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id health science

Volume 1, Issue 2, Year 2023
ISSN: 2980-2903

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Research Article

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INVESTIGATION OF THE ANTIEPILEPTIC EFFECTS OF WATER AND ETHANOL EXTRACTS OF *ARTEMISIA ABSINTHIUM* L.

Melahat HURMET[1]*, Hulya OZPINAR[2], Umit Muhammet KOCYIGIT[3]

Keywords

Epilepsy,
Carbonic anhydrase,
CA inhibitors,
Artemisia absinthium L

ABSTRACT

Epilepsy is a neurological condition that affects millions of people worldwide, regardless of social class, age, or race discrimination. Current medications used in the treatment of epilepsy are unable to provide a curative effect on more than twenty percent of patients, necessitating the need for additional treatment methods. Artemisia absinthium L., traditionally used for its insecticidal, antiseptic, antispasmodic, liver-inflammatory, and fever-reducing properties, is also employed in Turkish folk medicine as an antipyretic, antihelminthic, diuretic, tonic, and for relieving stomach pain. Carbonic anhydrase (CA) is a transmembrane metalloenzyme found in the structure of living organisms from the simplest to the most advanced, catalyzing the conversion of carbon dioxide to bicarbonate and containing a Zn2+ ion in its structure. CA inhibitors are used clinically as diuretics, antiglaucoma agents, and anti-epileptics. In our study, the effects of water and ethanol extracts of Artemisia absinthium L., collected in April, on carbonic anhydrase isoenzymes I and II were investigated spectrofotometrically. It was observed that both water and ethyl alcohol extracts did not significantly affect the enzyme activity. The ethyl alcohol extract of A. absinthium exhibited a higher inhibition potential compared to the water extract. However, when the in vitro enzyme activity test results were examined, it was found that these extracts did not have a significant impact on enzyme activities. This result, which is inconsistent with the literature, is thought to be due to the fact that the plant was not collected during its flowering period.

INTRODUCTION

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Issue: 2
Page: 41-45

Received:
27.07.2023

Accepted:
02.09.2023

Available Online:
15.10.2023

Epilepsy is a neurological condition that affects millions of people worldwide without regard to social class, age, or race. Three-quarters of these individuals live in areas where access to healthcare and treatment is limited[1]. Many people with this condition fear stigmatization in society, leading them to keep their symptoms hidden from others[2]. As a result, the data obtained from epidemiological studies on the prevalence of the disease can be insufficient in some cases. Seizures and the physical and psychological consequences they bring can have a negative impact on patients. However, treatment with antiepileptic drugs, the first-line therapy for epilepsy, has reduced the presence of these seizures by up to seventy percent[3]. Nevertheless, current medications used in epilepsy treatment are unable to provide a curative effect for more than twenty percent of patients, necessitating the need for additional treatment methods[4].

Artemisia genus is one of the most widespread and diverse genera in the Asteraceae family, containing numerous aromatic and medicinal species. This genus is predominantly found in temperate regions of Asia, Europe, and North America and comprises more than 500 species. The species we used in our

DOI: 10.5281/zenodo.8413808

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Artemisia absinthium L., is commonly known as "Wormwood" or "Pelin otu" in local parlance. It is a perennial shrub found in Asia, the Middle East, Europe, and North Africa[5]. Its flowering period occurs between June and September. Traditionally, it has been used for its insecticidal, antiseptic, antispasmodic, liver-inflammatory, and fever-reducing properties. In Turkish folk medicine, it is also employed as an antipyretic, antihelminthic, diuretic, tonic, and for relieving stomach pain[6-8].

Carbonic anhydrase (CA), a transmembrane metalloenzyme found in the structure of living organisms ranging from the simplest to the most advanced, catalyzes the conversion of carbon dioxide to bicarbonate and contains a Zn^{2}+ ion in its structure. Carbonic anhydrase plays crucial roles in mechanical, physical, and biochemical aspects. CA enzyme is known to function in maintaining acid-base balance and regulating pH in various tissues and metabolic processes. Additionally, it is involved in physiological and pathological events such as ureagenesis, gluconeogenesis, lipogenesis, electrolyte secretion, bone resorption, and tumorigenesis[9].

CA inhibitors are commonly used in clinical practice as diuretics, anti-glaucoma agents, and anti-epileptics. However, recently, new applications have been reported for these inhibitors in the treatment of cancer, neuropathic pain, sleep apnea, migraine, reducing intracranial pressure, and treating cerebral ischemia. This indicates that CA inhibitors are being explored for their potential therapeutic effects in a broader range of medical conditions, and their use is being investigated in various medical fields. These developments suggest that this class of drugs may have a role in addressing a wider range of medical issues in the future[10].

The aim of this study is to investigate the effects of water and ethanol extracts of the aerial parts of *Artemisia absinthium* L., collected in April, on carbonic anhydrase isoenzymes I and II spectrophotometrically.

Collection of Plant Materials and Preparation of Plant Extracts

Samples of *Artemisia absinthium* L. were collected in April from Hatay province, at an altitude of 50 meters, with coordinates of 36° 7' 16" North and 35° 55' 39" East. The collected plant species were identified Assist. Prof. Dr. Hulya Ozpinar. After collection and drying, the plant samples were initially washed with tap water and then with distilled water. Subsequently, they were dried. Next, the samples were ground in a grinder, and 100 grams of the ground material were taken and mixed with ethanol. After being left in a shaker for 48 hours, the samples were filtered through filter paper, and the filtrates were collected. The liquid portion was then completely evaporated using an evaporator (equipped with a Vacuum Pump V300 and Control Unit I-300, Buchi R-100). The same method was used for preparing the water extract.

Investigation of the Effects of Plant Extracts on Carbonic Anhydrase (CA) Isoenzymes Using the Esterase Activity Method

The method used to spectrophotometrically detect the antiepileptic, antiglaucoma, and anti-diuretic effects of the obtained extracts *in vitro* is the esterase activity method. This method relies on the esterase activity of carbonic anhydrase for the hydrolysis of *p*-nitrophenyl acetate as a substrate, which is part of the reaction mechanism involving *p*-nitrophenol or *p*-nitrophenolate. Both *p*-nitrophenol and *p*-nitrophenolate exhibit the same absorbance at 348 nm.

In this method, first, the data were prepared as described in the section for preparing solutions in Table 1. Subsequently, the spectrophotometer device at 348 nm was zeroed using the cuvette content prepared in accordance with the instructions. Then, a cuvette content containing the enzyme, differing from the blank cuvette, was prepared according to Table 1 and placed into the spectrophotometer device. Absorbance was measured at the first minute and the third minute at 348 nm. The difference in absorbance between these measurements represented the enzyme activity, i.e., the control activity. Then, plant extracts at different concentrations were added, and absorbances were measured again at 0 and 3 minutes, and the differences were calculated. The absorbance differences obtained from different concentrations of plant extracts were compared to the control activity. If the plants yielded higher absorbance compared to the control, it means they increased enzyme activity, whereas if they gave a lower absorbance difference, it means they decreased enzyme activity. To better understand this, the obtained enzyme activity values were converted to percentage activity, and graphs were plotted in Excel based on different concentrations of plant extracts (Figures 3 and 4). The IC_{50} value,

which is the concentration of plant extract that reduces enzyme activity by half, was determined. (In this case, since the plant extracts increased enzyme activity, the IC_{50} values, which double the enzyme activity, were interpreted.)[12-14].

Table 1. *Composition of 1 mL cuvette content used in esterase activity studies for hCA isoenzymes.*

Substances Used in the Experiment	Content of Control Tube (Blank) (µL)	Content of Sample Tube
Tris-SO4 (0.5 M) pH 7.4	400	400
p-Nitrophenyl acetate	360	360
Distilled water	240	220
Enzyme solution	-	20
Total final volume	1000	1000

Effects of Artemisia absinthium L. Water and Ethanol Extracts on Carbonic Anhydrase Enzyme Activity

The effects of *Artemisia absinthium* L. extracts on carbonic anhydrase enzyme activity were assessed using the esterase activity method. The data from the study are presented in Figure 1, Figure 2, and Table 2.

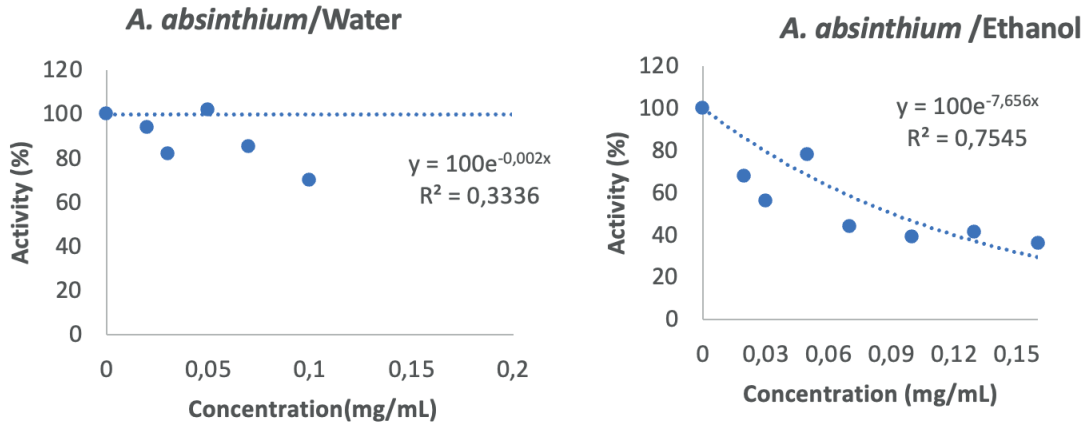

Figure 1. *Inhibition Graphs of Artemisia absinthium L. Extracts Against Carbonic Anhydrase I Enzymes.*

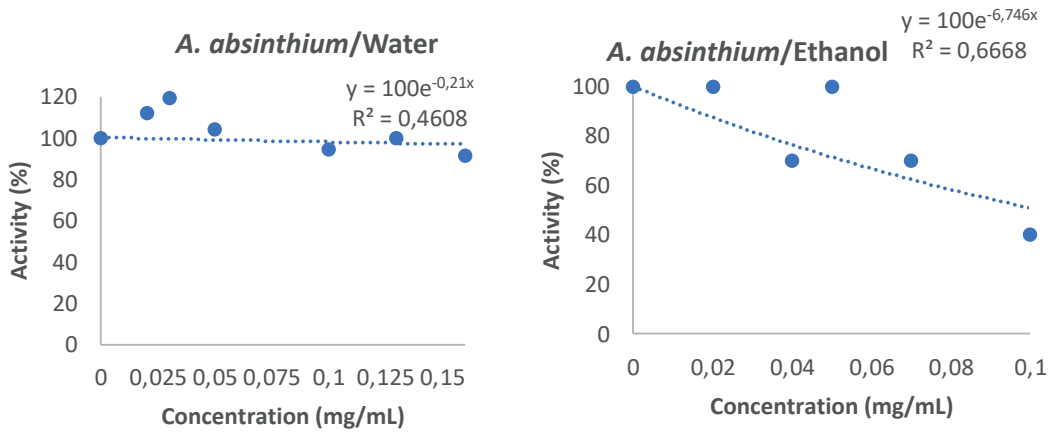

Figure 2. *Inhibition Graphs of Artemisia absinthium L. Extracts Against Carbonic Anhydrase II Enzymes.*

Table 2. *Summarized Inhibition Parameters of Artemisia absinthium L. Plant Extracts Against Human Carbonic Anhydrase I and II Isoforms.*

Comp. #	IC50 (mg/mL)			
	hCA I	r^2	hCA II	r^2
A. absinthium /Water	-	-	-	-
A. absinthium /Ethanol	0.090	0.624	0.102	0.675

Artemisia absinthium L. plant extracts were investigated spectrophotometrically for their effects on carbonic anhydrase isoenzyme I and II. The data obtained were used to plot the % Activity - Plant Extract Concentration graph (Figure 1 and 2). Based on this, it can be stated that both water and alcohol extracts of the plants did not have a significant effect on enzyme activity. It can be noted that the ethanol extract of *A. absinthium* exhibited a higher inhibition potential compared to the water extract.

CONCLUSION

In this study, the effects of *Artemisia absinthium* L. ethyl alcohol and water extracts on the carbonic anhydrase enzyme, which plays a role in various physiological and pathological processes in our body, primarily pH regulation, ureagenesis, gluconeogenesis, lipogenesis, electrolyte secretion, bone resorption, and tumorigenesis, were investigated. When the results of the in vitro enzyme activity experiments were examined, it was observed that these extracts did not have a significant impact on enzyme activities.

DISCUSSION

Plants are natural sources containing a variety of compounds with many different biological effects[15]. They play a significant role in the fight against numerous diseases such as cardiovascular diseases, diabetes, hypertension, Alzheimer's disease, atherosclerosis, and cerebral disorders[16]. The use of plants by humans dates back to the dawn of human history. Plants in both global and our country's flora are widely used not only in areas such as food, dye, resin, flavoring, and the cosmetic industry but also for therapeutic purposes. The World Health Organization (WHO) indicates that there are approximately 21,000 medicinal plants used for therapeutic purposes[17].

Oxidative stress, neuroinflammation, and excitotoxicity contribute to seizure-mediated neuronal damage and apoptosis, leading to potential effects such as epileptogenesis and cognitive impairment. There are numerous studies on the neuroprotective and antiepileptic potentials of certain species within the *Artemisia* genus, particularly the species we are working with, *Artemisia absinthium* L. This effect has been associated with antioxidant phenolic compounds that are effective against ROS-induced oxidative stress[18,19].

The reason for not being able to conclusively prove the antiepileptic potential of *Artemisia absinthium* L. in our study can be attributed to the timing of the species' collection. In the literature, this species is reported to have its flowering period in June and July in many studies where its antioxidant, antidepressant, and antiepileptic effects are observed[18,19].
The fact that there were no flower

parts in the above-ground portion of the samples collected in April may lead to differences in the study results due to its potential impact on the quantity and types of active substances in the extracts.

Conflict of interest statement

The authors declare that they have no conflicts of interests.

Acknowledgements

None.

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Research Article

health science

EVALUATION OF BIOCHEMICAL PARAMETERS IN CORONARY ARTERY PATIENTS WITH COVID-19 INFECTION

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Keywords

COVID-19, Coronary artery disease, Biochemical parameters

ABSTRACT

As a result of pneumonia brought on by coronavirus disease (COVID-19), acute myocardial infarction, and chronic cardiovascular system damage, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects host cells via ACE2 receptors. In patients with coronary artery disease (CAD) who are positive for COVID-19, early measurement of cardiac damage through biomarkers and careful monitoring of myocardial damage that may be caused by infection should be performed. The goal of this study was to retrospectively assess the results of biochemical laboratory testing in patients with CAD and COVID-19. Biochemical laboratory results of 70 patients with CAD and COVID-19 and 70 patients only with CAD were examined retrospectively. A significant difference was detected between groups in terms of LDH, CRP, and Troponin I parameters. These biomarkers are important to prevent and rapidly treat COVID-related myocardial damage in patients with CAD.

INTRODUCTION

An atypical viral pneumonia outbreak was caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which emerged at the end of 2019 in Wuhan, China. This coronavirus infection, also known as COVID-19, has rapidly spread over the world due to its high transmissibility[1]. COVID-19, a multisystemic illness, infection mostly affects the respiratory system. Increased pro-inflammatory cytokine and chemokine production, altered cellular immunological responses, cardiovascular and respiratory failure, abnormal coagulation indices, organ damage, and even death have all been displayed in severe COVID-19 instances[2]. These are all symptoms of SARS-CoV-2 infection of host cells through angiotensin-converting enzyme receptors (ACE2)[2,3]. The cardiovascular and immune systems depend heavily on the membrane-bound aminopeptidase ACE2. ACE2 has been linked to the onset of diabetes mellitus and hypertension in addition to its association with heart health. Furthermore, it has been discovered that ACE2 functions as a receptor for coronaviruses and SARS-CoV-2 infection is triggered by the viral spike protein binding to ACE2, which is abundantly expressed in the lungs and heart. Respiratory symptoms are brought on by SARS-CoV-2, which principally damages alveolar epithelial cells[3].

It is hypothesized that the cardiac injury lead by COVID-19 infection may have an important role in the progression of intense clinical manifestations or negative outcomes in infected people. In patients with COVID-19, myocardial injury is closely correlated with disease severity and even prognosis. Further preventive measures should be taken in patients with pre-existing coronary artery disease (CAD) in relation with the negative effects of COVID-19 on the cardiovascular system[4]. Therefore, it is crucial that patients with COVID-19 be treated promptly

Volume: 1
Issue: 2
Page: 46-50

Received:
21.07.2023

Accepted:
05.09.2023

Available Online:
15.10.2023

DOI:10.5281/zenodo.8413853

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to reduce mortality once the relevant symptoms appear. Therefore, in a patient with CAD, early measurement of cardiac damage via biomarkers and careful monitoring of any myocardial damage that may be caused by the infection are recommended after hospitalization for COVID-19[5,6].

Especially in the presence of concomitant CAD, COVID-19 infection is severe and the risk of death increases. COVID-19 infections can lead to many clinical pictures ranging from myocardial infection, myocarditis, heart failure, and arrhythmias to venous thromboembolism. Mechanisms such as inflammation, cytokine storm, increased coagulation functions, as well as an imbalance between myocardial oxygen supply and myocardial oxygen demand cause cardiac damage in COVID-19 infections[7]. The goal of this study is to retrospectively assess the results of biochemical laboratory testing in CAD patients who have positive COVID-19 results.

MATERIALS AND METHODS

Study Subjects

This is a retrospective study. The study group included 70 patients with CAD who had a positive PCR test followed up in the Cardiology Service at Mersin University Hospital between September 2020 and December 2021 and the control group included 70 patients with CAD who presented with clinical complaints with suspicion of COVID-19 but whose PCR test was negative. Patients with non-reference values due to malignancy, liver, or kidney disease were excluded from the study. The Mersin University Clinical Research Ethics Committee approved the study (11.05.2022, 2022/330).

Data Collection

The demographic characteristics and laboratory data of all participants were collected from their individual medical records retrospectively. In addition to their age, gender, COVID-19 PCR test results, biochemical data such as urea, Creatine Kinase (CK-MB), C Reactive Protein (CRP), Lactate dehydrogenase (LDH), creatinine, Troponin I, aspartate aminotransferase (AST), and lipid profiles (low-density lipoprotein (LDL), triglyceride (TG), high-density lipoprotein (HDL), total cholesterol), and alanine aminotransferase (ALT) were examined. AST, ALT, LDH, CK-MB, and urea were measured by an enzymatic method, creatinine by the colorimetric Jaffe method, and C Reactive Protein (CRP) by a turbidimetric method in an autoanalyzer (AU680, Beckman Coulter Inc. Japan). The lipid profile was studied via an enzymatic colorimetric method in a Cobas 501 autoanalyzer (Roche Diagnostics, Manheim GmbH, Germany). Troponin I was detected by the chemiluminescence immunoassay method on DXI 800 (Beckman Coulter, Inc.)

Statistical Analyses

It was determined using the SPSS Statistics software, demo version 22 (trial version, IBM Corporation, Somers, NY). The Box-Plot chart method was used to find and eliminate outliers in the continuous data. To detect if the distribution of continuous variables was normal, the Shapiro-Wilk test was applied. For continuous variables, interquartile range (25th–75th percentiles) was used to express mean, median, and SD. Depending on whether the distributions were normal, either Student's t-test or the Mann-Whitney U test was used to determine whether there was a difference between the mean/median values of the patient and control groups for each parameter. Statistics were judged significant for a p value less than 0.05.

FINDINGS

The mean age of the patient group (55 men and 15 women) and controls (48 men and 22 women) was 60.67±10.83 and 58.04± 6.69, respectively. Biochemical parameters are given in Table 1. LDH, CRP, and Troponin I parameters showed a significant difference between the groups. Although CK-MB level was higher in the patient group, it was not statistically significant.

DISCUSSION

In the literature, it was observed that 40% of the patients hospitalized due to COVID-19 had a history of cerebrovascular or cardiovascular disease and 7% had acute cardiac damage at the time of diagnosis and follow-up. Clinical presentation of patients with COVID-19 was considered to have acute cardiac injury. Enzyme elevation (hs-cTn), which indicates cardiac damage, alone is insufficient for the diagnosis of acute cardiac injury, especially acute MI[5,6]. For diagnosis, it is essential to assess symptoms, ECG, and CKMB elevation. In our study, Troponin I and CK-MB parameters were higher in the

patient group to controls, and the elevation in the troponin level was statistically significant. The most likely cause of cardiac enzyme elevation and myocardial damage in the course of COVID-19 is the direct myocardial damage caused by the virus. Due to the intense distribution of ACE2 in the binding site of SARS-CoV-2 in cardiac myocyte cells, the virus has a high affinity for these cells, and therefore, it causes destruction. It is held responsible for the increase in troponin by causing myocarditis [1,5,7,8]. Also, it was reported that there was cardiac damage and there was a significant increase in levels of cardiac troponin I (hs-cTnI) in five of the 41 patients with COVID-19 who received a diagnosis in Wuhan[9]. In another study, there was an increase in the CK-MB along with hs-cTnI in COVID-19 patients, and the reason for this outcome was thought to be complications including acute myocardial damage in patients with severe symptoms. Nevertheless, 58% of patients with severe COVID-19 symptoms were reported to have hypertension, 25% to have heart disease, and 44% to have arrhythmia[10]. Of patients with SARS-CoV-2, 35% had a history of hypertension, and 17% had a history of CAD, according to mortality statistics published in China[10]. Additionally, data show that systemic symptoms are more severe and the incidence of severe pneumonia is higher in patients over 60 years of age and infected with SARS-CoV-2 than in patients aged ≤60 years. It was reported that underlying CAD may aggravate pneumonia and increase the severity of symptoms in patients with SARS-CoV-2 infection[11].

Elevated levels of AST, ALT, and LDH are signs of damaged liver. In COVID-19 illness, immune-mediated injury resulting from a significant inflammatory response, direct cytotoxicity brought on by active viral replication in biliary epithelial cells expressing ACE2, hypoxic hepatitis brought on by anoxia, and drug-induced liver injury are all possible clinical causes[12]. According to our results, there was no difference between the groups in terms of AST and ALT, but LDH was higher in the patient group. Also, no statistical difference was detected between the patient group and controls in terms of lipid profile, urea, and creatinine levels. Most COVID-19 patients (75%–93%) have increased CRP levels[13]. Furthermore, we discovered that CRP, an inflammatory marker, was higher in the patient group compared to controls.

Our study had some limitations because it was retrospective. These limitations were that it was studied in a single center and that the results of D-dimer, Fibrinogen, and Ferritin, which are important in COVID-19 infection and CAD, were not complete in patient files.

CONCLUSION

In conclusion, myocardial damage in patients with COVID-19 is closely related to the severity and even progression of the disease. To reduce mortality, it is important to treat patients with CAD as soon as relevant COVID-19 symptoms appear. Therefore, early assessment of cardiac damage with these biomarkers is important to prevent and rapidly treat COVID-related myocardial damage in patients with CAD.

Table 1. *Biochemical parameters of the patient and control groups.*

Parameter	Patient n:70	Control n:70	p
AST* (U/L)	23.5 (16.5-32.5)	22.05(19-27.1)	0.64
ALT* (U/L)	21.7 (17.1-28.1)	22 (15-28.4)	0.57
LDH* (U/L)	183 (160-214)	161.5 (141-178)	0.004
CK-MB* (U/L)	94.5 (63-257)	80 (50-120)	0.072
CRP * (mg /dL)	5.29 (2.80-12.65)	1.85(0.75-3.35)	0.00001
Troponin I*(ng/mL)	3.11 (2.9-5.4)	0.004(0.002-0.006)	0.002
Urea # (mg /dl)	25.87±8.21	26.45±7.96	0.67
Creatinine# (U/L)	0.817±0.22	0.76±0.17	0.09
Total Cholesterol# (mg/dl)	179.89±42.84	184.3±61.03	0.61
HDL # (mg/dl)	43.6 ±20	41.36±12.7	0.44
LDL # (mg/dl)	104.02±37.09	105.36±41.2	0.87
Triglyceride# (mg/dl)	177.03±82.07	164.5±86.4	0.4

*# Continuous variables are given as mean±standard deviation, * variables are given as median (IQR: interquartile range) p: significance between groups, n: Number of samples.*

Conflict of interest statement

The author declares that they have no conflicts of interests.

Acknowledgements

We thank Prof. Dr. Lülüfer Tamer, Assoc. Prof. Dr. Şenay Balcı Fidancı, and Assoc. Prof. Dr. Buğra Özkan for their contributions to this study.

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Research Article

health science

THE EFFECT OF CLOSURE OF PERITONEUM AND ANATOMICAL LAYERS ON ADHESION FORMATION IN PATIENTS UNDERGOING CESAREAN SECTION

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Keywords

Cesarean section, Adhesion incidence, Peritoneal closure, Operative time

ABSTRACT

This study is to investigate the effect of closure of the peritoneum and other anatomical layers on adhesion formation in patients undergoing cesarean section, and to compare the effect of different closure of layers on adhesion formation. The operation notes of 1021 patients were retrospectively analyzed and the abdominal closure technique in the previous cesarean section was recorded. Presence and severity of adhesion in the second cesarean section was recorded using the NAIR's classification which was previously defined by the same operator. Four groups were formed according to the closure technique and the groups were compared with each other according to the adhesion scale recorded during the second cesarean section. There was no statistically significant difference between the groups in terms of age, BMI, number of pregnancies and cesarean section. Among the 4 groups formed according to the closure technique, the rate of adhesion formation was statistically the highest in the group in which the fascia was closed directly after the closure of uterus. Adhesion formation has decreased significantly as the number of sutured anatomical layers increased. Adhesion severity was found to be statistically significantly higher in the direct closure group. As the number of sutured layers increased, the severity of adhesion was found to be significantly lower. The operative time was found to be significantly longer as the severity of adhesion. Although not statistically significant, two major organ injuries occurred in the group without layered closure. The second operative time was found to be significantly higher as the severity of adhesion increased.

INTRODUCTION

Peritoneal adhesions are defined as pathological fibrotic bands formed between two surfaces within the peritoneal space[1]. The development of adhesion may be due to different reasons. Although adhesions are often due to a surgical intervention; peritonitis, endometriosis, pelvic inflammatory disease, long-term peritoneal dialysis, chemical peritonitis, radiotherapy and cancer can also cause adhesions[2,3,4]. At least one of these two surfaces must have a mesothelial damage for the development of adhesion[5]. Fibrinous exudate is released a few hours after mesothelial damage. Fibrous bands and newly formed capillaries are left behind after the absorption of exudate. These structures form the permanent fibrotic adhesions[5,6]. These adhesions can cause mechanical intestinal obstructions, secondary infertility and chronic abdominal pain. In addition, they increase the possibility of iatrogenic injury when intra-abdominal surgical intervention is required[7]. Many substances, including steroid and non-steroidal anti-inflammatory agents, have been used experimentally to prevent intra-abdominal adhesions. However, their use in clinical practice has been limited due to their systemic side effects[8].

Volume: 1
Issue: 2
Page: 51-56

Received:
01.08.2023

Accepted:
10.09.2023

Available Online:
15.10.2023

DOI:10.5281/zenodo.8413870

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Adhesions can also be seen after cesarean section and the rate of adhesions increases as the number of cesarean section operations increases. However, cesarean section differs from other abdominal and gynecological operations. All the factors such as removal of abdominal and pelvic organs from the surgical field by pregnant uterus, not applying primary surgery to organs with frequent adhesions such as omentum and ovary, changes in fibrin and fibrinolytic system as a result of physiological changes during pregnancy, change in the levels of adhesion molecules and chemotactic cellular mediators, the rapid entrance to the abdomen and therefore the relatively high tissue damage, presence of blood, clots and amniotic fluid in the peritoneal cavity, distinguishes cesarean section from other surgical procedures in terms of adhesion formation[9].

Postoperative intra-abdominal adhesions significantly affect quality of life in patients undergoing abdominal surgery and is still an important problem today. Despite the shortening of the operative time, the anti-infectious agents used, technological developments in suture materials, the incidence of adhesion is still at substantial levels.

There are many studies about adhesion. However, the materials used in these studies, which are still referenced, are not being used nowadays. Besides, antibiotics that were not used in out-of-date studies are currently used prophylactically, which reduces the incidence of adhesion. Suture materials have been replaced by synthetic materials with technological developments that cause less reaction and are absorbed faster. At the same time, with this progress, talcum powder, which is used in gloves and known to cause adhesion, is no longer used.

Surgical success increases and adhesions and complications decrease as a result of the positive developments in the pharmaceutical and medical materials industry. The aim of this study is to determine the conditions that may cause adhesion due to surgical technique by reviewing the intraoperative processes with these developments and minimizing the surgeon factor for the adhesion and further reducing the adhesions.

MATERIALS AND METHODS

Our single-center, prospective clinical study included 1021 patients with a previous cesarean section who applied to Private Sivas Medicana Hospital to give birth between November 2019 and November 2022 and were planned to have a second cesarean delivery with this indication.

Patients to whom an anti-adhesion barrier was used in their previous cesarean section, patients who have undergone different surgeries that may increase adhesion formation other than cesarean section, patients who have undergone abdominal surgery with another indication such as myomectomy, ovarian surgery, appendectomy, patients with a previous history of abscess or pelvic inflammatory disease (PID), patients with systemic disease such as endometriosis, collagen tissue disease, systemic lupus erythematosus, vasculitis and diabetes, and patients who underwent additional surgery (e.g, myomectomy, oophorectomy, cystectomy, drain placement) in a previous cesarean section were not included in this study. All patients who met the inclusion criteria were informed before participation and their consent was obtained. The study was carried out in accordance with the Declaration of Helsinki, after taking the approval of local ethics committee. Demographic data of all patients included in the study, such as age, body mass index (BMI), gravida, parity, and the number of previous cesarean sections were noted.

The previous surgery notes of the cases were reviewed. It was recorded whether visceral peritoneum, parietal peritoneum and muscle closure was performed, and if so, with which material. Since it was determined that similar materials were used in peritoneal and muscle closure, material comparison was not considered necessary. The patients were divided into 4 groups according to these records:

Preoperative grouping of patients according to their previous operation notes:

1. Group 1: Patients in whom the fascia was closed directly without closing the peritoneum and muscle (n=256)

2. Group 2: Patients in whom only the parietal peritoneum was closed (n=251)

3. Group 3: Patients with closure of the parietal and visceral peritoneum (n=261)

4. Group 4: Patients with closure of parietal, visceral peritoneum and muscle (n=257)

All patients' adhesions during the second operation were recorded in written and visually by a single operator. The duration of the second

operation performed by the same operator was also recorded. The presence and severity of adhesions formed after the first operation were graded intraoperatively by the operator using the NAIR classification system[6]. According to this classification, patients were evaluated in terms of intra-abdominal adhesions as follows:

Grade 0: no adhesion;

Grade 1: single adhesive band between organs or between organs and abdominal wall;

Grade 2: Two adhesive bands between organs or between organs and abdominal wall;

Grade 3: more than 2 adhesive bands between organs or between organs and abdominal wall;

Grade 4: adherence of an organ directly to the abdominal wall, regardless of the number of adhesive bands.

The groups were compared in terms of operative time and presence of a relationship between the number closed layers and adhesion scores.
SPSS for Windows 22.00 statistical program was used in the analysis of the data obtained in the study. Frequency analysis, percentage analysis, Pearson Product-Moment correlation analysis, One-Way Analysis of Variance ANOVA, Bonferroni Post Hoc test, Chi-square test were used in the analysis of the data. P<0.05 was considered statistically significant.

RESULTS

There was no statistically significant difference between the groups in terms of age, BMI (body mass index), number of pregnancies and cesarean section (p>0.05) (Table 1).

Table 1. *Comparison of surgical groups in terms of age, BMI, number of pregnancies, number of cesarean sections.*

	Group 1	Group 2	Group 3	Group 4	P value
Age	32,11±4,63	32,05±4,76	32,22±4,83	31,93±4,86	p=,926
BMI	33,14±2,95	33,27±3,01	33,16±2,99	33,04±2,99	p=,861
Number of pregnancies	2,00±,000	2,00±,000	2,00±,000	2,00±,000	*
Number of cesarean section	1,00±,000	1,00±,000	1,00±,000	1,00±,000	*

** Since the mean of all groups was the same, analysis could not be performed. Data are presented as Median±standard deviation(X±SD). No statistical difference was found between the groups (P<0.05).*

There was no adhesion in 649 patients (63.6%) and adhesion was present in 372 patients (36.4%). Adhesion was observed in 83.5% of the patients in Group 1, 42% of the patients in Group 2, 11.2% of the patients in Group 3, and 9.8% of the patients in Group 4. The difference between the groups in terms of adhesion was found to be statistically significant (p<0,05). According to this, adhesion is observed mostly in Group 1 patients and least in Group 4 patients (Table 2).

Table 2. *Comparison of surgical groups in terms of presence of adhesion.*

Surgical group	Presence of adhesion	n	%	P value
Group 1	Yes No	213 42	83,5 16,5	p=,000
Group 2	Yes No	105 145	42,0 58,0	p=,000
Group 3	Yes No	29 231	11,2 88,8	p=,000
Group 4	Yes No	25 231	9,8 90,2	p=,000

** P<0.5 was accepted as significant.*

The severity of adhesion in patients was determined according to the NAIR classification system as follows: Grade 1: 251 patients (67.5%), Grade 2: 58 patients (15.6%), Grade 3: 41 patients (11%), Grade 4: 22 patients (5.9%). According to these results, the severity of adhesion was found to be mild in the majority of patients. The difference between the groups in terms of the severity of adhesion was found to be statistically significant (p<0,05) (Table 3).

Table 3. *Comparison of surgical groups in terms of adhesion severity.*

Adhesion grade	Grade 1		Grade 2		Grade 3		Grade 4		P value
Group	n	%	n	%	n	%	n	%	
Group 1	111	52,1	46	21,6	34	16,0	22	10,3	p=,000
Group 2	95	90,5	6	5,7	4	3,8	0	0,00	p=,000
Group 3	26	89,7	0	0,00	3	10,3	0	0,00	p=,000
Group 4	19	76,0	6	24,0	0	0,00	0	0,00	p=,000

** P<0.5 was accepted as significant.*

Adhesion severity was found to be Grade 1, Grade 2, Grade 3 and Grade 4 in 52.1%, 21.6%, 16%, and 10.3% of patients in group 1, respectively. Adhesion severity was found to be Grade 1, Grade 2 and Grade 3 in 90.5%, 5.7%, 3.8% of patients in group 2, respectively. Adhesion severity was found to be Grade 1 and Grade 3 in 89.7% and 10.3% of patients in group 3, respectively. Adhesion severity was found to be Grade 1 and Grade 2 in 76.0% and 24.0% of patients in group 4, respectively (Table 3).

The mean operative time of patients with Grade 1, Grade 2, Grade3 and Grade 4 adhesions was found as 33.88, 37.71, 44.76 and 58.14 minutes, respectively. The time differences between the groups were found to be statistically significant (p<0,05). It has been determined that there is a correct relationship between the severity of adhesion and the duration of the operation (r=,81, p<0.05). As a result, it can be said that the severity of adhesion and the duration of the operation increase simultaneously (Table 4).

Table 4. *Findings related to the differences in terms of operation time according to the severity of adhesion of the patients included in the study.*

Surgical group	n	Duration of surgery	P value
Group 1	251	33,88±2,87	p=,000
Group 2	58	37,71±4,92	
Group 3	41	44,76±2,46	
Group 4	22	58,14±11,41	

** Data are presented as Median±standard deviation(X±SD). P<0.5 was accepted as significant.*

DISCUSSION

Adhesions after cesarean section are an important problem due to increased time to reach the abdomen and uterine cavity during repeated cesarean section operations, difficulty in exploring the abdominal cavity, Injuries to surrounding organs during adhesiolysis and making it difficult to suture the uterus outside the abdomen.

The incidence of adhesion after cesarean section has been reported as 43% (16% thin and 27% thick adhesion)[10]. In another study, pelvic adhesions were shown to occur at a rate of 46% after the first cesarean, 75% after the second cesarean, and 83% after the third cesarean[11]. Again, in a prospective cohort analysis, adhesion was observed in 52% of cesarean sections with closed parietal peritoneum and 73% in non-closure cesarean sections[12].

In our study, the incidence of adhesion was determined as 36.4% in all patients. The incidence of adhesion was 83.5% in the group where the layers were not closed, and 9.8% in the group where all layers were closed. The incidence of adhesion after intra-abdominal surgery is 67-93% in the surgical literature[13]. This difference in adhesion formation may be due to the fact that the pregnant uterus pushes the abdominal and pelvic organs away from the surgical field. The formation of fibrin bands during adhesion development, migration of cellular elements, and organization of fibrin bands as a result of ischemia or a decrease in fibrinolytic activity occur in the early postoperative period. The post-cesarean involution process of the uterus keeps the surrounding organs and intestines away from the uterine incision line. In addition, fibrinolytic activity and changes in adhesion molecules in the amniotic fluid and membrane during pregnancy may cause less adhesions after cesarean section[14]. In an animal study in rats, it was shown that the human amniotic membrane prevents the formation of adhesion[15].

There are also studies in the literature showing that the peritoneal closure increases the formation of adhesion[16]. We know that infection, which is one of the most effective causes of adhesions, cannot be controlled in a study of Conolly et al. in 1968 as well as today. In addition, this study is a study in which catgut, a surgical material that is not modern and is not used in surgery today and can increase adhesion with its reaction, is used.
On the other hand, there are studies in the literature showing that closing the peritoneal folds in accordance with surgical techniques in gynecological and obstetric surgeries reduces adhesions[17]. In our study, it was observed that closure of the peritoneum and muscle reduced the formation of adhesions.

Additionally, i it was found in a study examining 190 cesarean section cases that the incidence of adhesion increased 8 times in the group in which the peritoneum was not closed[18]. In another study examining 173 cesarean section cases, it was shown that peritoneal closure alone reduced the incidence of adhesion by 5 times[19]. In our study, the incidence of adhesion decreased 8 times in patients whose parietal and visceral peritoneum were closed. In our study, the incidence of adhesion was found to be 2 times lower in the group with only parietal peritoneum closure when compared with the non-closure group.

It was found that the incidence of adhesion was highest in the group (Group 1) where the fascia was closed directly after closure of the uterus. In addition, it was observed that the rate of Grade 4 adhesion, according to the NAIR classification, was significantly increased in this group ($p<0.05$). Studies in the literature show that adhesions increase the duration of the cesarean section [20]. In our study, it was shown that the adhesion severity and operation time increased simultaneously, in line with the literature ($p<0.05$).The increase in adhesions and their severity also increases the risk of intraoperative complications [21,22].

Major organ injury was observed in two cases with grade 4 adhesion although it was not statistically significant in our study.

Although there are surgical schools in which the parietal peritoneum, visceral peritoneum and muscle layers are closed after the closure of uterus during cesarean section, there are also surgical schools, in which the fascia is closed directly after the closure of uterus. There are also different closing techniques rather than these two methods. The aim of this study is to investigate the effect of postoperative abdominal closure techniques together with modern medical materials and prophylactic drugs on the incidence of adhesion, and to reduce the incidence of adhesion in the light of the findings.

Adhesions after cesarean section increase the operative time and complication rate in the next surgery. A dramatic decrease in the incidence of infections, which is one of the most common causes of postoperative adhesions, has been observed with the advancement in modern medicine. In addition, the use of fast-absorbing suture materials with minimized foreign body reaction is one of the factors that reduces the incidence of adhesion. No matter how good the surgical technique is, it is not possible to completely prevent adhesions. According to the results of our study, closure of visceral, parietal peritoneum and muscle separately reduces the formation of intra-abdominal adhesions after cesarean section.

The incidence of adhesion is more than twice the average incidence of adhesion when none of the layers is closed. Both in the literature and in our study, the incidence of adhesion was found to be 5 to 8 times lower in cases where two layers of the peritoneum were closed compared to non-closure patients. Major organ injury (bowel and bladder) has occurred in only two of 1021 patients included in the study and these two injuries has occurred in the non-closure group. Although the incidence of major organ injury was not statistically significant, the length of the operation time, the incidence of adhesion and the severity of adhesion significantly increased in the non-closure group.

CONCLUSION

In conclusion, it was found in our study that anatomical closure of the layers during cesarean section statistically reduced adhesion and shortened the subsequent operation time statistically. Although major organ injury was not statistically significant in two patients in whom the anatomical layers were not closed, it can be said that closure of the anatomical layers reduces the risk of major organ injury. Although more comprehensive multicentric studies are needed with modern medicine, we recommend closing the anatomical layers after cesarean section as a result of our study.

Conflict of interest statement

The authors declare that they have no conflicts of interests.

Acknowledgements

None.

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Research Article

health science

ANALYSIS OF 10-YEAR EXCISIONAL LYMPH NODE BIOPSY RESULTS

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Keywords

Biopsy,
Lymph node,
Lymphoma,
Malignancy

ABSTRACT

Lymph nodes become enlarged and prominent in the presence of infection or malignant cell infiltration. Lymph nodes that do not regress with treatment or whose findings indicate malignancy should be evaluated for biopsy. This study aimed to analyze lymph nodes considered malignancy suspicion retrospectively and underwent excisional biopsy. Patients who underwent excisional lymph node biopsy between January 2011 and December 2021 were evaluated retrospectively. The patient's age, gender, diameter of the excised lymph nodes, excision area, and histopathological examination results were assessed. It was determined that 174 excisional lymph node biopsies were performed. One hundred fifty-six of these patients were included in the study. The average age of the patients was found to be 49.63+15.16 years. It was determined that 51.28% of the patients were women. The average lymph node diameter was determined as 2.75+1.13 mm. It was observed that lymph node biopsy was most frequently performed from the right axillary region (n:49). Lymphoma was detected in 44 of 156 patients (28.2%). Four metastatic lymph nodes and tuberculosis were detected in 4 patients. Excisional lymph node biopsy remains important as an effective and rapid diagnostic method for diagnosing lymphoma.

INTRODUCTION

Enlarged lymph nodes are a condition that may appear as the first sign of diseases and cause serious concern for patients. After examining these patients, ultrasonography is first performed[1,2]. The necessity of biopsy comes to the fore when the lymph node is evaluated, along with radiological findings, and infection is not considered. In these patients, imaging-guided needle biopsies are performed primarily as a minimally invasive procedure[3,4]. However, these needle biopsies are not always sufficient for diagnosis, and lymph node excision may be required[3,5]. Excisional biopsy is the procedure that should be performed to confirm the diagnosis in granulomatous diseases, hematological malignancies, or in patients whose diagnosis cannot be made by needle biopsy[4,6]. The clinician may first request an excisional biopsy to evaluate hematological pathologies and lymph node capsule invasion. In this study, the results of patients who underwent excisional lymph node biopsy were evaluated and the results were analyzed.

Volume: 1
Issue: 2
Page: 57-60

Received:
02.08.2023

Accepted:
12.09.2023

Available Online:
15.10.2023

DOI: 10.5281/zenodo.8413902

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MATERIALS AND METHODS

Patients who underwent excisional lymph node biopsy between January 2011 and December 2021 were evaluated retrospectively. The patient's age, gender, lymph node diameter, lymph node localization, preoperative diagnosis, and histopathology result of the excised lymph node were evaluated. Lymph node diameter was taken as the largest diameter detected on ultrasonography. Data about the patients were taken from the hospital IT database. Retrospective study approval was received for this study (2021-2681). Patients diagnosed with fine needle biopsy and tru cut biopsy were excluded from the study.

Statistical Analysis

For statistical analysis, SPSS for Windows version 22.0 package software was used. Descriptive statistics include mean and standard deviation for numerical variables and number and percentage values for categorical variables. The Pearson correlation coefficient was used to test relations between numeric variables.

RESULTS

Among the patients who underwent excisional biopsy, seven patients, 11 of whom were diagnosed with malignancy and excised due to suspicion of metastasis, were excluded from the study after being detected in the operating room during the surgical procedures and sent for examination. A total of 156 patients were included in the study. It was determined that an excisional biopsy was planned in these patients to consider and diagnose malignancy. The average age of the patients was found to be 49.63+15.16 years. The average lymph node diameter was found to be 2.75+1.13 cm. The average diameter of malignant lymph nodes was found to be 3.4+0.35 cm. It was determined that 80 patients (51.28%) were women. It was determined that 72 of these 156 patients (46.15%) had a preliminary lymphoma diagnosis; therefore, an excisional lymph node biopsy was requested. As a result of histopathological examination of the lymph nodes removed from these 72 patients, it was determined that 26 (36.11%) had lymphoma. As a result of histopathological examination of all 156 patients, 44 (28.2%) lymphomas were detected. Malignant melanoma metastasis was detected in 3 patients, and Kaposi sarcoma was seen in 1 patient. Chronic Lymphocytic Leukemia (CLL) in 3 patients (1.92%), tuberculosis in 4 patients (2.56%), Ebstein Barr virus (EBV)-related lymphoproliferative disease in 3 patients (1.92%), and one patient (0.64%) Castleman Disease was detected. Granulomatous lymphadenopathy was seen in 17 patients (10.89%). Reactive or nonspecific lymphadenopathy was detected in 80 patients (51.28%) (Table 1). It was determined that the most common biopsy location was the right axilla (n: 49) (31.41%). It was determined that excisional lymph node biopsy was performed second most frequently from the left axilla (n: 40) and third most often from the right inguinal region (n: 30) (19.23%). Excisional biopsy performed from the periauricular area is noteworthy, with the most minor frequency occurring in 1 case (Table 2).

Table 1. *Distribution of diseases.*

Diagnosis	n	%
Lymphoma	44	28,2
Metastatic Lymph Node	4	2,56
Tuberculosis	4	2,56
CLL	3	1,92
EBV-Related Lymphoproliferative Disease	3	1,92
Castleman Disease	1	0,64
Granulomatous lymphadenitis	17	10,89
Reactive/nonspecific lymphadenopathy	80	51,28

** CLL: Chronic lymphocytic leukemia.*

Table 2. *Lymph node biopsy areas.*

Anatomical region	n	%
Right axillary region	49	31,41
Left axillary region	40	25,64
Right inguinal region	30	19,23
Left inguinal region	24	15,38
Right supraclavicular region	2	1,28
Left supraclavicular region	4	2,56
Right cervical region	3	1,92
Left cervical region	3	1,92
Periauricular region (Right)	1	0,64

DISCUSSION

Lymph nodes may enlarge due to viral, bacterial, or neoplastic cell infiltration[7]. Lymph nodes in the inguinal area can often be detected during adult examination. Cervical or submandibular lymph nodes can be seen in the presence of upper respiratory tract infections[8]. Lymphadenopathies that develop due to infectious agents regress with treatment. The need for biopsy arises in lymphadenopathies that do not regress despite the treatment given[9]. Physical examination findings of lymph nodes, radiological evaluation results, and the presence of widespread lymph nodes are the parameters that affect the biopsy decision[6,10].

Needle biopsies are frequently used to evaluate lymph nodes as a minimally invasive method. However, in cases where needle biopsies give insufficient results, especially in diagnosing lymphoproliferative diseases, lymph node excision remains essential. In this study, lymphoma was most frequently detected in the excised lymph nodes, which is compatible with literature data[3,11,12]. Among the patient data included in the study, 46.15% of the patients were referred for biopsy with a preliminary diagnosis of lymphoma, which appears to be a high rate. This may be why the clinician who thinks the patient has lymphoma prefers an excisional biopsy to reach a diagnosis quickly. Histopathology results highly confirm the clinician's suspicions. It allows patients to start early treatment with an accurate diagnosis obtained in a short time. The fact that needle biopsies cannot be diagnosed, especially in the diagnosis of low-grade lymphoma and diffuse large B-cell lymphoma, ensures that excisional lymph node biopsies still maintain their importance as a valuable and rapid diagnostic method in the diagnosis of lymphoma[13,15]. In our study, malignancy was detected in 51 (32.69%) of 156 patients who required excisional biopsy due to enlargement and structural change of lymph nodes. This rate attracts attention as a high malignancy detection rate. Notably, the right axillary region was preferred as the biopsy location.

In their study, Chan et al. highlight the importance of taking enough samples from the lesion for analysis. This is because, in cases of classical Hodgkin lymphoma, about one-third of small biopsy samples may not be diagnosed by Flow cytometry due to the low number of collected cells. Therefore, sufficient material is necessary to ensure accurate diagnosis. Interestingly, fibrosis associated with nodular sclerosis may be partially responsible for the low number of cells collected in some cases[16]. No patient in our study who underwent an excisional biopsy was shown to be unable to diagnose due to tissue insufficiency.

Nixon et al., in their study, multivariate analysis showed that lymph nodes smaller than 3.4 cm, young age, and rheumatological diseases were associated with non-malignant lymph nodes[17]. In a study by Bosch et al., it was found that lymph node size of 1 cm or larger and hard and fixed tissue are associated with a cancer diagnosis. Similarly, Kuhnl et al. reported that older age, male gender, supraclavicular node involvement, and multiple nodal sites were indicative of a malignant diagnosis. On the other hand, extranodal sites were linked to a lower risk. In our study, the average size of all lymph nodes was 2.75+1.13 cm, while the average size of malignant lymph nodes was 3.4+0.35 cm.

CONCLUSION

Excisional lymph node biopsy still maintains its importance, especially in diagnosing lymphoma. It is arguably still the most important diagnostic method in diagnosing low-grade lymphomas. In cases where lymphoma is suspected clinically and radiologically, performing an excisional lymph node biopsy as soon as possible to reach an early diagnosis may provide the advantage of starting early treatment.

Conflict of interest statement

The authors declare that they have no conflicts of interests.

Acknowledgements

None.

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Research Article

health science

RELATIONSHIP BETWEEN CORONARY COLLATERAL DEVELOPMENT AND SCUBE (SIGNAL PEPTIDE-CUB-EGF DOMAIN-CONTAINING PROTEIN) LEVELS IN PATIENTS WITH CORONARY ARTERY DISEASE

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Keywords

Coronary artery disease, Coronary collateral development, SCUBE1, Signal Peptide CUB-EGF like Domain Containing Protein

ABSTRACT

Our study focused on exploring the connection between serum SCUBE1 (Signal Peptide CUB-EGF like Domain Containing Protein) levels and the formation of CCC (Coronary Collateral Circulation) in patients diagnosed with CAD (coronary artery disease). In the study, we included 80 patients who underwent coronary angiography in the cardiology clinic between April 25, 2019 and April 25, 2020. Their mean age was 63.75 ± 10.7 years. Of them, 30 with normal coronary arteries were assigned to Group 1, 19 with CAD to Group 2, and 31 with CAD who developed CCC to Group 3. The mean SCUBE1 level was 30.61±2.6ng/ml in all the patients. There was no significant difference between the groups (P=0.272). As a result, we compared SCUBE1 levels according to the development of CCC in patients with CAD for the first time in the literature. The findings demonstrated that the measurement of SCUBE1 levels alone might be insufficient to predict the development of CCC in patients with CAD. To confirm these results, multicenter studies with larger samples should be conducted.

INTRODUCTION

Even with the progress made in science and technology, CAD continues to be a major contributor to mortality rates in developed nations. CAD most commonly develops in patients with atherosclerosis. Explaining the risk factors and underlying biological and anatomical connections of atherosclerosis complications can be challenging[1]. Collateral vessels, which help to protect the myocardium in patients with CAD, limit the infarct area and can prevent the development of left ventricular aneurysm and heart failure, which significantly reduces mortality and morbidity rates[2].

Therefore, it is important to investigate the biological factors likely to affect the development of collateral vessels[3]. Mechanisms of angiogenesis and arteriogenesis play a role in the development of CCC[4]. In studies conducted within this context, SCUBE (Signal Peptide CUB-EGF like Domain Containing Protein) molecule has been indicated to play a role in platelet aggregation, angiogenesis, arteriogenesis, carcinogenesis and the development of the nervous system[5,6]. Signal Peptide CUB-EGF Domain-Containing Proteins belong to the EGF superfamily, characterized by diverse domain structures such as epidermal growth factor (EGF)-like repeats, cysteine-rich repeat motifs, and the CUB (complement protein C1r/C1s, Uegf and Bmp1) domain.

Volume: 1
Issue: 2
Page: 61-68

Received:
30.06.2023

Accepted:
03.08.2023

Available Online:
15.10.2023

DOI:10.5281/zenodo.8414505

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The SCUBE molecule has been detected predominantly in the gonads, developing tissues, central nervous system, dermomyotomes, finger mesenchyme, limb buds, endothelium, and alpha granules of inactive platelets during early embryogenesis[7]. There are three different isoforms of the protein in mammals, namely SCUBE1, SCUBE2 and SCUBE3. It may exist in the cell as a peripheral membrane protein or as a protein secreted to the extracellular region[8]. SCUBE is highly expressed in most of the vascularized tissues. Endothelium[7,9] and platelets[10] are very rich in SCUBE1.

The protein SCUBE1 is expressed in the vascular endothelium and plays a significant role in both the inflammatory response and thrombosis[9]. SCUBE1 exists in the α-granules of platelets in high levels. It has been shown that SCUBE1 has been indicated to strengthen ristocetin-induced platelet agglutination and adhesion[10]. SCUBE1 proteins have also been detected in various cardiovascular diseases[11]. SCUBE protein levels reach their peak value at the earliest 6 hours after the onset of symptoms in acute coronary syndrome (ACS) and stroke, but continue to decrease until the 96th hour after the 36th-60th hours[5]. In their study, Yang et al. determined a direct proportional relationship between angiogenesis, which has an important place in the pathogenesis of rheumatoid arthritis, and SCUBE1 level[12].

The results of these studies suggest that SCUBE1 might be effective in one of the mechanisms of collateral vessel formation in CAD. According to our review of studies conducted so far in the literature, there is no data on the relationship between CCC development and SCUBE1 levels in patients with coronary artery disease.

In our study, we aimed to investigate the relationship between serum SCUBE1 (Signal Peptide CUB-EGF like Domain Containing Protein) levels in patients with CAD (coronary artery disease) who developed CCC. Thus, we contributed to the literature by presenting information to reveal the possible role of SCUBE1 levels in the development of CCC in patients with CAD.

MATERIALS AND METHODS

Determination of patient (inclusion) criteria and groups

We planned this study as a prospective single center study to investigate the relationship between coronary collateral development and SCUBE level. The article was produced from the thesis.

We included 80 patients who underwent coronary angiography performed by us in the Cardiology Clinic of the Cardiology Department of Adnan Menderes University Hospital between April 25, 2019 and April 25, 2020 in the study. We obtained the approval to conduct the study from the Non-Interventional Clinical Research Ethics Committee (Approval number: 66, Approval Date: April 25, 2019). We assigned the 80 patients into three groups: group 1: patients with normal coronary arteries, group 2: patients with CAD and group 3: patients with CAD who developed CCC. We compared them in terms of their SCUBE levels.

The inclusion criteria for the patients with normal coronary arteries were as follows:

1. Being in the age group of 18-90 years and having been diagnosed to have normal coronary arteries during coronary angiography

2. Having had hemogram and biochemical analysis of their blood samples

The inclusion criteria for the patients with CAD were as follows:

1. Being in the age group of 18-90 years, having been diagnosed to have 50% or more stenosis in at least one of his or her coronary arteries during coronary angiography and having no collateral circulation

2. Having had hemogram and biochemical analysis of their blood samples

The inclusion criteria for the patients with CAD who developed CCC were as follows:

1. Being in the age group of 18-90 years, and having been diagnosed to have coronary collateral circulation during coronary angiography

2. Having had hemogram and biochemical analysis of their blood samples

The exclusion criteria were as follows:

1. Having a history of acute coronary syndrome, acute cerebrovascular accident, acute pulmonary embolism, acute mesenteric ischemia and acute arterial occlusion in the past month

2. Having malignancy or rheumatic disease

Immediately after the coronary angiography procedure, we obtained informed consent from the patients who volunteered to participate in the study. Then, we took approximately 5 ml of arterial blood samples into biochemistry tubes (red caps). After keeping the samples in the room temperature for 5 minutes, we centrifuged them at 3,500 rpm for 10 minutes using centrifuge device. Then we portioned the serums obtained into Eppendorf tubes to include at least two samples and stored them at -80°C. After reaching the desired number of cases, we removed all the samples stored at -0°C and raised their temperature to room temperature.

We analyzed the blood samples obtained from the volunteers using the human SCUBE1 ELISA (Sunred Biological Technology Co. Cat No: 201-12-5378, Shangai, China) kit and Epoch 2, BioTek brand device in accordance with the kit protocol of the manufacturer company. The sensitivity for the Human SCUBE1 ELISA kit is 0.852 ng/mL, and the measurement range is 1-300 ng/mL.

Statistical analysis

We analyzed the results of the obtained data using the Statistical Package for the Social Sciences (SPSS, version 23) statistically. We used Kolmogorov-Smirnov test to find out whether the data were normally distributed, Mann-Whitney test to compare pairwise continuous variables in the analysis of the non-normally distributed data, Kruskal Wallis test to compare triple groups, and the chi-square test to compare categorical variables. We performed the correlation analysis of the data with the Spearman Correlation test.

We performed the ROC (Receiver operating characteristic curve) analysis to calculate the sensitivity and specificity of serum SCUBE1 level in predicting the presence of CAD and CCC.

RESULTS

Demographic and clinical data of the participants

The mean age of 80 volunteers included in the study was 63.75±10.7 years. Of them, 46 (57.5%) were men. Their demographic and clinical characteristics were presented in Table 1.

According to the results of coronary angiography, of the participants, 30 had normal coronary artery (Group 1), 19 had CAD (Group 2), and 31 had CAD and developed CCC (Group 3).

Of the participants, 33 (41.25%) had diabetes, 40 (50%) had hypertension, 31 (38.75%) had heart failure, 6 (7.5%) had chronic renal failure, 46 (57%) had hyperlipidemia. and 32 (40%) were smokers.

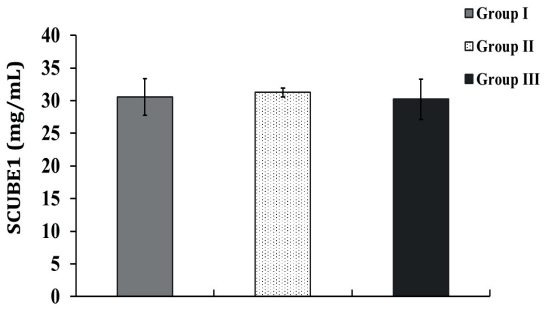
According to the Rentrop classification, used to determine and classify the coronary collateral circulation angiographically, of the patients in Group 3, 4 (12.9%) were Grade 1, 11 (35.5%) were Grade 2 and the majority (51.6%) were Grade 3 (Table 1).

Table 1. *Demographic and clinical characteristics of the participants.*

Characteristics	Total (N = 80)	Group 1 (N = 30)	Group 2 (N = 19)	Group 3 (N = 31)	P value
Age, X ± SD **Median [Min-Max]**	63.75 ± 10.7 65 [35–83]	59.23 ± 12.4 62 [35–77]	68.84 ± 9.2* 69 [48–82]	65.0 ± 8.2 64 [48–83]	0.027
Sex N (%) **Men** **Women**	 46 (57.5) 34 (42.5)	 13 (43.3) 17 (56.7)	 9 (47.4) 10 (52.6)	 24 (77.4) 7 (22.6)	0.016
Diabetes N (%)	33 (41.25)	6 (20.0)	11 (57.9)	16 (51.6)	0.010
Hypertension N (%)	40 (50)	12 (40.0)	15 (78.9)	13 (41.9)	0.015
Heart failure N (%)	31 (38.75)	9 (30.0)	4 (21.1)	18 (58.1)	0.015
Renal failure N (%)	6 (7.5)	1 (3.3)	1 (5.3)	4 (12.9)	0.334
Hyperlipidemia N (%)	46 (57.5)	12 (40.0)	12 (63.2)	22 (71.0)	0.043
Smoking N (%)	32 (40.0)	8 (26.7)	8 (42.1)	16 (51.6)	0.135
Rentrop classification N (%) **0** **1** **2** **3**	 49 (61.25) 4 (5.0) 11 (13.75) 16 (20.0)	 30 (100) - - -	 19 (100) - - -	 - 4 (12.9) 11 (35.5) 16 (51.6)	-
SCUBE1, ng/ml **X ± SS** **Median [Min-Maks]**	30.61 ± 2, 6 31.1 [15.3–32.6]	30.59 ± 2.8 31.2 [17.2–32.6]	31.25 ± 0.7 31.3 [29.3–32.3]	30.23 ± 3.1 30.8 [15.3–32.6]	0.272

The mean blood SCUBE1 levels in the participants according to the groups were given in Chart 1. As is seen in the chart, the SCUBE1 level was 30.59±2.8 ng/ml in Group 1, 31.25±0.7 ng/ml in Group 2, and 30.23±3.1 ng/ml in Group 3.

Chart 1. *SCUBE1 measurements by groups*



Comparison of patients' SCUBE1 levels in terms of demographic and clinical data

The result of the correlation analysis of SCUBE1 levels of the participants according to Rentrop classification revealed that there was not a significant relationship between their SCUBE1 levels and Rentrop grades (r:-0.176; P=0.119) (Table 2).

Table 2. *The result of the correlation analysis of patients' SCUBE1 levels according to Rentrop classification.*

		SCUBE1	Rentrop Class (Grade)
SCUBE1	*Spearman rho* *P value*	-	-0.176 0.119
Rentrop Class (Grade)	*Spearman rho* *P value*	-0.176 0.119	-

We presented the comparison of SCUBE1 levels according to demographic and clinical characteristics of all the participants in Table 3. As is seen in the table, there was no significant difference between them (P>0.05) (Table 3).

Results of the ROC analysis of the participants' SCUBE1 values

In Table 4 and Chart 2, we have shared the outcome of our ROC analysis that was conducted to establish the cut-off point for measuring the presence of coronary artery disease with SCUBE1. The results also include the sensitivity and specificity of this value. The SCUBE1 cut-off value for the presence of CAD was ≤30.94 ng/ml.

The sensitivity and specificity values of this value in predicting the presence of CAD were 46% [31.8 – 60.7] and 66.67% [47.2 – 82.7], respectively (Table 4). According to Chart 2, the AUC for the curve was 0.527 [0.412-0.640]. However, the predictive value of the SCUBE1 level for the presence of CAD was not significant as shown in Table 4 (P = 0.681).

In Table 5 and Chart 3, we showcased the findings of our ROC analysis aimed at identifying the cut-off point for SCUBE1 measurement in detecting the existence of Coronary collateral circulation, along with its sensitivity and specificity. The SCUBE1 cut-off value for the presence of CCC was ≤30.82 ng/ml. The sensitivity and specificity value of this value in predicting the presence of CCC were 54.84% [36.0-72.7], and 66.67%, respectively [47.2 – 82.7] (Table 5).

According to Chart 3, the AUC was 0.599 [0.483-0.707]. However, Table 5 shows that the SCUBE1 level's predictive value for the presence of CCC was not significant (P = 0.155).

Table 3. *Comparison of SCUBE1 levels of the participants according to their demographic and clinical characteristics.*

Characteristics	X ± SD	Median [Min-Max]	P value
Sex			
Men	30.5 ± 3.3	31.2 [15.3 – 32.6]	0.160
Women	30.7 ± 1.2	31.0 [27.3 – 32.6]	
Diabetes			
No	30.7 ± 2.3	31.2 [17.2 – 32.6]	0.361
Yes	30.4 ± 2.9	30.9 [15.3 – 32.5]	
Hypertension			
No	30.7 ± 2.7	31.1 [15.3 – 32.6]	0.570
Yes	30.5 ± 2.5	31.1 [17.2 – 32.]	
Heart failure			
No	30.8 ± 2.3	31.2 [17.2 – 32.6]	0.151
Yes	30.3 ± 3.0	30.8 [15.3 – 32.5]	
Renal failure			
No	30.6 ± 2.7	31.2 [15.3 – 32.6]	0.152
Yes	30.6 ± 0.8	30.4 [29.8 – 32.1]	
Hyperlipidemia			
No	30. 4 ± 0.5	31.0 [15.3 – 32.6]	0.459
Yes	30.8 ± 0.3	31.2 [17.2 – 32.5]	
Smoking			
No	30.6 ± 0.3	31.1 [17.2 – 32.6]	0.482
Yes	30.7 ± 0.5	31.1 [15.3 – 32.5]	
Rentrop classification			
0	30.8 ± 2.2	31.2 [17.2 – 32.6]	0.334
1	31.3 ± 0.6	31.3 [30.6 – 32.1]	
2	29.2 ± 4.8	30.8 [15.3 – 32.4]	
3	30.7 ± 1.4	30.6 [27. 9 – 32.6]	

Table 4. *ROC analysis of all the participants' SCUBE1 values to predict the presence of coronary artery disease.*

Cut-off Point	Sensitivity [%95 GA]	Specificity [%95 CI]	Positive Predictive Value [%95 CI]	Negative Predictive Value [%95 CI]	AUC [%95 CI]	P value
≤30.94	46.00 [31.8- 60.7]	66.67 [47.2– 82.7]	69.7 [51.3- 84.4]	42.6 [28.3-57.8]	0.527 [0.412-0.640]	0.681

**CI: Confidence Interval, AUC: Area under the Curve*

Chart 2. *ROC chart for the SCUBE1 values to predict the presence of CAD*

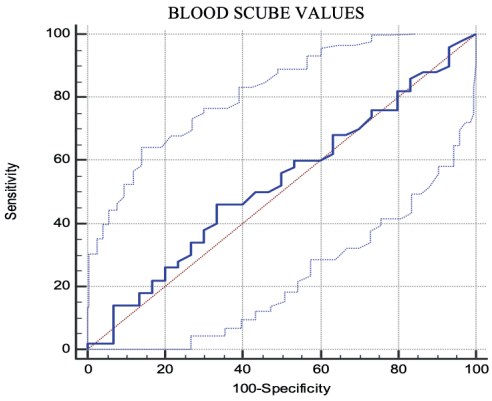


Chart 3. *ROC chart for the SCUBE1 values to predict the presence of coronary collateral circulation*

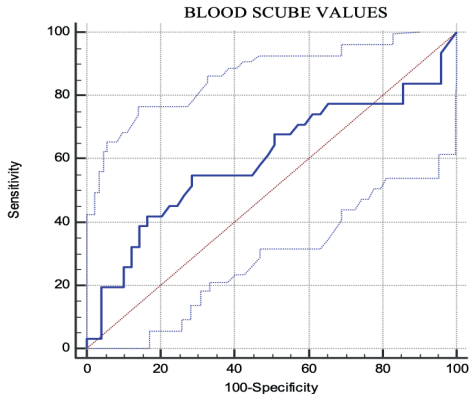


Table 5. *ROC analysis of all the participants' SCUBE1 values to predict the presence of coronary collateral circulation.*

Cut-off Point	Sensitivity [%95 GA]	Specificity [%95 CI]	Positive Predictive Value [%95 CI]	Negative Predictive Value [%95 CI]	AUC [%95 CI]	P value
≤30.82	54.84 [36.0-72.7]	71.43 [56.7-83.4]	54.8 [36.0-72.7]	71.4 [56.7-83.4]	0.599 [0.483-0.707]	0.155

**CI: Confidence Interval, AUC: Area under the Curve*

DISCUSSION

In our study, we investigated the serum SCUBE1 levels in patients with CAD who developed CCC by analyzing the relationship between these two parameters.

After the analysis, we determined that there was no significant relationship between their SCUBE1 levels and the presence of CCC, and that the SCUBE1 level was not significant in estimating the presence of CCC in patients.

We did not determine any significant correlation between the Rentrop grades, which are CCC classification, and the mean SCUBE1 level. We also determined that the predictive value of the presence of SCUBE1 level of CCC was not significant. The fact that the sample size of the study was small and that other SCUBE proteins were not included may be the reason why the relationship between SCUBE1 level and CCC could not be revealed. However, researchers of future studies can monitor SCUBE proteins that affect the progressive development of collateral vessels and investigate their relationship with other proteins involved in arteriogenesis mechanisms by conducting multicenter studies with larger samples. Thus, they can better understand the mechanisms of CCC in Patients with CAD and can assess the effectiveness of possible treatments.

Studies have demonstrated that patients with ACS and acute large vessel atherothrombotic stroke have higher levels of plasma SCUBE1, which is sourced from platelets. The release of plasma SCUBE1 is slow and comparable to that of other well-known biomarkers for acute myocardial infarction, like creatine kinase, troponins, lactate dehydrogenases and myoglobin[13]. In patients with acute platelet activation, the plasma SCUBE1 concentration was determined to rise 6 hours after the onset of activation and remained detectable for 3 to 4 days8. Therefore, plasma SCUBE1 can be considered as a new biomarker of platelet activation in acute thrombotic diseases[10]. Our study has found that patients with chronic CAD do not exhibit an increase in plasma SCUBE1 levels. This is due to the different pathogenesis of chronic CAD compared to ACS. While platelets do play a role in atherosclerosis, acute massive platelet activation is less common in chronic stable CAD. Therefore, it is reasonable to expect normal plasma SCUBE1 levels in patients with chronic CAD, unlike ACS. Furthermore, our research shows that there is no significant difference in SCUBE1 levels among patients with CAD without a history of ACS who developed CCC. This can be attributed to the low levels of platelet activation and inflammation involved in the pathogenesis of CAD[14,15].

Through in vitro studies, it has been demonstrated that serum proteases cleave the carboxyl-terminus CUB from the amino-terminal portion of EGF-like repeats in the secreted form of SCUBE1. The potential proteolytic cleavage site has been found to be located within the spacer region, as revealed by various mapping studies using SCUBE1 deletion mutants. The presence of multiple isoforms of SCUBE1 fragments suggests that SCUBE1 cleavage plays a complex role in regulating the pathological formation of ACS and acute ischemic stroke. However, further in vitro and in vivo studies are needed to understand the mechanism of SCUBE1 activation in chronic events such as CAD and CCC[16].

In our study, the SCUBE1 cut-off value was ≤30.94 ng/ml, the sensitivity was 46% [31.8 – 60.7], and the specificity was 66.67% [47.2 – 82.7] for the presence of CAD.On the other hand, as for the presence of CCC, the SCUBE1 cut-off value was ≤30.82 ng/ml, sensitivity was 54.84 [36.0-72.7], and specificity was 71.43 [56.7-83.4]. These results suggest that the predictive value of SCUBE1 level for the presence of CAD or CCC was not significant.

In our study, the sample size was relatively small, which had a limited statistical power to detect minor differences in the analysis of subgroups. In addition, the ELISA method used for plasma SCUBE1 in potential clinical applications has limited sensitivity and specificity. The analysis of SCUBE1 levels at different stages of CCC

development in patients with CAD may enable researchers to use it as a diagnostic or prognostic biomarker and it can be potentially useful in risk stratification of patients with CAD. However, we think that the use of plasma SCUBE1 as a biomarker will be insufficient to confirm its clinical application.

In this study, conducted at a single center, we conducted a comparison between the levels of SCUBE1 in CAD patients who did and did not develop CCC. This is the first study of its kind in the literature. Our findings indicate that relying solely on measuring SCUBE1 levels may not be sufficient to predict the development of CCC in CAD patients. Therefore, we recommend conducting multicenter studies with larger sample sizes to further validate these results.

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Research Article

health science

INVESTIGATION OF THE RELATIONSHIP BETWEEN THE FEAR EXPERIENCED BY THE FILIATION TEAMS AND THEIR PERCEPTION OF POSITIVITY AND ATTITUDES TOWARDS NURSING DURING THE COVID-19 PANDEMIC

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Keywords

Fear of COVID-19, Filiation team, Nurse, Professional attitude, Positivity, Healthcare staff

ABSTRACT

It was aimed to investigate the relationship between the fear experienced by the members of filiation(contact tracing) teams, and their perception of positivity and attitudes towards nursing during the COVID-19 pandemic. Nurses (n=154) working in the filiation teams constituted the sample. The data were collected using the Fear of COVID-19 Scale, Positivity Scale(POS) and Attitude Scale toward Nursing Profession(ASNP). The participating nurses had a moderate level of fear of COVID-19 and a high level of perception of positivity, and displayed positive attitudes towards nursing. Their high levels of fear of COVID-19 and positivity perception positively affected their attitudes towards the profession.

INTRODUCTION

COVID-19 which emerged in China for the first time in late 2019 is still an important public health problem[1]. The fatality rate varies between 2% and 3% worldwide, and the mortality rate increases inpeople in an advanced age group and in patients with an underlying disease[2-6]. Therefore, it is necessary for individuals of all ages to comply with the measures taken. During the pandemic, important roles and responsibilities to prevent the spread of COVID-19 and to carry out the care, treatment and filiation of individuals diagnosed with COVID-19 lie with health professionals.

Volume: 1
Issue: 2
Page: 69-81

Received:
29.06.2023

Accepted:
04.08.2023

Available Online:
15.10.2023

The main purpose of the filiation application is to prevent the spread of the disease by revealing the causative agent and the source in the early period. During the visits, treatment, isolation and follow-up processes are determined based on the evaluation/laboratory results. Thus, asymptomatic individuals are detected early, the spread of the disease is prevented, and the success rate increases thanks to early diagnosis/treatment[7].

According to the Guidelines for Combating Infectious Diseases issued by the Turkish Ministry of Health in 2017 as a circular order, filiation is carried out by health workers who perform preventive service activities in primary health care institutions and in the field. Among some of the duties of the filiation teams are contact tracing, patient education, taking blood samples for testing, initiating treatment, controlling the effectiveness ofisolation, and writing disease reports[8].

DOI:10.5281/zenodo.8414484

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According to the data released by the Turkish Ministry of Health, as of December 25, 2020, the average detection time in the contact chain of 2,118,255 confirmed cases was 10 hours, and the filiation rate reached 99.9%.

In filiation applications, in the management of the pandemic, the main human resource is the health personnel. According to the report released bythe International Council of Nurses (ICN) based on the data collected from its member National Nursing Societies in May 2020, at least 90,000 healthcare workers worldwide were infected with COVID-19. According to the results of some international studies, COVID-19 cases are 12 times more widespread in healthcare workers in the USA and England, and 29% of those who are infected with COVID-19 in China are healthcare workers[6,9]. According to articles published in the USA andChina, of the healthcare workers infected with COVID-19, 46.6% and52% were nurses respectively[10,11]. According to the statement made by the Ministry of Health in October 2020, inTurkey, while the number of health workers with positive COVID-19 test was over 40,000, the number of people who lost their lives due to COVID-19 was 107.343.

The level of fear of being infected is higher among healthcare workers than in the general population. On the other hand, they mostly fear not because they will be exposed to the virus but because theymight infect their family and close relations[12]. In various studies, it has been determined that the level of fear and anxiety of infecting family members is high among healthcare workers from China and Canada struggling with SARS[13,14]. According to the study on the "Map of Coronaphobia in Turkey", of the 897 healthcare professionals, 50% perceived the uncertainty of the process as worrying, 44% were worried about not having the opportunity to access adequate protective equipment, and 43% were worried about the future of their family members in case they died from COVID-19[15].

It was reported that a significant portion of health workers who worked during the previous pandemics experienced deterioration in mental health, which lasted for a long time[16]. Past pandemic experiences and the experiences of communities affected by COVID-19 earlier indicated that interventions to protect mental health should be included in the fight against the pandemic[17].

Besides mental problems, health personnel suffer from other problems during filiation applications, which adversely affectsthe provision of health services. While filiation applications are carried out, several problems have arisen. For instance,filiation teams which have very wide distribution have different structures and their job descriptions are not determined based on detailed guides, team members do not have enough information about filiation, they do not have opportunity to make preliminary preparations, availability andsuitability of local opportunities are not taken into account in central interventions, feedback by teams is delayed and there aredifferences between provinces/ districts in terms of applicationof filiation, communication, knowledge, skills and equipment[17]. Besides all these negativities, it is of great importance for health workers who play an active role during the pandemic to have a professional perspective, professional attitude and perception of positivity in terms of preventing the pandemic. In society, a person who regularly carries out a task with the least error is defined as a professional[18]. “Being a professional at a job” requires the person to have the ability “to understand the job down to the tiniest details” and “to be able to implement it”[19].

Professional attitudes and values in nursing which provide the basis for nursing practices enable nurses to interact with individuals they care for, society and their colleagues. In a study conducted on this issue, nurses’ professional values were determined as human dignity, responsibility, action taking, security and autonomy[20]. Within this context, nurses should be competent in all their practices, understand the philosophy of nursing, and act reasonablyand ethically. Communication and empathy skills are among the factors affecting nurses’ professional attitudes most. Professionalism is a dynamic process requiring effort, and it can be defined as the process in which certain values such as knowledge, autonomy, political awareness, volunteering to serve the community, conducting scientific studies, team, and organization necessary for professional identity are internalized, and all these values manifest themselves in an individual's behavior[21].

Positive perception refers to an individual's perceiving himself or herself as worthy and having an internally positive view of himself or herself[22]. In nursing, which is a professional occupation, nurses whose positive perspective levels are high are expected to have a low level of fear, to perform their profession with self-sacrifice and awareness, and to be better at volunteering to serve the society than nurses whose positive perspective levels are low. In a study conducted throughout Turkey, fear of COVID-19 was shown to be directly related to hopelessness[23].

Although health authorities around the world have made great effortsto bring the COVID-19 pandemic under control, the severe clinical course and rapid spread of the virus prolong the process and thus cause the social and psychological complexity suffered by healthcare professionals to continue.The review of the relevant literature demonstrated a gap regarding studies in which the relationship between the fear of nurses working in the filiation teams,and theirperceptions of positivity and professional attitudes were investigated. Therefore, in the present study, we aimed to investigate the relationship between fear experienced by nurses working in the filiation teams during the COVID-19 pandemic, and positivity and professional attitude. Accordingly, determining the views and thoughts of nurses working in the filiation teams about the pandemic and their fears and concerns about catching COVID-19 is thought to shed light both on their adaptation to the working environment and motivation to workhard and on the determination of the precautions to be taken in the working environments.

MATERIALS AND METHOD

Type of the study

The study is a descriptive cross-sectional study.

Location, duration and sample of the study

The study was carried out in Kayseri and Sivas, provinces located in the central and eastern regions of Turkey respectively. While there are 43 filiation teams affiliated to the Sivas Provincial Health Directorate, the number of filiation teamsaffiliated to the Kayseri Provincial Health Directorate varies between 180 and 190 depending on the case density. Each of the filiation teams consists of 2-3 health workers.

The population of the study consisted of 500 nurses working in the filiation teams of Sivas and Kayseri Provincial Health Directorates. Of the nurses working between 15 July and 15 September 2020, those to be included in the study sample were determined using the random sampling method. The minimum sample size was calculated as 174 by using the following formula used to calculate the sample size with a finite population: n=Nt2pq/(N-1)d2+t2pq (N= 500, p= 0.50, q= 0.50, d= 0.06, t= 1.96). Of 174 nurses, 20 were not reached; thus, the study was completed with 154 nurses who volunteered to participate in the study. Of them, 39 were from Sivas and 115 were from Kayseri.

Data collection tools

The Descriptive Information Form, Fear of COVID-19 Scale, Positivity Scale (POS) and Attitude Scale toward Nursing Profession (ASNP) were used as data collection tools.

Descriptive Information Form: The form developed by the researchers reviewing the literature consists of 26 items in three parts[15,24]. In the first part of the form, there are 10 items questioning the sociodemographic characteristics of the healthcare professionals such as age, sex, marital status, family type, economic status, health status, etc. The nine items in the second part question the healthcare professionals'working environment-related characteristics (length of service in nursing, unit they work in, caring for a patient diagnosed with COVID-19). The seven items in the third part question the participants' COVID-19 pandemic-related characteristics (fear of being diagnosed with COVID-19, fear of giving care to a patient with COVID-19, measures taken against the COVID-19 pandemic, etc.).

Fear of COVID-19 scale: The scale was developed by Ahorsu et al.[25] The validity and reliability study of the Turkish version of the scale was performed by Satici et al.[26] The 7-item Fear of COVID-19 Scale is a one-dimensional scale. Responses given to the items are rated on a 5-point Likert-type scale. The Cronbach's alpha internal consistency coefficient of the scale was 0.88 in Satici et al.'s study and 0.89 in the present study. The minimum and maximum possible scores to be obtained from the scale are 7 and 35 respectively. The higher the score obtained from the scale is the higher the level of fear of COVID-19 is.

Attitude scale toward nursing profession (ASNP): The scale developed by Coban et al. is used to assess attitudes towards nursing[27]. ASNP consists of the following three sub-dimensions: characteristics of the nursing profession, preference for nursing, and attitudes towards the general status of nursing. The Cronbach's alpha coefficient of the scale was 0.91 Coban et al.'s study and 0.88 in the present study. The ASNP is comprised of 40 items. Each item is rated on a 5-point Likert-type scale ranging from 1 to 5. Of the items,21, 23, 25, 26, 28, 30, 34, and 38 are reverse scored. The minimum and maximum possible scores to be obtained from the

ASNP are 40 and 200 respectively. A score over 120 indicates that the person displays positive attitudes towards nursing. A score of ≥54 obtained from the characteristics of nursingsub-dimension, ≥39 obtained fromthe preferring nursingsub-dimension, and ≥27 obtained fromthe general status of nursing sub-dimension indicate that the person displays positive attitudes towards the relevant sub-dimension.

Positivity scale (POS): The Positivity Scale was developed by Caprara et al. to assess a view of one's self, one's life, and one's future[28]. The validity and reliability of the Turkish version of the POS was performed by Cikrikci et al.[29]. The scale will measure individuals' self (Items 5, 7 and 8), their future expectations (Items 1, 4, and 6), their perception of confidence in other people (Item 3) and their satisfaction with life (Item 2) in order to determine the positive attitudes of individuals. The internal consistency coefficient of the POS was calculated as 0.75 in Caprara et al.'s study and 0.73 in the present study. The Positivity Scale consists of eight items, one of which is reverse scored (Item 6). Responses given to the items are rated on a five-point Likert-type scale ranging from 1 (strongly disagree) to 5 (strongly agree). The lowest and highest possible scoresto be obtained from the POS are 8 and 40 respectively. The higher the score is the higher the person's level of perception of positivity is.

Implementation of the study

Before the study was conducted, the ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee (numbered 2020-08/13, dated August 12, 2020). Then, institutional permissions were obtained from Sivas Provincial Health Directorate and Kayseri Provincial Health Directorate.The study was carried out between July 15, 2020 and September 15, 2020. The researchers administered the questionnaires and scales to the nurses working in the filiation teams online. In order to administer the Fear of COVID-19 Scale, POS andASNP in the present study, permissions were obtained from the authors who performed the Turkish validity and reliability studies of the scales by e-mail. The administration of the online questionnaires was carried out by sending a link to the nurses working in the filiation teams via social media (WhatsApp). In the link sent to the nurses, a brief explanation about the study was given to the participating nurses and they were asked to fill in the consent forms indicatingthat volunteered to participate in the study. In order to ensure the accuracy of the information given by the nurses participating in the study and to protect the confidentiality of their identity information, they were asked not to write their names in the online form and scales.

RESULTS

As is seen in Table 1, the mean age of the nurses participating in the study was 37.98±7.57 years (21-52 years). Of them, 64.9% were women, 83.8% were married, 95.5% had a nuclear family, 13.6% had a chronic illness, 1.3% had a chronic psychiatric illness, and 13% had a phobia affecting their life. As forthe working environment-related characteristics ofthe participants, 72.1% had more than 10 years of service in nursing, 70.1% worked in shifts, 57.1% considered the personal precautions taken against the COVID-19 pandemic in the institution they worked in as adequate, but 53.9% considered the general measures taken against the COVID-19 pandemic in the institution where there worked in as inadequate (Table 1).

As is seen in Table 2, of the nurses participating in the study, 97.4% were afraid of losing their loved ones due to COVID-19, 60.4% had someone diagnosed with COVID-19 in their family/immediate circle, 21.4% had someone in their family/immediate circlewho died due to COVID-19, 70.8% were afraid of being diagnosed with COVID-19, 57.1% were afraid of meeting/caring for a patient with a diagnosis of COVID-19, and 53.2% were considering getting a COVID-19 vaccine (Table 2).

As is seen in Table 3, the mean score the participants obtained from the Fear of COVID-19 Scale was 19.12±7.22, which indicates that their COVID-19 fear level was moderate. Their mean score for the POS was 27.7±5.35 indicating that their perception of positivity level was high. Their mean score for ASNP 163.77±15.92 which indicates that they displayed a positive attitude towards nursing (Table 3).

As is seen in Table 4, there was a positive and weak correlation between the mean scores the nurses obtained from the Fear of COVID-19 Scale, and Characteristics of Nursing sub-dimension of the ASNP (r=.246; p=.002). The result of the Linear Regression Analysis also demonstrated that the nurses' fear of COVID-19accounted for their attitudes towards the characteristics of nursing by 4.2% (R=.205, R2=.042, F(1, 152) =6.701, p=.011). There was a positive, weak significant correlation between the mean scores the nurses obtained from thePOS andoverall

ASNP(r=.359; p=.000)(Table 4).The result of the Linear Regression Analysis also showed that the positivity levels of nurses significantly accounted for their attitudes towards the nursing profession by 14.4% (R= .380. R2=.144. F(1.15) =25.646. p=.000).

As is seen in Table 5, of the participants, those who were women, those who were ≥41 years old, those who had income less than their expenses, andthose who had a chronic psychiatric illnessobtained statistically significantly higher scores from theFear of COVID-19 Scale (p<.05). Of the participants,those whose income was higher than their expenses obtained statistically significantly higher scores from the Positivity Scale (p<.05).Of the participants,those whose income was equal to their expenses obtained significantly higher scores from the overall ASNP (p<.05).

Of the participants,those who considered the general and personal precautions taken in the institution they worked in against the pandemic as adequate obtained higher scores from the POS and ASNP (p<.05).Of the participants,those who had a fear of losing their loved ones due to COVID-19, those who had a fear of being diagnosed with COVID-19, those who had a fear of meeting/ caring for a patient diagnosed with COVID-19, and those who considered having the COVID-19 vaccine obtainedstatistically significantly higher scores from theFear of COVID-19 Scale (p<.05). Of the participants,those who considered having the COVID-19 vaccineobtained significantly higher scores from the ASNP (p<.05) (Table 5).

Table 1. *Participating nurses' sociodemographic and working environment-related characteristics (n=154)*

Sociodemographic Characteristics	Number (n)	Percentage (%)
Age [Mean ±SD (min-max)] = [37.98±7.57 (21-52) years]		
21-30 years old	33	21.4
31-40 years old	61	39.6
≥41 years old	60	39.0
Sex		
Women	100	64.9
Men	54	35.1
Marital status		
Married	129	83.8
Single	25	16.2
The number of children		
None	31	20.1
1	25	16.2
≥2	98	63.7
Family type		
Nuclear family	147	95.5
Extended family	7	4.5
Family income status		
Income less than expenses	36	23.4
Income equal to expenses	102	66.2
Income more than expenses	16	10.4
Presence of a chronic illness		
Yes	21	13.6
No	133	86.4
Presence of a chronic psychiatric illness		
Yes	2	1.3
No	152	98.7
Presence of phobia affecting life		
Yes	20	13.0
No	134	87.0
Length of service in nursing (years)		
<1	7	4.5
1-5	18	11.7
6-10	18	11.7
≥10	111	72.1
Type of Work Schedule		
Shifts	108	70.1
Daytime	46	29.9
Are personal measures taken against the COVID-19 pandemic in the institution worked inare adequate?		
Adequate	88	57.1
Inadequate	66	42.9
Are general measures taken against the COVID-19 pandemic in the institution worked inare adequate?		
Adequate	71	46.1
Inadequate	83	53.9

Table 2. *Participating nurses' covid-19 pandemic-related characteristics (n=154)*

Characteristics	Number (n)	Percentage (%)
Fear of losing loved ones due to COVID-19		
Yes	150	97.4
No	4	2.6
Having a family member or someone in the immediate circle diagnosed with COVID-19		
Yes	93	60.4
No	61	39.6
Having a family member or someone in the immediate circle who died due to COVID-19		
Yes	33	21.4
No	121	78.6
Fear of being diagnosed with COVID-19		
Yes	109	70.8
No	45	29.2
Fear of meeting/caring for a patient diagnosed with COVID-19		
Yes	88	57.1
No	66	42.9
Considering getting a COVID-19 vaccine		
Yes	82	53.2
No	72	46.8

Table 3. *Mean score the participants obtained from the Fear of COVID-19 Scale, Positivity Scale (POS) and Attitude Scale toward Nursing Profession (ASNP) and the sub-dimensions of the ASNP.*

Scales and sub-dimensions	N	The number of the items	Min.-Max.	Median	Mean±SD
Fear of COVID-19 Scale	154	7	7-35	18	19.12±7.22
Positivity Scale	154	5	13-40	28	27.7±5.35
Attitude Scale toward Nursing Profession Total	154	40	116-191	166	163.77±15.92
Characteristics of nursing sub-dimension	154	18	46-90	86	83.03±8.04
Preferring nursing sub-dimension	154	13	22-65	47	47.20±9.51
General status of nursing sub-dimension	154	9	26-39	34	33.53±2.74

Table 4. *Relationship between the mean scores the participants obtained from the Fear of COVID-19 Scale, Positivity Scale (POS) and Attitude Scale toward Nursing Profession (ASNP) and the sub-dimensions of the ASNP*

Scales and sub-dimensions		1	2	3	4	5
1- Fear of COVID-19 Scale	r^a	-				
	P					
2- Positivity Scale total	r^a	-.027	-			
	P	.739				
3- Characteristics of nursing sub-dimension	r^a	.246*	.315**	-		
	P	.002	.000			
4- Preferring nursing sub-dimension	r^a	-.036	.313**	.342**	-	
	P	.658	.000	.000		
5- General status of nursing sub-dimension	r^a	.098	.158*	.443**	.347**	-
	P	.225	.050	.000	.000	
6- Attitude Scale toward Nursing Profession Total	r^a	.106	.359**	.694**	.863**	.595**
	P	.189	.000	.000	.000	.000

** Pearson's correlation analysis was applied, *p < .005, **p < .001.*

Table 5. *Comparison of the mean scores the participants obtained from the Fear of COVID-19 Scale, Positivity Scale (POS) and Attitude Scale toward Nursing Profession (ASNP).*

		FCV-19S Total Mean±SD	POS Total Mean±SD	ASNP Total Mean±SD
Age	N			
21-30 years old	33	15.87±6.40	26.90±5.381	160.18±14.683
31-40 years old	61	19.78±6.88	28.36±5.263	164.13±16.718
≥41 years old	60	20.23±7.58	27.68±5.438	165.38±15.701
Test value		[a]F=4.483	[a]F=.804	[a]F=1.164
Significance level		p=.013	p=.449	p=.315
Difference		3-2>**		
Sex				
Women	100	20.40±7.53	27.35±5.47	164.51±14.16
Men	54	16.75±6.00	28.59±5.05	162.40±18.82
Test value		[b]t=3.276	[b]t=-1.379	[b]t=.718
Significance level		p=.001*	p=.170	p=.175
Marital status				
Married	129	19.15±7.19	28.20±5.16	164.70±16.12
Single	25	18.96±7.53	25.64±5.85	158.96±14.19
Test value		[b]t=.123	[b]t=2.038	[b]t=1.660
Significance level		p=.902	p=.051	p=.099
The number of the children				
None	31	16.77±6.61	25.90±5.21	158.90±14.89
1	25	20.08±7.55	29.72±3.96	165.44±13.29
2	71	19.53±7.53	28.05±5.52	166.23±15.76
≥3	27	19.85±6.56	27.44±5.68	161.33±18.71
Test value		[a]F=1.417	[a]F=2.540	[a]F=1.868
Significance level		p=.240	p=.059	p=.138
Family type				
Nuclear family	147	19.33±7.11	27.80±5.27	164.09±15.98
Extended family	7	14.71±8.76	27.28±7.27	157.00±13.89
Test value		[b]t=1.661	[b]t=.252	[b]t=1.153
Significance level		p=.099	p=.801	p=.251
Length of service in nursing (years)				
<1	7	14.85±6.61	24.85±6.71	152.28±19.41
1-5	18	17.77±7.14	28.11±4.83	166.55±13.32
6-10	18	18.33±7.10	29.00±4.63	162.11±15.02
>10	111	19.73±7.25	27.72±5.44	164.31±16.10
Test value		[a]F=1.370	[a]F=1.036	[a]F=1.521
Significance level		p=.254	p=.378	p=.211
Type of Work Schedule				
Shifts	108	19.25±7.08	27.57±5.41	165.00±15.61
Daytime	46	18.82±7.63	28.28±5.21	160.89±16.44
Test value		[b]t=.332	[b]t=-.751	[b]t=1.471
Significance level		p=.740	p=.454	p=.143
Family income status				
Income less than expenses	36	20.30±8.13	25.13±6.00	163.52±16.86
Income equal to expenses	102	19.55±6.96	28.46±4.93	164.18±15.62
Income more than expenses	16	13.68±4.04	29.43±4.60	161.68±16.52
Test value		[a]F=5.494	[a]F=6.402	[a]F=8.765
Significance level		p=.005	p=.002	p=.000
Difference		1-2>3**	3>1-2**	3>1-2**

Presence of a chronic illness				
Yes	21	19.61±8.540	27.19±7.37	159.52±17.39
No	133	19.04±7.03	27.87±4.98	164.44±15.64
Test value		[b]t=.337	[b]t=-.414	[b]t=-1.319
Significance level		p=.737	p=.683	p=.189
Presence of a chronic psychiatric illness				
Yes	2	23.50±0.70	23.50±4.94	177.50±2.12
No	152	19.06±7.25	27.84±5.34	163.59±15.95
Test value		[b]t=5.740	[b]t=-1.231	[b]t=1.229
Significance level		p=.002*	p=.430	p=.221
Presence of phobia affecting life				
Yes	147	19.90±8.14	26.90±6.62	158.35±17.33
No	7	19.00±7.10	27.91±5.15	164.58±15.61
Test value		[b]t=.514	[b]t=-.793	[b]t=-1.641
Significance level		p=.608	p=.429	p=.103
Are personal measures taken against the COVID-19 pandemic in the institution worked in are adequate?				
Adequate	88	18.13±6.18	29.28±4.97	166.28±15.16
Inadequate	66	20.43±8.29	25.78±5.21	160.42±16.40
Test value		[b]t=-1.895	[b]t=4.229	[b]t=2.291
Significance level		p=.061	p=.000*	p=.023*
Are general measures taken against the COVID-19 pandemic in the institution worked in are adequate?				
Adequate	71	18.98±6.26	29.45±4.63	167.60±13.93
Inadequate	83	19.24±8.00	26.36±5.53	160.49±16.84
Test value		[b]t=-.222	[b]t=3.718	[b]t=2.825
Significance level		p=.825	p=.000*	p=.005*
Fear of losing loved ones due to COVID-19				
Yes	150	19.38±7.14	27.76±5.36	163.92±15.95
No	4	9.50±2.38	28.75±5.50	158.00±15.64
Test value		[a]t=2.755	[a]t=-.364	[a]t=.733
Significance level		p=.001*	p=.716	p=.464
Having a family member or someone in the immediate circle diagnosed with COVID-19				
Yes	93	19.53±7.54	27.64±5.74	161.78±17.17
No	61	18.49±6.72	28.00±4.72	166.80±13.38
Test value		[a]t=.899	[a]t=-.401	[a]t=-1.929
Significance level		p=.382	p=.689	p=.059
Having a family member or someone in the immediate circle who died due to COVID-19				
Yes	33	19.53±7.54	27.64±5.74	161.78±17.17
No	121	18.49±6.72	28.00±4.72	166.80±13.38
Test value		[a]t=.785	[a]t=-.180	[a]t=.412
Significance level		p=.434	p= .857	p=.681
Fear of being diagnosed with COVID-19				
Yes	109	21.98±6.30	27.85±5.362	165.27±15.84
No	45	12.20±3.85	27.62±5.37	160.13±15.69
Test value		[a]t=9.674	[a]t=.243	[a]t=1.836
Significance level		p=.000*	p=.808	p=.068

Fear of meeting/caring for a patient diagnosed with COVID-19				
Yes	88	22.45±6.54	28.26±5.00	165.46±14.22
No	66	14.68±5.53	27.15±5.75	161.51±17.80
Test value		[a]t=7.783	[a]t=1.276	[a]t=1.530
Significance level		p=.000*	p= .204	p=.128
Considering getting a COVID-19 vaccine				
Yes	82	20.54±6.80	27.81±5.12	166.60±15.42
No	72	17.50±7.40	27.75±5.62	160.54±15.97
Test value		[a]t=2.663	[a]t=.077	[a]t=2.395
Significance level		p=.009*	p=.938	p=.018*

**ANOVA Analysis of Variance,[b] t test in independent groups,*p < .05*

DISCUSSION

In our study, we investigated the relationship between the fear experienced by the nurses working in the filiation teams during the COVID-19 pandemic, andtheir perception of positivity and their attitudes towards nursing. We noticed that the female nurses had a higher level of fear of COVID-19 than did the male nurses. According to Caliskan et al.'s study conducted with nursing students (2021), the female students experienced a higher level of fear of COVID-19 than did the male students, consistent with our study[30]. In a study conducted at Cukurova University in Turkey, the female health workers had higher levels of a fear of COVID-19 than did the male health workers, and the female nurses suffered from mental disordersmore than did all the other health professionals, In the same study, the mean fear, anxiety and depression scores were significantly higher in women than were those in men[31]. According to another study conducted in China, nurses were affected more negatively in this process than were other occupational groups[16].

The majority of the nurses participating in the present study worked in shifts and their length of service in nursing was more than 10 years, and while the majority of these nurses did not consider the general measures taken against the COVID-19 pandemic in their institution as adequate, more than half of them considered personal precautions as inadequate.According to the results ofa study conducted with healthcare workers working in an emergency department in our country, Turkey, the rate of participants considering the measures taken against COVID-19 at the social level as sufficient was low, which was consistent with the results of our study[32]. In a study conducted in China, challenges faced by healthcare workers during the COVID-19 pandemic were due to inadequate personal protective equipment[4]. In another study conducted with healthcare professionals from different branches, the lack of appropriate personal protective equipment was identified as a source of concern among them[33]. In our study, those who regarded the measures as adequate had positive perceptions of positivity and attitudes towards nursing.

In our study, the difference between the nurses' scores they obtained from the Fear of COVID-19 Scale in terms the variables such as losing their loved ones due to COVID-19, being diagnosed with COVID-19, meeting/caring for a patient diagnosed with COVID-19, and getting a COVID-19 vaccine was significantly high (p<.005). It is thought that one of the leading reasons for this fear is that COVID-19 infection is most common among healthcare workers. In a study in which the data on approximately two million non-healthcare workers and approximately 100 thousand healthcare professionals in the USA and the United Kingdom were analyzed, COVID-19 was 12 times more widespread in healthcare workers[9]. According to the publications made in the early period of the pandemic in China, 29% of the patients with COVID-19 were healthcare workers[6]. In an article published in the USA, of the patients with COVID-19,9.6% were healthcare workers and 46.6% of those healthcare workers were nurses[10]. In an article published in China, of 2457 healthcare workers who had COVID-19,52% were nurses[11]. In our study, the majority of the participants had a family member/ someone in their immediate circle diagnosed with COVID-19, and they had a fear of losing their relatives due to COVID-19. Because of this fear, most of them were afraid of meeting/ caring for a patient with a diagnosis of COVID-19, and they considered getting a COVID-19 vaccine.

Those who considered being vaccinated against COVID-19 obtained higher scores from the ASNP (p<0.005). Similarly, a large majority of the participants in a study conducted in our country

had COVID-19-related concerns[32]. In their study, Shanafelt et al. stated that many healthcare professionals were very worried about being infected with COVID-19, and that they were most worried about spreading the virus to their relatives and vulnerable individuals in the hospital or community[33]. In studies conducted in India and Egypt, the majority of the participants had concerns about being infected with COVID-19, and they were worried about infection[34,35]. In some studies conducted in China, the psychological effects of the COVID-19 pandemic were more severe in healthcare workers[6]. In a study, of the nurses, 36.3% read books on mental health, 50.4% performed self-coping activities mentioned in social media, and 17.5% received professional psychological support after the onset of the COVID-19 pandemic[36].

In a study conducted with health personnel working in emergency health services in our country, approximately one quarter of the participants had contact with patients with COVID-19[32]. This situation can also cause health professionals to feel unsafe and fearful, andaffect theirperception of positivity and attitudes towards nursing[37]. In this context, a positive and statistically significant relationship was determined between the positivity perception levels of the nurses participating in the present study and their choosing nursing as a profession, whichcan be explained by their knowledge and experience levels. Similarly, in a study conducted in China, 92% of the healthcare workers did not think of quitting their job during the COVID-19 process[38]. However, to determine the level of this rate in our country, more studies should be conducted. In a study in which the mood and burnout levels of health professionals working in intensive care units during the COVID-19 process in our country were investigated, the occupational group whose level ofpositive mood was the highest was nurses in the comparison made according to the professions of health workers[39]. In the study conducted by Kale & Cicek (2015), unlike the aforementioned study, nurses were asked about their perceptions of metaphors regarding their profession and it was determined that most of them produced analogies with negative meanings about their professions and they were generally dissatisfied with their profession[40].

In our study, there was a positive relationship between the participating nurses' level of fear of COVID-19 and their attitudes towards the characteristics of nursing. This finding can be attributed to the effect of their professional identities. This professional commitment can also be associated with the fact that nurses constitute a professional group that plays a vital role in society, and that they perform their tasks based on the principle of saving many patients, especially during crisis. According to Caliskan et al.'s study conducted with nursing students (2021), as the level of fear of COVID-19 increased, so didthe level of positive attitude they displayedtowards the general status of nursing[30]. The reason for this difference between our study and the other studies can be attributed to the differences between the samples. Consistent with this finding of our study, in the literature, it is reported that in individuals with stronger tendency towards professional values, the frequency of displaying caring behaviors is higher[41]. In international publicationswhich support our findings, it is indicated that lack of motivation, work pressures, challenges nurses face while they care for patients can affect their perceptions of professional values while they perform their duties[42,43].

One of the factors affecting professional attitude, perception of positivity and fear of COVID-19 is individuals' perceived income status. In our study, of the participants, those who stated that their income was less than their expenses experienced fear more ($p<.005$). On the other hand, individuals who perceived their income higher than their expenses had a higher level of perception of positivity ($p<.005$). Within this context, it can be stated that the COVID-19 infection has also causedindividuals to haveeconomic concerns.

In conclusion, the COVID-19 fear levels of the nurses participating in our study were moderate, and their positivity perception levels were high. The fear of COVID-19 had a positive effect on theparticipants' attitudes towards nursing, and encouraged them to get vaccination against COVID-19, but almost half of them still did not think of being vaccinated against COVID-19. The positivity perception levels of the participants also positively affected their attitudes towards nursing. While of the participants, those who had a good income level and who considered the personalmeasures, and general measures taken by the institution hadperceptions in favor ofpositivity, those who had the fear of being diagnosed with COVID-19, who cared for patients with a diagnosis of COVID-19, who had the fear of losing their loved ones, and who had close relativeswith a diagnosis of COVID-19 had higher levels of fear of COVID-19.

In line with these results, it is recommended that;

- occupational health and safety of the nursesin the filiation teamsshould be ensured by providing them with protective equipment against COVID-19, and strategies encouraging those in the filiation teams to be vaccinated should be developed
- to help nurses overcome their fears and anxieties, psychological support units should be stablished in health institutions and they should be given more in-service training on stress coping techniques
- nurses' working conditions should be reorganized during the pandemic, factors causing fear in the workplace should be eliminated, and their motivation and social integration should be improved.

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Research Article

health science

EVALUATION OF THE IMPACT OF THE COVID-19 PANDEMIC PROCESS ON THE TYPE OF BIRTHS PERFORMED AT SIVAS CUMHURIYET UNIVERSITY OBSTETRICS AND GYNECOLOGY HOSPITAL

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Keywords

COVID-19 pandemic,
Birth trends,
Birth rates,
Societal impact

ABSTRACT

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has emerged as one of the most significant global health crises in recent history. This study aims to evaluate the effect of the pandemic process on the delivery type of a group of women who gave birth in Cumhuriyet University Faculty of Medicine, Gynecology and Obstetrics Hospital. Our study was prepared in a retrospective screening style, and 2804 births were included. Sociodemographic information of all participants, their way of giving, gestational week, birth, baby and birth weight of their babies were questioned. Of all the participants included in the study (births 1 year before the pandemic and in the 1-year period including the first year of the pandemic), 33.9% (n:951) had a normal delivery, and 66.1% (n:1853) had a cesarean section. 42.8% (n:1199) of births occurred in the first year of the pandemic, 57.2% (n:1605) before the pandemic. While the rate of cesarean section was 45.3% (n:839) among all deliveries in the year before the pandemic, the rate of cesarean section among all deliveries in the first year of the pandemic was 54.7% (n:1014) and was found to be significantly higher (p<0, 05). After women are informed about the epidemic, normal birth should be encouraged, their concerns about the pandemic should be eliminated, and cesarean section should be avoided unless necessary.

Volume: 1
Issue: 2
Page: 82-86

Received:
18.07.2023

Accepted:
25.08.2023

Available Online:
15.10.2023

INTRODUCTION

The COVID-19 pandemic, a global health crisis in early 2020, has had profound implications on numerous aspects of society, including healthcare systems, economic structures, and daily routines. Amidst this backdrop of unprecedented challenges, the realm of childbirth has not remained untouched. The pandemic's far-reaching effects have extended to the very fabric of birth experiences, prompting a need for in-depth evaluation and analysis[1-3].

The process of childbirth is a deeply personal and significant milestone in the lives of individuals and families. It encompasses not only the biological act of bringing a new life into the world but also the emotional, psychological, and societal dimensions of motherhood, family dynamics, and healthcare practices[3]. With its swift and often unpredictable nature, the pandemic has engendered a host of modifications across these dimensions, reshaping the contours of childbirth experiences in previously unimagined ways[4-6].

DOI:10.5281/zenodo.8413909

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As we navigate the complexities of the pandemic and its ongoing repercussions, it is crucial to ascertain the implications for maternal health, newborn well-being, and the broader healthcare infrastructure. By examining how the pandemic has altered the trajectories of childbirth experiences[7], we can derive valuable insights that inform healthcare policy, shape clinical practices, and support individuals and families as they navigate the intricate terrain of pregnancy and birth during these unprecedented times.

This publication aims to delve into the intricate interplay between the COVID-19 pandemic and the methods, preferences, and outcomes related to childbirth by exploring the multifaceted impacts of the pandemic on the type of births.

MATERIALS AND METHODS

The study aims to assess the potential impact of the COVID-19 pandemic on the distribution and characteristics of births. A retrospective observational study design was employed, utilizing birth data from pre-pandemic and pandemic periods. Ethical approval for the study was obtained from the Sivas Cumhuriyet University Noninvasive Clinical Research Ethics Committee. All data analyzed were anonymized to ensure the privacy and confidentiality of the individuals involved.

This dataset contained demographic information, including maternal age, gestational age, delivery method, and birth weight. Patients with incomplete file data were excluded from the scope of the study.

The study was divided into two periods: pre-pandemic (March 2019 – March 2020) and the first year of the pandemics (March 2020 – March 2021). This division allowed comparing birth trends before and during the pandemic.

Statistical Analysis

Statistical tests were conducted to determine the significance of observed differences between pre-pandemic and pandemic birth characteristics. Depending on the nature of the data, an independent sample t-test was used to determine the relationship between women's birth timing (pre-pandemic and the first year of the pandemic) and their ages and birth weights. Additionally, a Mann-Whitney U-test was employed to identify the relationship between gestational periods. Pearson's Chi-Square analysis was conducted to determine whether the number of cesarean births, normal births, and first births differed significantly based on birth timing. The significance level for the research was set at $p<0.05$.

RESULTS

To assess the impact of the COVID-19 pandemic on the type of births, we collected and analyzed data from covering the period from March 2019 to March 2021. The dataset comprised 2851 of birth records. 47 patients were excluded from the study due to insufficient data.

Upon analyzing the birth data, we observed notable shifts in birth trends during the COVID-19 pandemic compared to the pre-pandemic period. The following key findings were identified (Table 1).

The study included 2804 pregnant women who gave birth in one year before the pandemic and in the first year of the pandemic. The average age of women giving birth before the pandemic was 29.1±5.7, while the average age of women giving birth during the pandemic was 29.0±5.8. The average gestational week for women giving birth before the pandemic was 37.5±2.6, whereas the average gestational week for women giving birth during the pandemic was 37.9±2.4. The average birth weight of babies before the pandemic was 3041.9±648.1, while the average birth weight of babies during the pandemic was 3304.6±595.2.

Before the pandemic and during its first year, out of all women who gave birth, 951 (33.9%) had normal deliveries, while 1853 (66.1%) had cesarean sections. Among all births, 1199 (42.8%) occurred before the pandemic, and 1605 (57.2%) occurred in the first year of the pandemic. Among the women, 964 (34.4%) had their first births, while 1840 (65.6%) had second or subsequent births. Before the pandemic, there were 360 (30.0%) women who had their first normal delivery, while in the first year of the pandemic, 591 (36.8%) women had normal deliveries. Additionally, before the pandemic, 839 (70.0%) women had their first cesarean section, while in the first year of the pandemic, 1014 (63.2%) women had cesarean deliveries.

Before the pandemic, out of the 1199 births, 404 (33.7%) occurred between the 20th and 37th gestational weeks, while 795 (66.3%) occurred between the 38th and 42nd gestational weeks. In the first year of the pandemic, out of the 1605 births, 1130 (70.4%) occurred between the 20th and 37th gestational weeks, while 425 (29.6%) occurred between the 38th and 42nd gestational weeks.

Table 5. *General information about pregnancy, birth and demographic characteristics of patients*

	Before Pandemic (n=1199) (%)	During Pandemic (n=1605) (%)
Age (years)	29,1 ± 5,7	29,0± 5,8
Gestational week	37.5±2.6	37.9±2.34
Birth wight of babies	3041.9±648.1	3104.6±595.2
Number of Delivery		
• 1	426(44.2%)	538 (55.8%)
• 2 and over	773(42.0%)	13 (16,5%)
Number of Abortus		
• No	858 (41.4%)	1216 (58.6%)*
• 1 and over	341 (46.7%)	389 (53.3%)
Type of Delivery		
• Vaginal Delivery	360(30.0%)	591(36.8%) *
• Cesarean Section	839(70.0%)	1014(63.2) *
Type of Delivery		
• Vaginal Delivery	148(41.1)	212(58.9)
• Cesarean Section	278(46.0)	326(54.0)
Birth Week		
• Between 20-37 Week	404(33.7%)	475(29.6%)
• Between 38-42 Week	795(66.3%)	1130 (70,4%)
Birth Weight		
• 1500 gr and below	34(2.8%)	29(1.8%)
• Between 1501-2500gr	185(15.4%)	203 (12.6%)
• Between 2501-4000gr	915(76.3%)	1306(81.4%)
• 4001gr and over	65(5.4%)	67 (4.3%)

**p<0.05, Chi-square test*

When considering all births, there was no significant difference in the ages of mothers who gave birth before the pandemic compared to the first year of the pandemic. However, when looking at the average ages, it was observed that mothers giving birth during the first year of the pandemic were slightly younger (p>0.05).

The indication for cesarean section in the first birth significantly increased as the number of delivering patients increased (p<0.05). There was no significant difference in the weeks of gestation between births before the pandemic and during its first year (p>0.05). Babies born during the first year of the pandemic were found to be delivered later than those born before the pandemic, with statistical significance (p<0.05), but there was no significant difference in birth weights between babies born before the pandemic and during its first year (p>0.05).

Babies born during the pandemic had a slightly higher birth weight than babies born before the pandemic (p>0.05). No significant relationship was found between cesarean indications and the number of abortions in both groups (p<0.05). In the first year of the pandemic compared to before the pandemic, there was a significant increase in both the number of normal births and cesarean births (p<0.05). The number of normal births approximately doubled during the first year of the pandemic compared to before the pandemic (Table 1).

DISCUSSION

The present study aimed to evaluate the impact of the COVID-19 pandemic process on the type of births, considering various dimensions such as birth rates, birth outcomes, and maternal healthcare utilization. Our findings reveal several noteworthy trends and implications that shed light on the multifaceted influence of the pandemic on the birthing process.

The overall birth rate exhibited an increase during the pandemic compared to the pre-pandemic period. Specifically, there was a percentage 40 in the birth rate. When evaluating the impact of the pandemic on birthing methods among women, it was found that the rate of cesarean deliveries had increased compared to the pre-pandemic period. It was observed that births occurring during the pandemic year had higher gestational weeks and average baby weights than the previous year. We concluded that this increase in the number of

births could be attributed to cases where deliveries not performed in the public hospital due to the outbreak were referred to the university hospital.

When evaluating the impact of the pandemic on women's birthing methods, it was found that the rate of cesarean deliveries had increased compared to the pre-pandemic period. Births during the pandemic year were observed to have a higher gestational week and a higher average baby weight compared to the previous year. We concluded that this increase in the number of births could be attributed to cases where deliveries not conducted at the public hospital due to the outbreak were referred to the university hospital.

In a study conducted by Mutlu et al., it was determined that 60.6% of the births were before the pandemic, and 39.4% were after the pandemic[8]. According to data from the Turkish Ministry of Interior's Population Directorate, of the total births that occurred in 2019 and 2020, 51.7% were in 2019 (pre-pandemic), and 48.3% were in 2020 (during the pandemic)[9]. In our study, we found that 42.8% of the births were a year before the pandemic, and 57.2% were in the first year of the pandemic. The reason for this increase could be the referral of patients who did not give birth at the public hospital due to the outbreak to the university hospital.

In a study by Eleje et al. conducted in Nigeria during three months of the pandemic, when they compared cesarean delivery rates to the pre-pandemic period, they found that cesarean rates had decreased compared to the pre-pandemic period, from 46.8% to 40%[10]. In contrast, in a study by Mutlu et al.[8], they found that 40.5% were normal deliveries and 59.5% were cesarean deliveries during the first year of the pandemic. Cai et al., in a research covering the first six months of the pandemic year and involving the detailed evaluation of the delivery methods of 1019 pregnant women, found that 59.71% were cesarean deliveries and 40.29% were vaginal deliveries[11]. In our study, during the first year of the pandemic, we found that cesarean delivery rates were higher (36.8%) compared to the pre-pandemic period (30%).

In a survey conducted by Şenol et al., the average gestational week was 38.23±1.84[12]. In a study by Janevic et al.[13] involving 8026 pregnant women, they found that the preterm birth rate was 8.8% before the pandemic and 8.9% during the pandemic year. Llorca et al.[14] conducted a study involving 969 pregnant women before the pandemic and 1168 pregnant women during the pandemic year. This study found a preterm birth rate of 6% before the pandemic and 5% during the pandemic year. Consistent with the literature, our study found an average gestational week of 37.5 weeks before the pandemic and 37.9 weeks during the first year of the pandemic. The preterm birth rate was 33.7% before the pandemic and 29.6% during the first year of the pandemic. The pandemic process resulted in a decrease in preterm birth rates. Given these results, we attribute the higher preterm birth rate to the fact that we are a university hospital (tertiary care).

Several limitations of our study warrant consideration. Firstly, our analysis is based on retrospective data, which inherently carries biases and constraints regarding data accuracy and completeness. Additionally, the research predominantly focuses on quantitative trends, and qualitative insights from birthing individuals and healthcare providers could provide a more holistic understanding of the pandemic's impact. As the pandemic continues to evolve, longitudinal studies are required to assess the persisting effects and potential recovery trajectories.

CONCLUSION

In conclusion, our evaluation of the impact of the COVID-19 pandemic process on the type of births underscores the complex interplay of socioeconomic, psychological, and healthcare-related factors. The observed deviations in birth rates, birth outcomes, and maternal healthcare utilization emphasize the need for adaptive healthcare policies and support systems that can address the evolving needs of expectant mothers during times of crisis. As we navigate the post-pandemic landscape, continued research and interdisciplinary collaboration are imperative to inform evidence-based strategies for enhancing maternal and neonatal health in the face of unforeseen challenges. Overall, this study contributes to understanding how a global pandemic can reverberate through the very fabric of birth processes.

Acknowledgments

None.

Connfict of Interest

No conflict of interest is reported by the authors.

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Case Report

health science

CARDIOMYOPATHY CAUSED BY STRESS DUE TO FEAR OF UNDERGOING MAGNETIC RESONANCE IMAGING

Burak Ogulcan YILDIRIM[1*]

Keywords

Cardiomyopathy,
Magnetic resonance,
Stress,
Takotsubo

ABSTRACT

Takotsubo cardiomyopathy is a primary and acquired form of non-ischemic cardiomyopathy. Usually, a psychologically, emotionally, or physically stressful event precedes it. We have documented a case of a 67-year-old woman who experienced chest pain after undergoing magnetic resonance imaging (MRI). Electrocardiography (ECG) indicated changes and cardiac markers consistent with acute coronary syndrome (ACS). Coronary angiography revealed no coronary artery disease. Left ventriculography showed depressed LV systolic function with anteroapical akinesia, consistent with Takotsubo cardiomyopathy.After the cardiac catheterization and echocardiography patient is diagnosed with Takotsubo cardiomyopathy. Clopidogrel and atorvastatin were discontinued and the patient was treated with metoprolol, aspirin, and lisinopril. Two weeks later, during her follow-up, she described no symptoms and the control echocardiogram showed normal findings.

INTRODUCTION

Takotsubo cardiomyopathy is a primary and acquired form of non-ischemic cardiomyopathy[1]. This heart condition, known as stress cardiomyopathy, transient left ventricular apical ballooning syndrome, or broken heart syndrome, causes a temporary disorder in the way the left ventricular apex moves. Usually, a psychologically, emotionally, or physically stressful event precedes it. The exact cause of the disease is not fully understood, but it is believed that factors such as too much adrenergic stimulation, vascular spasm, microvascular dysfunction, temporary blockage of the left ventricular outflow tract, or regional myocarditis may play a role[2,3].

The disease is frequently seen in postmenopausal women. It usually develops as a result of an emotionally or physically stressful event. Although the disease presents itself almost identical to acute myocardial infarction, coronary angiography does not reveal any lesion that may explain left ventricular wall motion disorder. Elevations in cardiac biomarkers are consistent with acute coronary syndrome. The most commonly observed electrocardiography (ECG) finding is anterior ST-segment elevation. However, it is also possible to observe ST-segment depression and T-wave inversion[3,4].

Volume: 1
Issue: 2
Page: 87-89

Received:
27.06.2023

Accepted:
05.08.2023

Available Online:
15.10.2023

DOI:10.5281/zenodo.8414570

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The Mayo Clinic uses specific diagnostic criteria to diagnose diseases[5].

1. Transient hypokinesia or akinesia of the middle and apical regions of the left ventricle

2. Normal coronary arteries confirmed by arteriography (luminal narrowing of less than 50% in all the coronary arteries) in the first 24 h after the onset of symptoms

3. ECG findings including ST-segment elevation or depression

4. Absence of recent significant head injury, intracranial hemorrhage, suspicion of pheochromocytoma, myocarditis, or hypertrophic cardiomyopathy

Although the prognosis of the disease is generally good, severe complications such as hypotension, acute heart failure, ventricular rupture, LV apex thrombus, and malignant arrhythmia have been reported[5].We have documented a case of a 67-year-old woman who experienced chest pain after undergoing magnetic resonance imaging (MRI). Electrocardiography (ECG) indicated changes and cardiac markers consistent with acute coronary syndrome (ACS). Further diagnosis revealed Takotsubo cardiomyopathy.

CASE REPORT

67 years old woman who is scheduled to undergo MRI due to severe neck pain developed typical chest pain during MRI. According to the patient's history, she experienced claustrophobic fear, panic, and anxiety during the MRI procedure. Shortly after that, she began to feel retrosternal, pressure-like chest pain. She has no known cardiac history. She has a history of hypertension. On physical examination, the arterial blood pressure was 130/80mm Hg and the heart rate was 72 beats/min and regular. Electrocardiography (ECG) showed T wave inversion in DI, aVL, and V1-V6. The blood analysis revealed Hb:11,6 g/dL, creatinine:1,0 mg/dL and troponin 946 pg/ml. The echocardiographic examination showed akinesis of the apical segment of the left ventricular. The ejection fraction was %35-40 and grade 1 mitral regurgitation was present. The patient was using lisinopril and hydrochlorothiazide. The patient was loaded with oral 300 mg clopidogrel, 300 mg aspirin, 40 mg atorvastatin and given 5000 U heparin intravenously.

Coronary angiography revealed no coronary artery disease. Left ventriculography showed depressed LV systolic function with anteroapical akinesia, consistent with Takotsubo cardiomyopathy.After the cardiac catheterization and echocardiography patient is diagnosed with Takotsubo cardiomyopathy. Clopidogrel and atorvastatin were discontinued and the patient was treated with metoprolol, aspirin, and lisinopril. Two weeks later, during her follow-up, she described no symptoms and the control echocardiogram showed normal findings.

DISCUSSION

Takotsubo cardiomyopathy is a type of acquired, non-ischemic cardiomyopathy that affects the heart. It is also known as stress cardiomyopathy, transient left ventricular apical ballooning syndrome, or broken heart syndrome. One of its main features is the reversible wall motion disorder of the left ventricular apex. Generally, there is a stressful psychological, emotional or physical event before[2,3]. The disease is frequently seen in postmenopausal women. It usually develops as a result of an emotionally or physically stressful event. Although the disease presents itself almost identical to acute myocardial infarction, coronary angiography does not reveal any lesion that may explain left ventricular wall motion disorder. Clinical presentation, elevation in cardiac markers' and ECG findings are consistent with acute coronary syndrome however they have two different pathophysiologies[3,4].

The specific cause of the disease is unknown, but it is believed that a variety of factors such as excessive adrenergic stimulation, vascular spasm, microvascular dysfunction, temporary blockage of the left ventricular outflow tract, or regional myocarditis may contribute to its development. The most commonly discussed mechanism for this condition is stress-induced catecholamine release[2,3].

To our best knowledge, this is the first case of Takotsubo cardiomyopathy triggered by MRI fear. Our patient was undergoing an MRI procedure when she developed cardiac symptoms. According to her history, it is clear that during the procedure she had a severe panic attack and fear due to being in an MRI machine which triggered excessive sympathetic stimulation. Excessive sympathetic stimulation and the consequent release of catecholamines have been known to trigger microvascular spasm and direct toxicity in the heart muscle, which is believed to be the primary cause of Takotsubo cardiomyopathy[3].

While Takotsubo cardiomyopathy is typically a rare and harmless condition, certain patients may experience severe complications such as low blood pressure, fluid buildup in the lungs, heart muscle tearing, and unexpected death. Due to the rising cases of Takotsubo cardiomyopathy, it is important to consider it as a potential differential diagnosis for acute myocardial infarction.

Acknowledgments

None.

Conflict of Interest

No conflict of interest is reported by the authors.

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Review Article

health science

HASHIMOTO'S DISEASE REVISITED: THE γδ T CELL PERSPECTIVE

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Keywords

γδ T cells, Hashimoto's disease, Pathogenesis, Immune dysregulation

ABSTRACT

Hashimoto's disease is a prevalent autoimmune disorder characterized by chronic thyroid gland inflammation. With an emphasis on CD4+ and CD8+ T cells, several research has been done on T cells in connection to Hashimoto's disease. Gamma delta (γδ) T cell involvement in the immunological dysregulation of Hashimoto's disease is not well understood, yet. This review aims to comprehensively examine the impact of γδ T cells on the pathophysiology of Hashimoto's disease, exploring their mechanisms of action and discussing their potential as therapeutic targets. The study utilizes a literature review approach based on current literature and available data. γδ T cells are a distinct subgroup with distinct tissue distribution, antigen recognition, and functional characteristics. Recent research suggests they may contribute to the genesis of Hashimoto's disease according to evidence of their existence and altered subsets in thyroid tissue. It may be possible to understand the precise role of γδ T cells in the immunopathogenesis of the disorder by learning more about their interactions with thyroid autoantigens and regulatory capabilities. Based on the reviewed literature and available data, this study highlights the need for further research on the role of γδ T cells in Hashimoto's disease. Understanding their mechanisms of action, interactions with thyroid autoantigens, and regulatory capacities could lead to the development of therapeutic targets for the disease.

Volume: 1
Issue: 2
Page: 90-100

Received:
27.07.2023

Accepted:
29.08.2023

Available Online:
15.10.2023

INTRODUCTION

Hashimoto's disease is an autoimmune disorder characterized by chronic thyroid gland inflammation. According to Chaker et al., it is the leading cause of hypothyroidism worldwide[1]. Several genetic, environmental, and immunological variables interact in a complicated manner throughout the etiology of Hashimoto's disease[2]. Gamma delta (γδ) T cells are involved in the immunological dysregulation of Hashimoto's disease, but their involvement has not gotten nearly as much attention as $CD4^+$ and $CD8^+$ T cells. A unique T cell receptor (TCR) made up of gamma and delta chains is expressed by γδ T cells, a subpopulation of T lymphocytes. They differ from conventional alpha-beta (αβ) T cells in terms of antigen recognition, tissue distribution, and functional traits[3]. γδ T cells have been connected to a variety of immune responses, such as host defense against infections and the management of autoimmune conditions[4,5].

Recent evidence suggests that γδ T cells may be involved in the development of Hashimoto's disease. Several studies have discovered γδ T cells in the thyroid tissue of people with Hashimoto's disease, proving that these cells have been locally activated and have migrated to the site of inflammation[6,7]. Furthermore,

DOI:10.5281/zenodo.8432610

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research on Hashimoto's disease has shown altered γδ T cell subsets and functions, suggesting that these cells may contribute to the disordered immune response seen in this condition[6].

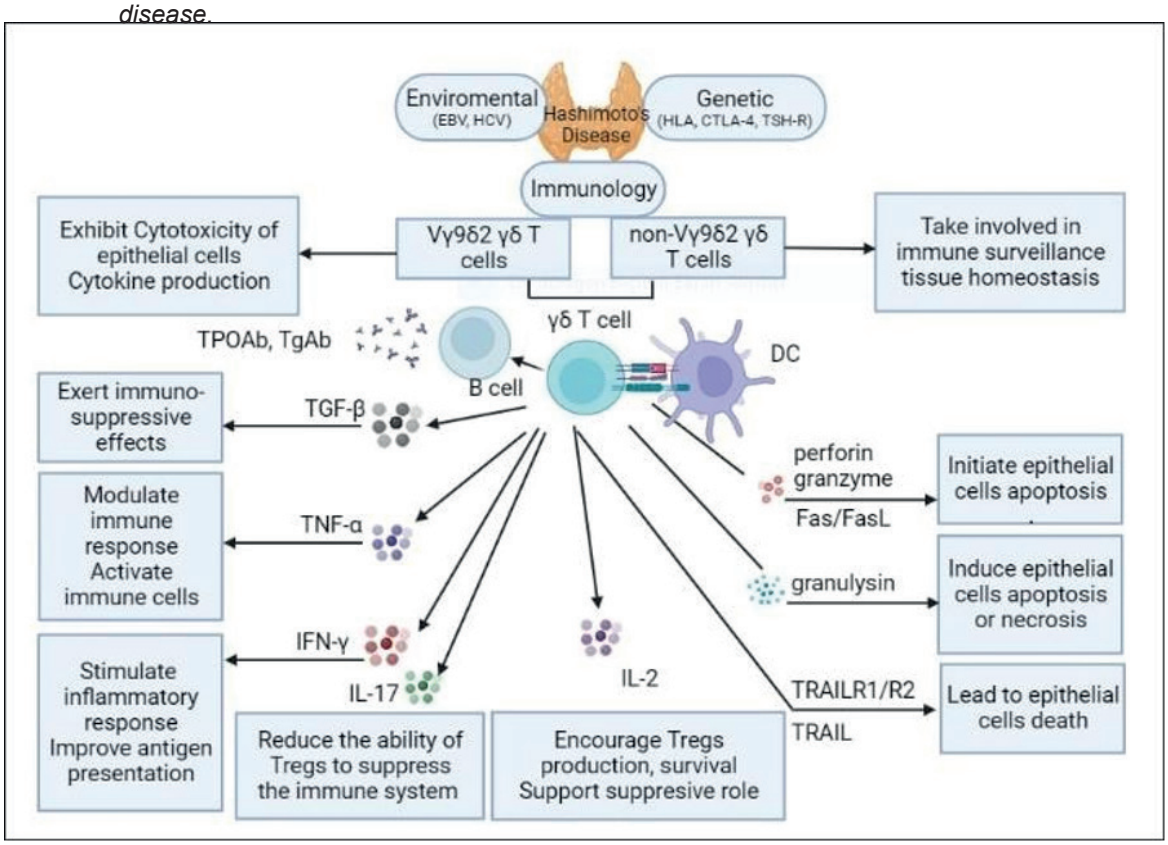
For the complicated immunological mechanisms underpinning the onset and course of the ailment, it is crucial to understand the specific role that γδ T cells play in Hashimoto's disease pathogenesis. Understanding the regulatory and effector functions of γδ T lymphocytes in relation to thyroid autoantigens may help to clarify the immunopathogenesis of Hashimoto's disease and open up new treatment avenues. This review's goal is to extensively analyze how γδ T cells impact the pathogenesis of Hashimoto's disease. We will examine the evidence for the involvement of γδ T cells in the immune dysregulation seen in Hashimoto's disease, elucidate their mechanisms of action, and discuss their potential as diagnostic markers and therapeutic targets by reviewing the current literature and synthesizing the data that is available.

Overview of Hashimoto's Disease

Hashimoto's disease is an autoimmune disorder in which the immune system mistakenly attacks the thyroid gland, leading to persistent inflammation[8]. The illness primarily affects women, with an about 10:1 female-to-male ratio[9]. It is widespread in iodine-sufficient regions including North America, Europe, and some regions of Asia. Hashimoto's disease is likely to have a hereditary and environmental component, while its exact cause is yet unclear. A genetic predisposition plays a significant role, as evidenced by the increased concordance rate in monozygotic twins[10]. The human leukocyte antigen (HLA), TSH receptor, and cytotoxic T-lymphocyte antigen-4 (CTLA-4) genes have all been connected to Hashimoto's disease[11].

Environmental triggers or exacerbations of the autoimmune response in vulnerable individuals include virus infections and exposure to certain substances[12]. Thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) are examples of autoantibodies that are produced when the immune system detects thyroid-specific antigens[13]. These autoantibodies interfere with hormone production and the destruction of thyroid cells (Figure 1).

Figure 1. *Genetic, environmental, and immunological factors contribute to the etiology of Hashimoto's disease.*



Vγ9Vδ2 and non-Vγ9Vδ2 T cells are the two types of γδ T cells. Vγ9Vδ2 T cells are capable of producing cytokines and cytotoxicity, among other powerful effector actions. Non-Vγ9Vδ2 T cells, on the other hand, have unique functional traits and tissue-specific distribution patterns that suggest they play specialized roles in local immune responses. Dendrite cell-γδ T cell interaction contributes to immunological control, stimulates cytokine synthesis, and has an impact on other immune cells. The autoimmune process may become more intense if γδ T cells and B cells interact. γδ T cells can release cytotoxic substances that kill thyroid epithelial cells.

Importance of Investigating γδ T Cells in Hashimoto's Disease

The pathogenesis of Hashimoto's disease is complex and involves a number of immune cell subtypes. According to current data, its development may be greatly controlled by γδ T cells. According to research, the thyroid glands of people with Hashimoto's disease contain γδ T cells[14]. Since these cells can be found in thyroid tissue, it is possible that they contribute to local immune responses. The thyroid's stimulation and recruitment of γδ T cells may play a role in the ongoing tissue damage and inflammation that are symptoms of Hashimoto's disease[6].

IFN-γ and IL-17, two cytokines that γδ T cells can produce, have an impact on the thyroid gland and immune system performance[15]. The imbalance between pro-inflammatory and regulatory immunological responses seen in Hashimoto's disease may be caused by altered cytokine production by γδ T cells. The existence of autoantibodies against thyroid-specific antigens like TPO and Tg is a defining feature of Hashimoto's disease. γδ T cells may be involved in the autoimmune response by interacting with B cells and promoting the production of autoantibodies[14]. It may be possible to comprehend the mechanisms causing autoantibody development in Hashimoto's disease by learning how γδ T cells and B cells interact.

Pathogenesis of Hashimoto's Disease

Hashimoto's disease involves a complex interplay of genetic, environmental, and immunological factors. The onset of Hashimoto's disease is significantly influenced by genetic factors[16]. According to studies, there is a substantial familial correlation, which points to a hereditary propensity[17]. HLA genes, CTLA-4 gene, protein tyrosine phosphatase non-receptor type 22 (PTPN22) gene, and forkhead box P3 (FOXP3) gene are just a few of the genes that have been linked to the pathogenesis[2]. These genes have an impact on immunological responses and immune tolerance, which helps to cause Hashimoto's disease.

The pathophysiology of Hashimoto's disease is also influenced by environmental variables. Viral infections (e.g., Epstein-Barr virus, hepatitis C virus) and exposure to environmental pollutants are just two examples of certain triggers that have been linked to the beginning or worsening of the autoimmune response[18]. These catalysts may cause the immune system to get activated, target thyroid antigens, and start the autoimmune process[18]. Research is currently being done to determine the precise pathways that lead to the loss of self-tolerance and the activation of autoreactive T cells[19].

Role of Thyroid Autoantigens

Tg and TPO are two thyroid autoantigens that are important initiators of the abnormal immune response in Hashimoto's disease. These primarily thyroid-expressed autoantigens are recognized by autoreactive T cells and B cells, which sets off a series of immunological responses[16]. The thyroid gland is attacked by the immune system as a consequence of the coaction between autoantigens and immune cells, which causes persistent inflammation and consequent tissue destruction[20]. A distinguishing feature of Hashimoto's disease is the development of autoantibodies against thyroid autoantigens. TgAb and TPOAb are examples of autoantibodies that are produced by autoreactive B cells that are triggered by autoreactive T cells[21]. When these autoantibodies connect to their specific target antigens and enter the thyroid gland through circulation, further immune-mediated death of thyroid tissue is triggered. The interaction of thyroid autoantigens and autoantibodies intensifies the autoimmune response, causing chronic inflammation and aiding in the development of Hashimoto's disease's clinical symptoms[22].

Immune Dysregulation in Hashimoto's Disease

Immunological dysregulation, which is the result of complex interactions between various immune cell types and signaling molecules, has a significant impact on the pathophysiology of the

disease. In Hashimoto's disease, immune cells—particularly T and B cells—are inappropriately active[23]. Pro-inflammatory cytokines including IFN-γ and IL-17 are secreted by activated γδ T cells and have been associated with thyroid tissue inflammation and damage. When B cells interact with autoreactive T cells to transform into plasma cells and produce autoantibodies against thyroid antigens, the autoimmune response is maintained[24] (Figure 1).

Overview and Functions of γδ T Cells

Unlike αβ T cells, which are mostly found in secondary lymphoid organs like the lymph nodes and spleen, γδ T cells are distributed in a range of tissues throughout the body. They are particularly common in epithelial tissues including the skin, gastrointestinal tract, and lung mucosa, according to Hayday et al.[25]. Their specific role in immune protection and monitoring at barrier regions is shown by their distinctive tissue localization. γδ T cells are very functionally adaptable. Unlike αβT cells, which largely identify peptide antigens presented by major histocompatibility complex (MHC) molecules, γδ T cells may detect a range of antigens, including microbial products, stress-induced molecules, and self-antigens[26]. They can mount quick immune responses thanks to this property in situations including infection, and tumor surveillance. γδ T cells can also create cytokines, influence other immune cells, and take part in immunological regulation[27]. They can also cause direct cytotoxicity. As shown by their ability to integrate innate and adaptive immune responses, they are crucial in bridging innate and adaptive immunity.

Due to their special characteristics, γδ T cells offer an exciting potential for participation in a variety of physiological and pathological processes. γδ T cells may help maintain immunological homeostasis, defend against pathogens, and monitor the immune system in barrier locations, according to recent research[27,28]. Furthermore, both autoimmune diseases and inflammatory disorders have been linked to dysregulation or modification in the activity of γδ T cells[29,30]. Future research on the complex biology of γδ T cells could result in the creation of brand-new therapeutic targets and therapy regimens.

Vγ9Vδ2 and non-Vγ9Vδ2 T cells are the two main categories of γδ T cells, which can be broadly classified based on the expression of different gamma and delta chain combinations. The majority of the circulating population of γδ T cells in adult humans is made up of Vγ9Vδ2 cells. They exhibit the Vγ9 and Vδ2 chains and respond to phosphoantigens such as isopentenyl pyrophosphate (IPP), which are produced by microorganisms or stressed cells[31]. Vγ9Vδ2 T cells exhibit potent effector functions, including cytokine production and cytotoxicity, enabling them to respond rapidly to infections and malignancies. However, non-Vγ9Vδ2 T cells, which do not express Vγ9 and Vδ2, are made up of a wide variety of T cells that express various gamma and delta chain combinations. Non-Vγ9Vδ2 T cells have distinct functional characteristics and tissue-specific distribution patterns, which point to specialized roles in local immune responses[32]. They are involved in immune surveillance and tissue homeostasis and are capable of recognizing a wide range of antigens, including self-antigens (Figure 1).

γδ T cells can offer early immunological protection because of their quick and innate-like responses. Through the production of cytotoxic chemicals like perforin and granzymes, γδ T cells may specifically identify and eliminate infected or altered cells[33]. They can destroy infections and target malignant cells thanks to their cytotoxic activity. γδ T cells also secrete a variety of cytokines, including TNF-α, IFN-γ, and IL-17, which help to modulate immune responses, activate other immune cells, and have antimicrobial effects[3] (Figure 1).

γδ T cells bridge innate and adaptive immunity by their uncommon ability to combine features of adaptive immune cells with prompt innate responses. Dendritic cells and conventional T cells that receive antigens from γδ T cells can influence immunological responses and shape adaptive immunity[26]. Other immune cells can receive co-stimulatory signals from γδ T cells, which promotes their activation, proliferation, and the development of effective immune responses[27]. γδ T cells are also engaged in immunological regulation, which prevents the immune system from overreacting and keeps it under control. γδ T cells have the ability to modify the actions of other immune cells such as conventional T cells, B cells, and dendritic cells in order to regulate immunological responses and prevent immunopathology[4,34]. One subtype of γδ T cells called regulatory γδ T cells suppresses autoreactive immune responses and delays the onset of autoimmune diseases[27,35].

Involvement of γδ T Cells in Hashimoto's Disease

Through the use of flow cytometry and immunohistochemistry, γδ T cells have been discovered inside the thyroid gland[14]. Due to their proximity to lymphoid clusters and inflammatory infiltrates, these cells may be implicated in the thyroid tissue's local immune response. Additionally, research has revealed that Hashimoto's thyroiditis patients have a higher frequency of γδ T cells in their peripheral blood than healthy individuals. Higher percentages of γδ T cells, particularly the Vδ2 subset, were seen in the patient's peripheral blood samples after being subjected to flow cytometry analysis[36]. The increasing of γδ T cells in the circulation suggests their systemic involvement in the immune dysregulation observed in Hashimoto's disease. γδ T cells have been discovered to have cytotoxic action against thyroid epithelial cells[37]. The loss of thyroid tissue and the subsequent onset of hypothyroidism may be caused by this cytotoxicity. γδ T cells are hypothesized to support the maintenance of the autoimmune response in the thyroid gland, which causes ongoing tissue damage and inflammation[14]. Furthermore, the autoimmune process may become more severe as a result of γδ T cells' interactions with B cells and regular T (Treg) cells[38].

Modulation of Immune Response by γδ T Cells

γδ T cells have a variety of skills that help maintain and regulate immunological homeostasis. The control of immunological responses by γδ T cells has an impact on the development of therapeutic strategies as well as physiological immune regulation[39]. γδ T cells produce a variety of cytokines to regulate the immune response. Depending on the exact situation, these cytokines may have pro-inflammatory or anti-inflammatory effects. γδ T cells generate IL-17, a chemical that is essential for triggering inflammation and enticing immune cells to areas of infection or tissue injury[40]. In addition, IL-17 can promote autoimmune and inflammatory disease development. IFN-γ, a cytokine having a variety of immunomodulatory effects, is produced in large quantities by γδ T cells[41]. IFN-γ may increase cytotoxic responses and activate macrophages. Additionally, it affects immune cell movement and controls adaptive immunological responses[28]. Some subsets of γδ T cells can generate TGF-β, which has immunosuppressive effects and can regulate immune cell development, proliferation, and survival[42,43]. TGF-β promotes immunological tolerance as well as the maturation of Tregs. γδ T cells can also regulate other immune cells' activities, influencing immunological responses and protecting immune homeostasis[44]. γδ T cells and dendritic cells can communicate with one another and affect how each other develops, presents antigens, and produces cytokines[45]. This contact may influence the ensuing immunological response and aid in immune control. γδ T cells can impact the activation, proliferation, and differentiation of conventional T cells through interactions[30]. The balance between effector and regulatory T-cell responses may be impacted by this crosstalk, which also supports immunological control[27].

Interaction between γδ T Cells and Thyroid Autoantigens

The interaction between γδ T cells and thyroid autoantigens is an area of ongoing research in the context of autoimmune thyroid disorders. Understanding the interplay between γδ T cells and thyroid autoantigens may provide insights into the mechanisms driving autoimmune thyroid disorders, such as Hashimoto's disease[46]. γδ T cells may be able to recognize and react to thyroid autoantigens in autoimmune thyroid diseases, according to the newly available information. Some investigations have shed light on the coaction between γδ T cells and thyroid autoantigens, even though the precise mechanisms are not yet fully understood. Tg, a key protein found in thyroid follicles, has been linked to autoimmune thyroiditis as a possible target for γδ T cells[47]. γδ T cells may be involved in the immune response to thyroid-specific antigens as studies have demonstrated that they can recognize and react to peptides produced from Tg. A thyroid hormone production enzyme called TPO has also been linked to the interaction with γδ T cells[48]. Studies have shown that TPO-specific γδ T cells are present in the thyroid tissue of people with autoimmune thyroiditis, indicating that these cells may play a part in autoimmune reactions that target TPO.

The etiology of autoimmune thyroid diseases may be influenced by the mutual effect between γδ T cells and thyroid autoantigens. The local inflammatory response seen in autoimmune thyroid diseases may be influenced by γδ T cells' identification of thyroid autoantigens within the thyroid gland[49]. The autoimmune process may continue to develop if thyroid autoantigens activate γδ T cells, releasing pro-inflammatory cytokines. γδ T cell-mediated cytotoxicity, induced by thyroid autoantigen recognition, may

be a factor in thyroid follicular cell apoptosis seen in autoimmune thyroiditis[2]. The onset of thyroid dysfunction and the clinical symptoms of autoimmune thyroid diseases may be influenced by this cytotoxic action.

Mechanisms of Action of γδ T Cells in Hashimoto's Disease

γδ T cells are capable of a variety of cytotoxic actions that aid in immune monitoring, anticancer responses, and host defense against infections. These abilities include the ability to directly kill cells as well as the ability to produce cytotoxic substances and activate death receptors[50]. Contact-dependent mechanisms enable γδ T cells to directly kill target cells. This direct cell killing is caused by a number of mechanisms, including the release of granzymes, serine proteases, and perforin by γδ T cells into the immunological synapse made with target cells[51]. Perforin, which makes holes in the target cell's membrane so that granzymes can enter the cytoplasm and start apoptosis, causes target cell death. By expressing the FasL protein on their cell surface, γδ T lymphocytes can interact with the Fas receptors on target cells[3]. The apoptotic signaling pathways of the target cells are activated through this interaction, resulting in programmed cell death.

γδ T cells have the ability to release cytotoxic substances that kill target cells. γδ T cells have the ability to create TNF-α, a cytokine that can kill target cells[52]. TNF-α, which also induces apoptosis and can activate more immune cells, further destroys target cells. Granulysin, a cytolytic protein that may quickly kill a target cell, is produced by γδ T cells[53]. Granulysin disrupts target cell membranes and causes either apoptosis or necrosis, depending on the dose. Additionally, γδ T cells can connect with target cells' death receptors to activate apoptotic signaling pathways. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), which γδ T cells can express on their cell surfaces, binds to the death receptors TRAIL-R1 and TRAIL-R2 on target cells[33]. Target cell death results from the activation of caspase-mediated apoptotic pathways by the binding of TRAIL to its receptors (Figure 1).

γδ T Cell-Mediated Inflammation

γδ T cells, a vital component of the immune system, play a critical role in mediating inflammation. γδ T cells can affect the inflammatory milieu in a number of normal and pathological settings because they create pro-inflammatory cytokines, activate immune cells, and draw tissue. The cytokine IL-17, which is crucial for causing inflammation, is mostly produced by γδ T cells[40]. IL-17 activates neutrophils, encourages the draw of immune cells to inflammatory areas, and boosts the production of additional pro-inflammatory cytokines and chemokines. IFN-γ, a cytokine with pro-inflammatory properties, can also be produced by γδ T cells[41]. IFN-γ may stimulate the inflammatory response, activate macrophages, and improve antigen presentation. γδ T cells can activate and modify the activities of other immune cells, which supports the inflammatory response. T cells can interact with DCs to help them mature, present antigens, and produce cytokines[54]. Through this contact, additional immune cells are more effectively activated by DCs, and inflammatory responses are more effectively launched. γδ T cells can induce macrophages to generate cytokines and chemokines that promote inflammation[27,55]. By increasing their phagocytic and antibacterial capabilities, macrophage activation causes tissue inflammation. γδ T cells may help draw immune cells to areas of inflammation, so enhancing the inflammatory response.

Additionally, chemokines like CCL3, CCL4, and CXCL8 that γδ T cells are capable of producing help draw immune cells to inflamed areas[56]. These chemokines draw immune cells like neutrophils and monocytes to the area of inflammation, where they trigger the inflammatory cascade. Adhesion molecules whose expression can be enhanced by γδ T lymphocytes include intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1). Its expression promotes immune cell migration and adhesion, which feeds the inflammatory response[57].

Duty of γδ T Cells in Regulatory T Cell Imbalance

γδ T cells, are important for controlling immunological responses. γδ T cells may have an impact on Treg production, survival, and suppressive ability, altering immunological control and perhaps causing autoimmune disorders and immune dysregulation. Interleukin-2 (IL-2) is a cytokine that γδ T cells can produce and is crucial for the growth and maintenance of Tregs[58]. IL-2 supports Treg survival and growth while simultaneously promoting their suppressive function. γδ T cells may operate as a source of IL-2, assisting Treg homeostasis. Indoleamine 2, 3-dioxygenase (IDO) is activated by γδ T cells,

which helps Treg formation and function[59]. By creating an immunosuppressive environment, IDO-mediated tryptophan metabolism promotes the production and activation of Treg.

γδ T cells may potentially obstruct Treg action, upsetting the immune system's delicate balance. γδ T cells have the capacity to release IL-17, which has been shown to lessen Tregs' capacity to inhibit the immune system[60]. The disruption of Treg stability and function by IL-17 may have an effect on immune dysregulation. When IL-23, a cytokine associated with inflammatory reactions, activates γδ T cells, Treg function may be inhibited[34]. γδ T cells activated by IL-23 release chemicals that inhibit the immune system's capacity to be suppressed by Treg[61]. The ratio of γδ T cells to Tregs may affect immunological dysregulation and autoimmune diseases[62].

Clinical Implications and Therapeutic Potential

γδ T cells have drawn interest as potential prognostic and diagnostic biomarkers for many diseases. This section examines the importance of γδ T cells for diagnosis and prognosis, emphasizing their potential use in clinical settings. γδ T cells show potential as useful indicators in the assessment and management of various medical disorders due to their correlation with disease activity and predictive usefulness for therapy response and patient outcomes[63]. γδ T cells link to numerous autoimmune disorders as diagnostic indicators. Autoimmune diseases such as rheumatoid arthritis[64], systemic lupus erythematosus[36], and multiple sclerosis[65] have abnormal amounts or dysregulated functions of γδ T cells.

Future Directions and Research Opportunities

γδ T cell research is an area that is still being explored and has exciting potential. Continued research, which involves looking at new targets and looking into developing technology, may help unlock the full potential of γδ T cells in various disease scenarios. Additional investigation into the diversity and characteristics of γδ T cell subsets may produce illuminating findings. Understanding the distinctive behaviors and therapeutic potential of tissue-specific γδ T cell subsets may be possible[66]. It is possible to gain knowledge on the heterogeneity, flexibility, and functional states of γδ T cells in intricate immunological settings by combining single-cell sequencing and high-dimensional profiling approaches[67,68]. Research into the therapeutic potential and functional roles of γδ T cells is accelerated by the use of genome editing tools like CRISPR-Cas9, which can enable precise genetic modifications in these cells[69,70].

CONCLUSION

The functions and therapeutic potential of γδ T cells have been clarified by a number of important discoveries. To create tailored therapeutic strategies, it is essential to understand how γδ T cells activate, how their effectors work, and how they interact with tissues. γδ T cells are linked to autoimmune thyroid disorders, changing immune responses and causing cytotoxicity and inflammation. In order to enable tailored therapeutic interventions, they operate as markers for disease activity, therapy response, and patient outcomes. Overall, γδ T cells are a unique and adaptable class of immune cells with therapeutic potential, providing chances for cutting-edge therapies.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

No conflict of interest is reported by the authors.

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