±18.1 months. The correct use rates of iron and vitamin D by the parents were 60.7% and 83.3%, respectively. 147 of the parents (49%) used at least one supportive product to their children, and multivitamin (12.5%), molasses (8.3%), cumin (7.3%), honey (6.3%), fish oil (6.3%) was observed to be among the preferred products. It was found that supportive products were most frequently started due to growth and development retardation (27.7%) with the suggestions of neighbors-close relatives (45.8%) and doctors (30.7%).

Conclusions: Iron and vitamin D preparations are distributed free of charge in our country; however, we believe that the correct usage rates are not at the desired level, and more training and information should be given to healthcare professionals and parents in terms of compliance with prophylaxis and correct use. Although there is not enough data in our country regarding use of supportive products, more reliable results can be obtained with more comprehensive studies.

Key words: Iron, Vitamin D, Supportive Product, Children, Prophylaxis.
and continued for at least 1 year is important. Rickets due to vitamin D deficiency is a preventable health problem in our country. Its frequency varies between 1.6-19% (3). One liter of breast milk, which is the most important source of nutrition for babies in the first six months, contains 12-60 IU of vitamin D, and this amount cannot meet the 400 IU, which is the daily requirement for babies. For this reason, it is important to give appropriate vitamin D supplements to babies for an appropriate amount of time. In our country, it is recommended that all babies be given 400 IU of vitamin D per day for at least one year from birth, preferably until the end of three years, regardless of their diet (3).

Use of supporting products is generally based on traditional skills and practices that may not always be explained. It may also be based on theories, beliefs and experiences specific to different cultures. Supporting products are generally used for protection against physical and mental illnesses, diagnosing, healing or treating them, as well as maintaining good health (4). They are traditional or technological methods used in the treatment of common cold, flu, nausea, heart disease, kidney disease, depression and many other diseases (5). According to World Health Organization (WHO) data, approximately 80% of the population in developing countries use herbal supplements to meet basic health care requirements (6). Despite the lack of scientific data explaining the interactions, side effects and benefits of herbal supplements with medicines, their use is quite high. While useful information about these products usually refers to traditional uses, clinical side effects due to their herbal properties and pharmacological interactions with foods and drugs are difficult to evaluate (7). Supporting products are used in infants and children in cases such as upper respiratory tract infections, anorexia, gas pain, gastrointestinal disorders, sleep disorders, kidney stones, urinary tract infections, allergies and asthma (5).

The aim of this study was to determine the frequency of use of vitamins, minerals and supporting products in children in Adana province of Turkey; the methods of use and the level of knowledge families have on this subject.

**MATERIALS AND METHODS**

Parents of 300 children aged 0-5 who presented with an acute illness or for routine follow-up of healthy children and who wanted to participate in the survey voluntarily were included in the study. Patients over the age of 5 and who did not want to participate in the study were excluded. The patients were evaluated in 3 groups. The groups were determined according to the healthcare center that the patients first applied to; Çukurova University Faculty of Medicine Balcalı Hospital (Group-1), Adana City Training and Research Hospital General Children’s Polyclinics (Group-2), Family Health Centers located in Sarçam, Çukurova and Seyhan districts (Group-3). Each group included 100 participants. The mothers of 300 children were asked questions about the demographic characteristics of their family and children, their socioeconomic status, their knowledge and practices on iron, vitamin D and various supplements, using face-to-face questionnaires. The surveys were then recorded and the statistical analysis of the data was made. Verbal and written consents were obtained after the participants were informed about the study.

The correct dose of protective iron treatment has been accepted as 2 mg / kg / day for preterm babies and 1 mg / kg / day for term babies. For the protective vitamin D, 400 IU of daily intake was accepted as the correct dose.

In order to carry out the study, a permit document from Adana Provincial Health Directorate dated 03.04.2019 and numbered 60247264-799 and an Ethics committee approval from Adana Çukurova University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee with meeting number 84 and decision number 34, dated 04.01.2019 were obtained.

**Statistical analysis**

SPSS 23.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, while continuous measurements were summarized as mean and standard deviation (median and minimum - maximum where necessary). Chi-square test statistics were used to compare categorical variables. For the comparison of continuous measurements between the groups, distributions were checked, one-way Analysis of Variance was used for variables showing parametric distribution, and Kruskal Wallis test was used for variables that did not show parametric distribution. Statistical significance level was accepted as 0.05 in all tests.
RESULTS

300 children between the ages of 0-5, 190 of whom were healthy, 110 of whom presented with an acute illness were included in the study. Their average age was 24.3±18.1 months (min-max: 1-61), and 140 (47.7%) were male and 160 (53.3%) were female. There was no difference between the groups in terms of age and gender distribution (p=0.460 and p=0.498, respectively). The demographic characteristics of the groups were as shown in Table 1. The average age of the mothers who answered the questionnaire was found to be 30.1±5.4 (min-max: 19-48) years.

Considering the education level of the mothers, 96 participants (32%) were university graduates, 78 participants (26%) were high school graduates, 47 participants (15.7%) were middle school graduates, 46 participants (15.3%) were elementary school graduates, 16 participants (5.3%) were literate, 17 participants (5.7%) were illiterate. Education levels were found to be lower in Group 3 than the other two groups, but this was not statistically significant (p=0.509).

When the monthly incomes of the groups were evaluated, 79 families (26.3%) earned 2000-3000 ₺, and 69 families (23.0%) were earning 3000-5000 ₺. The monthly income of 20 families (6.7%) was <1000 ₺, and 39 families (13%) were >10.000 ₺. It was observed that the monthly income of the families in Group-3 was statistically higher (p = 0.011). The working status of the mothers and the total monthly income of the families were as shown in Table 1.

Table 1: Demographic characteristics by groups

<table>
<thead>
<tr>
<th></th>
<th>Group-1 Mean±SD</th>
<th>Group-2 Mean±SD</th>
<th>Group-3 Mean±SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (month)</td>
<td>25.3±17.1</td>
<td>26.3±13.3</td>
<td>24.2±16.4</td>
<td>0.460</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>12.5±5.4</td>
<td>10.2±5.6</td>
<td>11.2±4.7</td>
<td>0.263</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>84.2±16.4</td>
<td>80.9±16.2</td>
<td>82.6±15.4</td>
<td>0.361</td>
</tr>
<tr>
<td>Mothers’ age (year)</td>
<td>30.4±5.1</td>
<td>30.1±5.7</td>
<td>29.7±5.4</td>
<td>0.656</td>
</tr>
<tr>
<td>Fathers’ age (year)</td>
<td>33.9±4.9</td>
<td>32.3±6.1</td>
<td>32.9±5.0</td>
<td>0.089</td>
</tr>
<tr>
<td>Sibling number</td>
<td>Median (min-max)</td>
<td>Median (min-max)</td>
<td>Median (min-max)</td>
<td>0.365</td>
</tr>
<tr>
<td>Duration of breastfeeding (month)</td>
<td>9 (0-28)</td>
<td>8 (0-50)</td>
<td>9 (1-36)</td>
<td>0.842</td>
</tr>
<tr>
<td>Time to start supplementary food (month)</td>
<td>6 (3-10)</td>
<td>6 (4-9)</td>
<td>6 (5-7)</td>
<td>0.428</td>
</tr>
<tr>
<td>Mothers’ Job Status</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td></td>
</tr>
<tr>
<td>Working</td>
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<td>31 31.0</td>
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<tr>
<td>Not working</td>
<td>59 59.0</td>
<td>66 66.0</td>
<td>69 69.0</td>
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<tr>
<td>Total Monthly Income</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td></td>
</tr>
<tr>
<td>&lt;1000 TL</td>
<td>12 12.0</td>
<td>5 5.0</td>
<td>3 3.0</td>
<td>0.011</td>
</tr>
<tr>
<td>1000 –2000 TL</td>
<td>22 22.0</td>
<td>17 17.0</td>
<td>8 8.0</td>
<td></td>
</tr>
<tr>
<td>2000 –3000 TL</td>
<td>27 27.0</td>
<td>26 26.0</td>
<td>26 26.0</td>
<td></td>
</tr>
<tr>
<td>3000 –5000 TL</td>
<td>18 18.0</td>
<td>27 27.0</td>
<td>24 24.0</td>
<td></td>
</tr>
<tr>
<td>&gt;5000 TL</td>
<td>14 14.0</td>
<td>13 13.0</td>
<td>19 19.0</td>
<td></td>
</tr>
<tr>
<td>&gt;10.000 TL</td>
<td>7 7.0</td>
<td>12 12.0</td>
<td>20 20.0</td>
<td></td>
</tr>
</tbody>
</table>
Only 95 (31.7%) of all mothers were using iron support for their children during the time of the study; but 182 of all participants (60.7%) knew the correct use of iron medication. When the rates of using iron supplements and correct usage information were compared, no statistically significant difference was found in all three groups (p=0.148, p=0.127, respectively). Participants were asked when to start protective iron treatment in children and 99 (33.0%) of all participants said “4th month”. This answer caused a statistically significant difference when compared with other options (p=0.011). When all the participants were questioned about whom the protective iron therapy was recommended by; it was determined that in 132 (44.0%) patients it was recommended by pediatricians, 116 (38.7%) by family physicians, 52 (17.3%) by nurses and midwives. While the rate of recommendation by the pediatrician in Group 1 was 57%, it was found to be 42% in Group 2 and 33% in Group 3, and this difference was statistically significant (p=0.003). The questions about the protective iron treatment and the answers given by the mothers were presented in Table 2.

Table 2: Evaluation of questions and answers about prophylactic iron therapy

<table>
<thead>
<tr>
<th></th>
<th>Group-1</th>
<th></th>
<th>Group-2</th>
<th></th>
<th>Group-3</th>
<th></th>
<th>Total</th>
<th></th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Do you give your child iron supplements?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>39</td>
<td>39.0</td>
<td>27</td>
<td>27.0</td>
<td>29</td>
<td>29.0</td>
<td>95</td>
<td>31.7</td>
<td>0.148</td>
</tr>
<tr>
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<td>61.0</td>
<td>73</td>
<td>73.0</td>
<td>71</td>
<td>71.0</td>
<td>205</td>
<td>68.3</td>
<td></td>
</tr>
<tr>
<td>Knowledge of correct use of iron medication.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doesn’t know the correct use</td>
<td>32</td>
<td>32.0</td>
<td>46</td>
<td>46.0</td>
<td>40</td>
<td>40.0</td>
<td>118</td>
<td>39.3</td>
<td>0.127</td>
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<tr>
<td>Knows the correct use</td>
<td>68</td>
<td>68.0</td>
<td>54</td>
<td>54.0</td>
<td>60</td>
<td>60.0</td>
<td>182</td>
<td>60.7</td>
<td></td>
</tr>
<tr>
<td>When should preventive iron treatment be initiated in children?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>As soon as birth</td>
<td>14</td>
<td>14.0</td>
<td>7</td>
<td>7.0</td>
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<td>1.0</td>
<td>22</td>
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<td>0.011</td>
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<tr>
<td>At 1-2 months</td>
<td>16</td>
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<td>17</td>
<td>17.0</td>
<td>14</td>
<td>14.0</td>
<td>47</td>
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<td></td>
</tr>
<tr>
<td>At 4 months</td>
<td>33</td>
<td>33.0</td>
<td>34</td>
<td>34.0</td>
<td>32</td>
<td>32.0</td>
<td>99</td>
<td>33.0</td>
<td></td>
</tr>
<tr>
<td>At 6 months</td>
<td>19</td>
<td>19.0</td>
<td>31</td>
<td>31.0</td>
<td>38</td>
<td>38.0</td>
<td>88</td>
<td>29.3</td>
<td></td>
</tr>
<tr>
<td>At 1 year</td>
<td>18</td>
<td>18.0</td>
<td>11</td>
<td>11.0</td>
<td>15</td>
<td>15.0</td>
<td>44</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>How many times a day should preventive iron treatment be given?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once a day</td>
<td>77</td>
<td>77.0</td>
<td>76</td>
<td>76.0</td>
<td>80</td>
<td>80.0</td>
<td>233</td>
<td>77.7</td>
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<tr>
<td>Twice a day</td>
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<td>15</td>
<td>15.0</td>
<td>16</td>
<td>16.0</td>
<td>46</td>
<td>15.3</td>
<td></td>
</tr>
<tr>
<td>Three times a day</td>
<td>8</td>
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<td>9</td>
<td>9.0</td>
<td>4</td>
<td>4.0</td>
<td>21</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>How should iron medicine be given?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Should be taken on an empty stomach</td>
<td>49</td>
<td>49.0</td>
<td>57</td>
<td>57.0</td>
<td>56</td>
<td>56.0</td>
<td>162</td>
<td>54.0</td>
<td>0.378</td>
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<tr>
<td>Should be taken on a full stomach</td>
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<td>28.0</td>
<td>22</td>
<td>22.0</td>
<td>17</td>
<td>17.0</td>
<td>67</td>
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<td></td>
</tr>
<tr>
<td>It does not matter</td>
<td>23</td>
<td>23.0</td>
<td>21</td>
<td>21.0</td>
<td>27</td>
<td>27.0</td>
<td>71</td>
<td>23.7</td>
<td></td>
</tr>
<tr>
<td>Who recommended the iron preventive therapy?</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family medicine doctor</td>
<td>34</td>
<td>34.0</td>
<td>41</td>
<td>41.0</td>
<td>41</td>
<td>41.0</td>
<td>116</td>
<td>38.7</td>
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<tr>
<td>Pediatrician</td>
<td>57</td>
<td>57.0</td>
<td>42</td>
<td>42.0</td>
<td>33</td>
<td>33.0</td>
<td>132</td>
<td>44.0</td>
<td></td>
</tr>
<tr>
<td>Nurse-midwife</td>
<td>9</td>
<td>9.0</td>
<td>17</td>
<td>17.0</td>
<td>26</td>
<td>26.0</td>
<td>52</td>
<td>17.3</td>
<td></td>
</tr>
</tbody>
</table>
When the use of vitamin D was examined, 115 (38.3%) of all mothers were regularly giving protective vitamin D to their children during the study period, and 250 (83.3%) of all participants knew the correct use. When the rates of vitamin D supplementation and correct usage information were compared, no statistically significant difference was found in all three groups (p=0.765, p=0.157, respectively). Participants were asked when to start preventive vitamin D treatment in children, 110 (36.7%) participants said “15th day”, 107 of them (35.7%) answered as “as soon as birth”, which created a statistically significant difference between the groups (p=0.001). When all the participants were questioned about whom protective vitamin D treatment was recommended by; it was determined that in 145 (48.3%) patients it was recommended by pediatricians, 109 (36.3%) by family physicians, 46 (15.3%) by nurses and midwives, and no statistically significant difference was found between the groups in this regard (p=0.306). The questions about protective vitamin D treatment and the answers given by the mothers were as presented in Table 3.
The use of supportive products was evaluated and it was determined that 153 (51%) of the parents did not give any supportive products to their children. 147 parents (49%) were found to use one or more supportive products. Similar results were obtained for all three groups (p=0.619) (Table 4). Of the participants, 37 (12.5%) preferred multivitamin,
25 (8.3%) molasses, 22 (7.3%) cumin, 19 (6.3%) honey and 19 (6.3%) fish oil. The usage rates of these products were similar in all three groups. Olive oil use was determined in 10% of the patients in Group 1, which was higher than the other two groups. This difference was statistically significant (p = 0.032) (Table 4).

Table 4: Evaluation of questions and answers regarding the use of supplementary products

<table>
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<th></th>
<th>Group-1</th>
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<th>Group-2</th>
<th></th>
<th>Group-3</th>
<th></th>
<th>Total</th>
<th></th>
<th>p</th>
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<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Do you give your child any product other than iron, vitamin D and nutrients for growth and development and/or chronic disease?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
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<td>53.0</td>
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<td>47</td>
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<tr>
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<td>1.7</td>
<td>0.816</td>
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<td>7</td>
<td>7.0</td>
<td>9</td>
<td>9.0</td>
<td>22</td>
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<td>0.709</td>
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<td>5</td>
<td>1.7</td>
<td>0.816</td>
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<td>Centaury</td>
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<td>4</td>
<td>4.0</td>
<td>4</td>
<td>4.0</td>
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<td>13.0</td>
<td>37</td>
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<td>5.0</td>
<td>7</td>
<td>7.0</td>
<td>16</td>
<td>5.3</td>
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<td>1.0</td>
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<td>2.0</td>
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<td>1</td>
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<td>2</td>
<td>2.0</td>
<td>4</td>
<td>1.3</td>
<td>0.776</td>
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<tr>
<td>Fennel</td>
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<td>0.137</td>
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<td>4.0</td>
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<td>2.0</td>
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<td>11</td>
<td>11.0</td>
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<td>8.0</td>
<td>25</td>
<td>8.3</td>
<td>0.436</td>
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<td>TV programs</td>
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<td>6</td>
<td>12.2</td>
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<td>5.4</td>
<td>12</td>
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<td>7</td>
<td>14.3</td>
<td>6</td>
<td>10.7</td>
<td>17</td>
<td>11.1</td>
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<td>0.0</td>
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<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Doctor</td>
<td>17</td>
<td>35.4</td>
<td>11</td>
<td>22.4</td>
<td>19</td>
<td>33.9</td>
<td>47</td>
<td>30.7</td>
<td></td>
</tr>
<tr>
<td>Nurse-midwife</td>
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<td>4.1</td>
<td>0</td>
<td>0.0</td>
<td>5</td>
<td>3.3</td>
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<td>Neighbors-close relatives</td>
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<td>22</td>
<td>44.9</td>
<td>28</td>
<td>50.0</td>
<td>70</td>
<td>45.8</td>
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</tbody>
</table>

Participants were questioned about whom recommended the usage of supporting products; it was determined that supporting product usage started with neighbor-close relative recommendation at a rate of 45.8%. 30.7% of the participants reported that they have started supporting product usage by recommendation from a doctor and 11.1% of the participants started based on the information they obtained from the internet. These results were similar in all three groups, and there was no statistically significant difference between the groups (p = 0.531) (Table
Participants were asked about the reasons for using supportive products and it was found that 83 (27.7%) of the participants used it for growth-developmental delay and 38 (12.7%) were using it for constipation. The reasons for using the supporting product / products were as given in Table 5.

Table 5: Usage reasons of supporting products

<table>
<thead>
<tr>
<th></th>
<th>Group-1</th>
<th>Group-2</th>
<th>Group-3</th>
<th>Total</th>
<th>p</th>
</tr>
</thead>
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<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Do you give your child any product other than iron, vitamin D and nutrients for growth and development and/or chronic disease?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Treatment of chronic disease</td>
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<td>7</td>
<td>7.0</td>
<td>4</td>
</tr>
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<td>Growth-development delay</td>
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<td>28</td>
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<td>8</td>
<td>8.0</td>
<td>8</td>
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<td>10.0</td>
<td>15</td>
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</tr>
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<tr>
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DISCUSSION

Vitamin D deficiency and iron deficiency anemia is a public health problem affecting growth and development, psychosocial skills, neuromotor development, cellular and humoral systems, especially in infants. Therefore, prophylaxis is very important in terms of preventing vitamin D deficiency and iron deficiency anemia under 2 years of age. In order to prevent vitamin D deficiency and insufficiency, the daily vitamin D requirement for babies was determined as 400 IU by WHO (8). In our country, as of May 2005, within the scope of vitamin D prophylaxis, the Ministry of Health General Directorate of Mother and Child Health and Family Planning has put “prevention of vitamin D deficiency and protection of bone health” project on the agenda and free vitamin D preparations have been distributed in all family health centers. According to this project, 400 IU vitamin D should be given to all newborn babies starting from the first week of birth. Also, babies between 0-12 months who do not use vitamin D should immediately be started on vitamin D preparations for at least 12 months from that moment on. Iron deficiency anemia is considered in the world as a public health problem that is as current as vitamin D deficiency. In this context, WHO and various health institutions recommend iron supplementation to all children starting from the 4th month, in countries with iron deficiency anemia rates above 5% (9). Looking at our country, the “Iron-like Turkey Program” was initiated by the Ministry of Health in 2004 and in accordance with this application, free iron support has been provided to all children aged 4 months to 1 year (10).

Studies on vitamin D deficiency and nutritional rickets have shown that the rates of vitamin D use and regular use after starting vitamin D are low. In a study by Göker et al. (11) on 101 children, it was found that 12.9% of them used vitamin D irregularly, incorrectly and for a short amount of time. In our study, it was observed that 83.3% of the families knew the correct use of vitamin D, 26.8% of the parents neglected to give vitamin D to their children for various reasons, and the rate of starting vitamin D within the first 15 days after birth was 72.4% among all cases. Our study revealed that vitamin D prophylaxis is not at the desired level considering the ideal period of initiation and usage rates.
In a study conducted by Pehlivan et al. (12) on 204 physicians, it has been stated that 3.9% of physicians do not recommend vitamin D drops to children, 58.6% of the physicians who recommend vitamin D recommend vitamin D drop form, and the remaining physicians recommend vitamin D in the form of multivitamin. In our study, it was observed that 92.3% of the patients used vitamin D in drop form. It was determined that 48.3% of the parents who received suggestions for using vitamin D were recommended to use vitamin D from pediatricians, 36.3% from family physicians and 15.3% from nurses and midwives.

In a study conducted by Vatandaş et al. (13) in 2007, in Ankara, the prevalence of iron deficiency was found to be 20% in children who receive regular oral iron prophylaxis until the age of 1, while the prevalence of iron deficiency anemia was found to be 2%. The prevalence of iron deficiency was found to be 26%, and the prevalence of iron deficiency anemia was 30% in children who did not receive prophylaxis. In our study, the correct use rate of iron preventive therapy was found to be 60.7%. As the reasons for not giving the appropriate dose; even though the dose should be increased in proportion to the weight gain of the baby, the same dose was continued without increasing or the previous preparation dose was continued even though the current form was changed to a different form. Moreover, it was observed that the parents confused and mistakenly gave wrong doses of vitamin D and iron drops that were used simultaneously. According to a study conducted by Yalçın et al. (14), the proportion of children who did not use prophylactic oral iron support was 31.2%. In a study conducted by Iıarslan et al. (15), the rate for the same parameter was 44.3%. Reasons for stopping prophylaxis were; because the family found it unnecessary (31.1%), neglect (26.6%), side effects (16.6%), taste disturbance (15.3%). Also, 6.3% were not informed by healthcare workers and 4.1% feared possible side effects indicated by their family members (15). Karapinar et al. (16) found that iron prophylaxis was not initiated in 16% of children, 44.5% discontinued prophylaxis. The reasons for discontinuing prophylaxis except for discontinuation of the treatments under the doctor’s control were; vomiting (3%), diarrhea (2%), stool staining (3.5%) and neglect (forgetting, ignoring) (36%). Similarly, while the most common reasons for stopping prophylaxis in our study were negligence (29.1%), constipation (14.8%) and bad taste (11%), other causes were also found.

The use of herbal supplements for the treatment or prevention of diseases is as old as human history. WHO stated that they still meet 80% of the health needs of especially underdeveloped and developing countries with herbal supplements and that around 20,000 plant species are used for this purpose (6). Herbal products and their use have gained great popularity as a result of the “return to nature” trend that started in Western societies in the last 30 years. Studies in the USA show that the use of complementary and alternative medicine in children is becoming more common and that herbal medicine is the most common form among these (17,18). In a study conducted by Jean and Cyr (19) with 114 parents, it was determined that 54% of parents had used at least one kind of complementary and alternative treatment. Similar results (51%) were found in the study conducted by Lim et al. (20) with 503 parents. In this study, it was determined that 19% of the parents preferred to use multivitamins and minerals, 13% preferred vitamin C and 12% preferred other herbal remedies. In our study, 72 out of 147 participants who stated that they used supportive products for their children preferred herbal supplements. 37 participants were using multivitamins. In a study conducted in the USA, it was found that echinacea was the most commonly used supportive product, which was used for common cold symptoms. In the same study, fish oil was the second most commonly used product, which was used for sleep disorders and attention deficit (17). However, the most commonly used supplements in our study were multivitamins; and fish oil usage was in third place. It was determined that both of these products were used for growth and developmental delay. No statistical difference was found between the three groups regarding the frequency of supportive product use. However, it was determined that olive oil was used statistically significantly more in Group 1 (p = 0.032). This difference may be explained by the higher number of patients in this group who frequently applied to a tertiary healthcare institution due to growth and development retardation. This data shows that growth and development retardation is still a serious problem in our country, and especially mothers are extremely sensitive about this issue.
In a study conducted in the USA, 9% of babies were given herbal supplements or various teas (baby gas relieving mixture, dental tablets, peppermint, chamomile, fennel, anise, wild hyacinth and echinacea teas, herbal cold healers, etc.). It was found that the babies were treated with these remedies in the first year and even in the first month of their lives (21). Gastrointestinal diseases (in the treatment of constipation and hemorrhoids), infection and parasitic diseases (fever and malaria), respiratory tract infections and neuropsychiatric diseases have been shown as the most common reasons for the use of herbal supplements in children (22,23). In our study, these products were most commonly used for reasons such as growth and development retardation, constipation, cough, gas pain, and loss of appetite, respectively.

The limitation of this study was that our study was conducted in a single region and the number of patients included in the study was relatively low.

Considering the supported use of iron and vitamin D in our country and the free of charge distribution of these preparations, the rate of correct use of iron and vitamin D preparations are expected to be higher. Since compliance with prophylaxis is low in our city, we believe that informative seminars for both healthcare professionals and parents, which increase sensitivity towards iron and vitamin D usage, should be conducted in primary family health centers. In addition, more information should be given to families by not only family physicians but also pediatricians about iron and vitamin D prophylaxis for patients who come to them for any reason, especially in the first year of life. Although there is not enough data on the use of supportive products in our country, more reliable results can be obtained with more comprehensive studies.

Declarations
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References


Phytocontact Dermatitis Due to Ranunculus Kotschyi Boiss: Adverse Effect for Artralgia Treatment

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INTRODUCTION

There are so many plants in the world that it may be really challenging sometimes to determine the cause of dermatitides in a patient. Plants may contain a wide range of substances that may induce an allergic response. Many types of plant-induced dermatitis such as contact urticaria, phototoxic contact dermatitis, allergic contact dermatitis, irritant contact dermatitis, and photoallergic contact dermatitis have been identified in the past. Phytodermatitis is described as damage caused by an acute inflammatory reaction in a part of the skin that has contacted the relevant plant. The plant in this case is Ranunculus kotschyi Boiss (Figure 1) which is a type of Ranunculus kotschyi. Sub-species of Ranunculus kotschyi contain an ingredient called Ranunculin which causes phytodermatitis (1-3).

CASE REPORT

A 60-year-old female patient complained of pain, redness and bullous lesions on her knees. She lives in Gölbaşı County of the City of Ankara, capital city of Turkey. She stated that two days ago, she had applied a plant to her knee for the relief of joint pain for 3 hours. She applied that plant to the knee only once. She also stated that...
she had picked up the plant from a nearby rural area. Dermatological examination revealed 10 x 15 cm bullous, blister-like lesions on an erythematous base. Severe pain, burning sensation, redness, vesicles, blisters, crusts, bullae, post-inflammatory hyperpigmentation and ulcerated erosive plaques were also seen. There was no restriction regarding range of mobility of the joints (Figure 2). Partially spontaneously drained zones were observed. The medical history and laboratory tests of the patient were unremarkable.

The plant brought by the patient was searched for in the literature and examined by the specialists upon which it was identified to be R. kotschyi. Most people resort to herbal therapeutic agents due to medical conditions. They may sometimes be very useful, whereas they mostly may have unexpected adverse effects. These may include contact dermatitis and secondary infections. These contact dermatitides may cause phytodermatitis. And our patient has phytodermatitis since it is identified with contact dermatitis developing in the affected area following herbal administration (4). Species of the Ranunculus genus are a group of plants frequently used in Turkey for joint pain. There are 6 known cases of R. Kotschyi-associated contact dermatitis reported so far. These cases have been reported in the city of Van, Turkey (5). Our case has similar results to these cases. The lesions are similar.

DISCUSSION

Ranunculaceae family is a large group with nearly 2000 species. It is used as an herbal therapeutic agent in East and Central Anatolia (6). It can grow at an altitude of 2,000 km. Members of the Ranunculaceae family, which are annual plants, have a wide range of traditional therapeutic uses such as abscess drainage, hemorrhoid, burns, cuts, muscle pain, joint pain and abrasions. Ranunculaceae family phytometabolites has been shown to have a key role in their anticancer, antioxidant, cytotoxic, rheumatic pain, analgesic, anti-inflammatory and antiseptic activities (7, 8).

Usually, Ranunculin is responsible for the irritant effects. Ranunculin causes toxic effects with oxygen radicals it produces by inhibiting DNA polymerase. Ranunculin is an unstable and acrid glucoside (9, 10). It may be contained in either the roots or the leaves. Upon contacting the skin, it is decomposed into glucose and the toxin ‘protoanemonin’ because of a number of enzymatic processes. Protoanemonin is a volatile and irritant fatty molecule. The level of protoanemonin in the plant is directly proportional to the maturity and quantity of flowers of the plant. Their systemic intake may cause GIS irritant effects, nausea, vomiting, stomachache, diarrhea, and neurological symptoms.

The patient was discharged early from the hospital. This patient was treated with systemic antibiotics and non-steroidal anti-inflammatory drugs (NSAIs). Additionally, topical wet dressings with eau de borique solution and prednisolone + iodochlorhydroxyquin pomade were applied to the lesion zones daily. Dermatology control was recommended to the patient 3 weeks later. It was observed that the lesions tended to heal when the patient came for control (Figure 3).
R. kotschyi Boiss is a subspecies within Ranunculaceae family and causes phytodermatitis also known as irritant contact dermatitis. The present case is one of the rare cases reported concerning R. kotschyi.

**Declarations**

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A Rare Clinical Presentation Caused by Atrial Myxoma: Right Heart Failure

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Abstract

Primary heart tumours are rarely encountered. Myxomas, which are included in this group of tumours, are the most common primary benign neoplasms of the heart and approximately 75-80% of them are found in the left atrium. In our case, a 72-year-old female patient, who had complaints of shortness of breath, pain in the chest and swelling in the legs that increased in the last three months. We present a case with a myxoma in the right atrium with a dimension of 80x60x15 mm attached to the interatrial septum. According to the echocardiographic examination, it clinically shows signs of right heart failure, almost completely obstructs the right atrium and extends to the right ventricle. Ascending aortic aneurysm was also detected on the echocardiography. Despite the fact that the right atrial mass obliterating the cardiac chambers was removed by surgery, the valve pathology caused by the lesion did not regress.

Key words: Atrial Myxoma, Right Heart Failure, Tricuspid Valve Insufficiency, Dyspnea.

INTRODUCTION

The majority of heart tumours (75%) are benign and the most commonly seen heart tumour is atrial myxoma (1). Most myxomas develop in the left atrium, but rarely they may develop in the right atrium (2). Large myxomas typically remain clinically silent until they reach a significant size, or they simply cause non-specific symptoms such as fatigue and palpitations. However, giant myxoma in the right heart cavity is a rare clinical presentation (3, 4). Clinically significant embolic events are much less common in patients with right atrial myxoma compared to those with left atrial myxoma (5). Additionally, myxomas may lead to syncope and sudden death due to tricuspid valve obstruction (6). Echocardiography is the standard diagnostic test and surgical approach is the curative treatment (7).

CASE REPORT

72-year-old female patient presented with complaints of shortness of breath, oedema in the ankles and pain in the chest that increased within the last three months.
Physical examination revealed no pathological findings other than a third degree systolic murmur in the tricuspid valve and bilateral pretibial oedema. The patient’s vital signs were stable at the initial evaluation. There was no comorbid disease other than hypertension in the medical history of the patient. Cardiothoracic index was increased on the postero-anterior (PA) chest radiography and normal sinus rhythm was detected in the electrocardiogram. The echocardiographic examination revealed normal left ventricular dimensions, but inferior wall was found to be hypokinetic. Ejection fraction was found to be 42% in the evaluation performed with the modified Simpson method. Left atrium size was measured at the upper limit. Aortic valve had a senile structure, and 2nd degree aortic insufficiency was detected. Mitral valve structure was thick, coarse and 1st degree mitral insufficiency was also detected. Diameter of the ascending aorta was measured to be 5.3 cm. The right heart cavities were large and had severe tricuspid insufficiency. In the interatrial septum, there was a mass with a dimension of 78x47 mm attached to the right atrium (Figure 1-2-3). It was determined that the mass obstructed most of the right atrium in the ventricular systole, extended to the right ventricle to the tricuspid valve during the diastole, obstructed the valve and resulted in severe tricuspid valve insufficiency. Although there was severe insufficiency in the tricuspid valve, no gradient increase was observed and systolic pulmonary arterial pressure (sPAP) was measured as normal. Right coronary artery system and left coronary artery system were found to be normal in the coronary angiography. Surgical procedure was planned for the patient. The rib cage was opened with median sternotomy during the surgery. A right atriotomy was performed to remove the mass with a dimension of 80x50 mm attached to the secundum septum compatible with atrial myxoma (Figure 4). The ascending aortic dilatation was then repaired. In the pathological examination, a gray-white bright patchy hemorrhagic tissue with a dimension of 80x60x15 mm was reported as myxoma due to its spindle shape and stellate appearance (Figure 5). No mass was detected in echocardiography in the postoperative 6th month follow-up. The patient had grade 3 tricuspid valve insufficiency and jet velocity was measured as 3.7m/s. No change was observed in the patient’s right ventricle diameters. At the last evaluation, the patient had no symptoms.
DISCUSSION

Tumours found in the heart are less than 1% in the general population. The familial form, which usually occurs sporadically, is encountered as Carney syndrome. Atrial myxomas constitute more than 50% of benign cardiac tumours (8). Although they appear between the ages of 30 and 60 on average, they most often start to show symptoms around 50 years of age (7). In our case, the symptoms appeared in a patient in her 70s. Symptoms and indications of cardiac tumours may not be clear and vary depending on the localization of the mass. Cases may present with a clinical picture that is similar to the findings of heart failure as a result of failure and obstruction of the valves in intracardiac tumours. As in right heart failure, jugular venous fullness, ascites and oedema may be observed.

The diagnosis of myxomas is simple and does not require special imaging methods other than two-dimensional echocardiography (7). In echocardiography, the tumour can be differentiated from normal anatomic structure with smooth lines. In addition, pericardial effusion may also be observed (9). However, pericardial effusion was not identified in our case. If the results of two-dimensional transthoracic echocardiography are unclear, transesophageal echocardiography might be required (10). Once diagnosed, surgical excision is recommended to prevent embolism and sudden cardiac death. As the recurrence rate after surgical excision is high, echocardiographic follow-up is recommended. Even though the recurrence of myxomas resected surgically is typically within the first 4 years, recurrence was also reported after 14 years (7). Pathologies caused by right atrial myxomas in the tricuspid valve after surgical excision have been reported to be completely reversible (11). However, in our case, significant tricuspid insufficiency continues even after six months. Atrial myxomas that reach large dimensions should be treated with surgical resection. Even though valvular pathologies caused by right atrial giant myxomas are reversible, it was permanent in our case. Thus, this should be considered in interventions of valvular pathologies during surgery.
Declarations
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