HEALTH SCIENCES IN A GLOBALIZING WORLD

Editor
Assist. Prof. Ayşe AK

DUVAR

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Chapter 1

Use Of Different Materials in Episiotomy Repair

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Episiotomy is the most common method used to widen the diameter of the perineal outlet (Sherif & El-Shourbagy, 2020; Shahrahmani et. al., 2017; Woldegeorgis, 2022). Episiotomy was first performed in the United States in 1850, with the lowest rate recorded in the Netherlands and the highest in Eastern Europe. Routine episiotomy was questioned in the late 1980s and fell out of favor in the 1990s. Factors behind this change have included increased women's health awareness, the natural birth movement, professional competition, and evidence-based practices. (Chang et. al., 2011). The World Health Organization and ACOG recommend limiting episiotomy repair and applying it at a rate of 10% (Al-Ghammari et. al., 2016).

Episiotomy; the main reasons for not giving up on episiotomy are that it is a clean, straight incision, it is easier to repair and heals faster than laceration, episiotomy prevents fetal brain damage by reducing the pressure of the fetal head on the pelvic floor, and prevents pelvic floor damage by shortening the second stage of labor. In the studies carried out; this causes episiotomy to be preferred frequently by health professionals in cases such as advanced age pregnancy, breech presentation, macrosomia, primiparity, meconium presentation, occiput position, dystocia, postterm pregnancy, use of oxytocin, fetal distress, maternal chronic disease, vaginal delivery after cesarean section, and maternal malnutrition. (Melo et. al., 2014; Woldegeorgis, 2022).

There is no proven benefit of episiotomy at birth, and it has been reported that it may cause unnecessary pain, bleeding and infection in the short term, and it may cause dyspareunia, urinary and rectal incontinence, sexual dysfunction, lack of self-confidence, anxiety, delayed healing and pelvic organ prolapse in the long term (Al- Ghammari et. al., 2016; Caroci-Becker er. al., 2021; Deyaso, 2022). Ideal method for episiotomy repair; it should be fast, painless and easy to apply, and preferably should not increase pain and dyspareunia during puerperium (Sherif & El-Shourbagy, 2020; Deyaso, 2022; Feigenberg, et. al., 2014).

Looking at the literature, pain is one of the common side effects of episiotomy. A woman's desire for pain relief is considered a medical indication for the use of pain relief methods. Poor pain management reduces the effectiveness of therapeutic intervention (JahaniShoorab et. al., 2015). In addition, the comfort of mothers is affected due to episiotomy pain, mother-infant bonding is impaired, breastfeeding success decreases, and it even affects the birth preferences of women who are afraid of labor pain and episiotomy pain (Shahrahmani et. al., 2017; Temizkan, 2018; Vakili et. al., 2018).).

Episiotomy is one of the most routine surgical procedures that causes pain and anxiety in women. Episiotomy is performed in 8% of normal births in the

Netherlands, 14% in the United Kingdom, 50% in the United States, and 99% in Iran and many Eastern European countries. In Turkey, although this rate varies between 64% and 74%, it has been reported that it reaches up to 94% in primiparous women. The use of local analgesics for nerve blockade during episiotomy or the use of opioids to reduce anxiety may cause fetal heart rate changes, adverse effects such as apnea hypotonia in the newborn, hypothermia and low blood pressure in the mother (Aradmehr et al., 2017; Kırca & Gül, 2020; Sheikhan, 2012).

Ideal method for episiotomy repair; it is fast, easy to apply and preferably causes minimal pain and dyspareunia after delivery. By using the closure technique that eliminates traumatizing the skin, it will reduce inflammation and scarring by minimizing foreign body entry. There are several recommendations for postpartum episiotomy repair. Techniques such as not suturing the incision, continuous, locking stitches or intermittent non-locking stitches are used. Whichever technique is used, a successful tissue union results in less pain and wound infection in women, better cosmetic results, and shorter hospital stays. Classical methods for episiotomy repair are now being replaced by modern methods such as skin staples, skin adhesives and tapes (Sherif & El-Shourbagy, 2020).

The materials that can be used to close the episiotomy incision should be non-allergenic, easy to use and low cost. In order for the incision site to heal, the skin edges should be kept in apposition. Although silk from the skin sutures used is a safe method, due to its tendency to swell, it is bacterial and can cause keloid formation. Skin staplers are fast, reliable and manageable methods. Equal wound tension is ensured by the constant depth and regular shape of the stapler. Synthetic skin adhesives; when applied to the surface, it creates a solid polymer texture. It offers a waterproof and antibacterial coating. A small layer is placed over the entire wound and forming a bond causes heat generation on the skin (Mastud et. al., 2022).

Skin adhesives have been used since 1998. Short application time, easy use, hemostatic and bacteriostatic properties provide advantages for use. It is also biodegradable and has adequate tensile strength (Tence Marks, et al., 2020). In some studies comparing skin adhesives with skin sutures; skin adhesives have been shown to cause significantly less erythema and edema than the traditional method, and also have better cosmetic results (Sherif & El-Shourbagy, 2020). Skin adhesives have been used for many years in different mucous and skin structures such as aphthous ulcers, joining wound lips, closing facial wounds. In addition, it is seen that it is used successfully in obstetrics-gynecology, such as

closure of cesarean section incisions and clitoris injuries. The use of skin adhesives in wet areas resembling the vaginal mucosa suggested that they may also be useful in the treatment of postpartum perineal tears (Feigenberg, et. al., 2014).

In another randomized controlled study comparing skin adhesive and skin suture; It is seen that women who used skin adhesive had less pain intensity, less repair time, better recovery score and more patient satisfaction than suture. Therefore, it is thought that skin adhesive can reduce perineal pain intensity and improve perineal pain process compared to skin suture (Caroci-Becker er. Al., 2021).

In the study of Chamariya et al.; it is seen that skin closure time is faster when skin adhesive is used for episiotomy. In addition, significantly less pain was recorded during skin closure and in the first three days after delivery. It has been reported that wound healing takes place in a shorter time compared to the suture group. However, skin complication rates were higher in the study group. The ease of application of the skin adhesive, less pain during and after the procedure, was found to be superior to skin sutures. This can be explained by the natural differences in skin characteristics in the perineal area and the inability to keep the perineal area clean and dry after birth (Chamariya et. al., 2016).

In the study where Sherif & El-Shourbagy compared skin tape and skin suture; there was a significant difference in favor of adhesive tape in terms of pain between the first 4 and 6 hours after birth. There was no significant difference between the two groups in terms of skin closure time. There was a significant difference in favor of the adhesive tape group in terms of pain on the 3rd, 4th, 5th and 7th days. There was no difference between the two groups in terms of wound healing assessed by the REEDA scale (Sherif & El-Shourbagy, 2020).

As a result, modern methods may be superior to skin suture in reducing perineal pain after delivery; however, more clinical studies are needed to assess long-term effects, calculate costs, and accurately measure patient satisfaction.

The concept of pain is the most universal complaint in the world. Pain is the result of illness or invasive medical procedures. Pain can be acute, intermittent or chronic in nature. It has been determined that pain causes fear and anxiety, causes post-traumatic stress disorder, eating and drinking problems and wound healing problems. It is thought that the use of modern suture materials in various scars has both physical and cosmetic benefits and that it is an innovative application in episiotomy repair, which will attract attention to the international literature and will pave the way for the use of innovative methods in episiotomy repair.

Mother-Friendly Hospital Practices in our country are being tried to be disseminated by the Ministry of Health. The main purpose of the applications is to reduce the fear of the woman, to reduce her pain, to ensure her comfort, and to ensure rapid adaptation to her prenatal life. By using innovative methods, it is aimed to reduce the continuity of pain and scar tissue experienced by women at the time of birth as much as possible by requiring as little intervention as possible. The fact that modern suture materials, which are very frequently used in surgical procedures, have never been used in episiotomy repair, is expected to make a new contribution to the applications in this field.

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Chapter 2

Nursing Care For Patients With Covid 19 Liver Involvement And Underlying Liver Disease

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INTRODUCTION

COVID-19 is a respiratory disease. It can involve many organs and tissues. In COVID-19 patients, the liver is the second most frequently affected organ after the lungs (Kukla et al., 2020). First publications reported COVID-19-related liver injury manifested as elevated serum aminotransferases and/or cholestatic enzyme activities in 32.6% of patients (Struyf et al., 2020). There are studies reporting that this rate rises to 50% at the time of admission and over 75% during hospitalization. Liver damage is related increased importance of COVID-19 in patients from China (Ding et al., 2021). It has also shown that underlying liver disease, including metabolic disease, worsens the prognosis in patients with COVID-19 (Webb, Moon, Barnes, Barritt, & Marjot, 2020). SARS-CoV-2 enters cells in the human lower respiratory tract using the receptor angiotensin converting enzyme 2 (ACE2). It has been reported that ACE2 receptors are found in both cholangiocytes and hepatocytes, although they are more common in cholangiocytes. The level of ACE2 in cholangiocytes is found to be similar to that in the lungs. This makes the SARS-CoV-2 virus a potential infection target for the liver and biliary tract (Singh & Khan, 2020). This receptor is abundant in gastrointestinal epithelial cells, (Wong, Lui, & Sung, 2020) SARS-CoV-2 particles can be found in the esophagus, stomach, duodenum, stool, rectum, as well as in nasopharyngeal swabs (Lee, Huo, & Huang, 2020).

Since COVID 19 can sometimes only present with gastrointestinal symptoms, it should be examined especially in terms of liver involvement. In chronic liver patients, COVID-19 infection can cause hepatic decompensation without respiratory symptoms in 25% of patients (Moon et al., 2020). Therefore, it is recommended that patients with liver disease should be evaluated for COVID19 infection when signs of decompensation develop and liver enzyme levels are elevated (ALIRAVCI & Çeviker, 2020). When evaluated for liver involvement, the clinical manifestation of COVID-19 may include acute hepatitis-like symptoms and abnormal liver biochemical tests (Zhang, Shi, & Wang, 2020). During SARS-CoV-2 infection, liver enzyme deterioration may develop due to drug-induced hepatotoxicity, cytokine storm in critically ill patients, or hypoxia associated with pneumonia (Zhang et al., 2020). A large number of cases of patients diagnosed with COVID-19 presenting with gastrointestinal symptoms such as diarrhea, nausea, vomiting and abdominal pain have been reported. The prevalence of gastrointestinal symptoms largely ranges from 2% to 57% (Pan et al., 2020).

Many cases of abnormal liver have been reported in the literature during disease progression in COVID-19 patients, and higher liver dysfunction has been found in patients with severe disease (Guan et al., 2020; Shi et al., 2020; Yang et

al., 2020; Zhang et al., 2020). It has been reported that 2-11% of patients with COVID-19 have underlying liver disease (Zhang et al., 2020). In one study, it was reported that 19% of hospitalized COVID-19 patients had concomitant chronic liver disease.(Hashemi et al., 2020) On the other hand, it has been claimed that COVID-19 infection causes worse outcomes in those with liver disease.(Iavarone et al., 2020; Singh & Khan, 2020) In addition, higher rates of hospitalization have been reported in COVID-19 patients with accompanying liver disease (Singh & Khan, 2020). It has been reported that non-alcoholic fatty liver disease (NAFLD) in patients with liver disease is the liver disease most common in COVID-19 patients with a rate of 42%. In subgroup analyzes, cirrhosis was associated with a higher risk of mortality in the group with liver disease. It has been reported that the mortality rate increased 4.6 times in patients with cirrhosis. It has been reported that the mortality rates associated with COVID-19 in patients with chronic liver disease are 2.8 times higher than those without chronic liver disease (Singh & Khan, 2020).

In general, there may be significant changes in the parameters of liver diseases, which cause significant mortality and morbidity. Although ACE2 receptors are much more expressed in cholangiocytes rather than hepatocytes, the elevation of Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) is much more prominent than the elevation of Gamma Glutamyl Transferase (GGT) and Alkaline Phosphatase (ALP) (Chai et al., 2020). No specific finding is observed in patients with COVID-19 who underwent liver biopsy. Microvesicular lubrication and focal necrosis can be seen in the lobular and portal areas of the liver.(Xu et al., 2020) Farcas et al. also has show fatty degeneration and central lobular necrosis in liver tissue (Farcas et al., 2005). In an autopsy series examining liver histology in patients with COVID-19, it has been reported that inflammation in the liver has minimal and focal lymphocyte infiltration was observed in the portal and lobular areas. In the same study, partial or complete thrombosis has been observed in portal and sinusoidal vessels, and it was suggested that this might be the findings of hepatic vascular involvement (Sonzogni et al., 2020). In addition, it has been reported that SARS-CoV-2 virus RNA was detected in the liver of patients who died due to COVID-19 (Xu et al., 2020). It has been reported that extrapulmonary involvement may occur frequently during the course of SARS-CoV infection, and almost half of the patients experience varying degrees of liver function damage (Fan et al., 2020). It has been determined that liver damage may result from SARS-CoV-2 infection or drug-induced liver damage (Xu et al., 2020).

Liver dysfunction in COVID-19 patients can affect approximately one-third of patients.(Portincasa, Krawczyk, Machill, Lammert, & Di Ciaula, 2020) A large

study in China has been found higher rates of liver dysfunction in severe COVID-19 patients (Shi et al., 2020). During the course of COVID 19 infection, it has been reported that liver enzyme elevations are detected more frequently in patients with underlying liver disease than in patients without previous liver disease (Fan et al., 2020). In the study of Mao et al., liver function tests were found to be abnormal in 19% of the cases (Mao et al., 2020). In the study of Kulkarni et al., liver function tests were found to be abnormal in 23.1% of the patients. In the same study, the prevalence of those with pre-existing liver disease was reported to be only 3.6% (Kulkarni et al., 2020). Chen and his friends have shown that 28 %of the 99 COVID-19 patients applied with sub-high levels and 35 %with subordinate high levels (Chen et al., 2020). Published reports indicate that AST rises more frequently than ALT (Girardi, Petrosillo, Aloisi, Rava, & Ippolito, 1998; Xu et al., 2020). This is the case in Gordon et al. In his study, it has been explained that the SARS-CoV-2 virus developed AST elevation as a result of the direct interaction of mitochondrial proteins with the virus and causing direct liver damage (Gordon et al., 2020).

Symptoms of liver damage during the course of COVID-19 are usually mild and often asymptomatic. In general, during the course of COVID-19 infection, when liver biochemical parameters were examined in hospitalized patients in various studies, elevations in AST, ALT and mild bilirubin levels were reported in 14% to 53% of patients. However, in general, the most common abnormality in COVID-19 patients is aminotransferase (AST and ALT) elevation (Bertolini, van de Peppel, & Bodewes, 2020; Fan et al., 2020; Xu et al., 2020; Zhang et al., 2020). ALT and AST elevations are usually 5 times below the upper limit of normal (Zhang et al., 2020). It has been reported that ALT and AST elevations above 5 times may be associated with severe acute hepatitis (Anna Bertolini et al., 2020). AST and ALT elevations has been reported more frequently in patients from the USA (39%) than in patients from China (4-33%) (A Bertolini et al., 2020). Chen et al. has been evaluated 99 COVID-19 patients in their studies, reported that 43 patients had high ALT-AST values and one critical COVID-19 patient had severe hepatitis (Chen et al., 2020). In another study, AST and ALT has been elevated in patients with subclinical disease in 8.7% and 8.9% of patients, respectively (Shi et al., 2020). While AST has been increased in 62% of patients in the intensive care unit, it has been found to be high in 25% of those who did not need care in the ICU (Huang et al., 2020). Richardson et al. in their study with 5700 patients in the USA, they reported that AST values increased in 58.4% of the cases and ALT values in 39% (Richardson et al., 2020). As the severity of the disease increases, the rates of ALT and AST elevations accompanying the disease further increase. Although mild bilirubin elevation

may occur, it has been reported that elevations of GGT and ALP are very rare (Zhang et al., 2020). Fan et al. ALP values of 148 COVID-19 patients has been also found to be 2-5% in patients with liver function damage, and aminotransferase values has been found to be high in 37.2% of patients (Fan et al., 2020). Elevated GGT levels were reported in approximately 50% of cases in one report (Gordon et al., 2020). Zhang et al. in their study covering the case of COVID-19, they found an increase in GGT value by 54% (Zhang et al., 2020).

It is unclear whether patients with chronic liver disease are more susceptible to SARS-CoV-2 infection. In the absence of immunosuppressive therapy, chronic liver disease is not known to be associated with an increased risk of contracting SARS-CoV-2 infection (Zhang et al., 2020). If liver involvement occurs during COVID-19 infection, caution should be exercised. This is especially true if patients are elderly or have a history of pre-existing liver disease. Liver damage during COVID-19 infection impairs prognosis and prolongs hospital stay (Portincasa et al., 2020). Singh et al. in the study conducted by, 2780 COVID-19 patients has been evaluated, and it was reported that patients with chronic liver disease developed higher mortality compared to those without liver disease (Singh & Khan, 2020). In the current literature; there are several studies suggesting that pre-existing liver disease is associated with worse outcomes in COVID-19 patients (Singh & Khan, 2020). Although elevations in liver function tests are common in hospitalized patients with a diagnosis of COVID-19, this should not be assumed to be due to COVID-19. For these patients, first of all, a good anamnesis should be taken to determine the etiology of liver enzyme elevation (medication, toxin, chronic liver damage) and diagnostic evaluation should be performed (hepatitis markers, abdominal ultrasonography, etc.) (ALIRAVCI & Çeviker, 2020). Yang et al. A study of 52 critically ill patients treated in the intensive care unit for COVID-19 showed that hepatitis was not associated with a high risk of death. Hepatitis from COVID-19 was detected in 30% of surviving patients and 28% of those who died (Yang et al., 2020). People with pre-existing liver disease, especially cirrhosis, have a higher risk of death than people without a known liver pathology (Singh & Khan, 2020).

Nursing care has an important place for patients with COVID 19 liver involvement and underlying liver disease, which has such a significant mortality and morbidity rate. With nursing care, patients' quality of life can improve, their acceptance of the disease, self-care and self-efficacy can increase.

Suggestions for Nursing Care

- Patients with COVID 19 liver involvement and pre-existing liver disease, patients at risk of infection represent a severe course of Covid-19. The pandemic requires an unconventional allocation of health resources that can negatively impact the care of patients with chronic liver disease who require medical attention (ALIRAVCI & Çeviker, 2020).
- Treatment and surveillance of patients with advanced liver disease and on immunosuppressive therapy is usually carried out in larger centres. However, these institutions are mostly places where patients under the influence of the COVID-19 virus are treated. Therefore, outpatients for chronic liver disease are at risk for nosocomial infections. Therefore, nurses caring for these vulnerable patients need to consider several important aspects (Boettler et al., 2020).
- Measures to maintain physical distancing are officially implemented in many countries around the world to prevent the spread of SARS-CoV-2. The purpose of these measures is to prevent a rapid increase in SARS-CoV-2 infections to reduce the number of COVID-19 patients and enable healthcare providers to maintain medical/intensive care.
- All patients should be given training on protective measures such as frequent hand washing, maintaining social distance and wearing a face mask.
- Telemedicine service can reduce the exposure of healthcare team members and patients to COVID-19 infection and minimize the consumption of personal protective equipment (Fix et al., 2020; John et al., 2020).
- Nurses are at risk of contracting an infection and spreading the virus due to the face-to-face communication and individual contacts that should be between the nurse and the patient. Therefore, it seems appropriate to limit the amount of face-to-face contact.(Hollander & Carr, 2020) Therefore, telemedicine applications can be used to monitor patients under quarantine at home. In this way, the risks of contacting the health care team members with the virus and spreading the virus are minimized. Telemedicine applications should be used wherever possible or the care needs of the patients should be monitored continuously by phone.
- Visits to crowded tertiary health care services may be delayed in patients with compensated liver disease. Routine laboratory tests should be performed especially in primary health care services and should be provided after careful evaluation of the frequency and individual risk-benefit assessment (Boettler et al., 2020). Laboratory findings of patients

who are much more at risk should be taken by the filiation teams, the results should be evaluated via telemedicine, and the e-prescription system should be used for prescription.

- The importance of vaccination for Streptococcus pneumoniae, influenza and COVID-19 should be emphasized (Boettler et al., 2020).
- SARS-CoV-2 routine testing during liver transplantation should be performed before transplantation in both donors and recipients, assuming that a negative test cannot completely exclude infection. Transplantation from a living donor should be considered on a case-by-case basis (Boettler et al., 2020).
- Close collaborations are required between specialist hepatologists and primary care providers (Boettler et al., 2020).
- Overdose of acetaminophen should be avoided in the care of hospitalized patients. For this reason, the nurse doctor requires a close cooperation. Patients and their relatives should be educated about rational drug use.(Chandok & Watt, 2010) It is important not to administer nonsteroidal anti-inflammatory drugs in patients with cirrhosis and portal hypertension (Chandok & Watt, 2010).
- Liver enzymes should be monitored as the COVID-19 process progresses. In severe cases, platelets, albumin, ferritin, and C-reactive protein should also be monitored. Additional blood tests should also be considered, including viral hepatitis serology.(Hamid et al., 2021) Laboratory findings should be monitored daily and changes should be shared with the healthcare team (Ayar, Ersoy, & Soyak, 2016; Croghan, 2011; Nowicki, 2015).
- As practiced in patients who are negative for Covid-19, care should be taken to exclude liver test abnormalities and drug-induced liver injury in patients with COVID-19, especially treatments promoted by social media (Hamid et al., 2021).
- In suspected or confirmed cases of COVID-19, endoscopy should be performed in a negative pressure room. An advanced disinfection policy should be implemented for endoscopy rooms and reprocessing (Chiu et al., 2020). It is recommended that non-urgent endoscopies be postponed (Liu et al., 2020; Sultan et al., 2020).
- Hepatocellular carcinoma (HCC) represents the sixth most common cancer worldwide. HCC surveillance is associated with both early tumor detection and better survival (Hamid et al., 2021). Patients with HCC are, in theory, at serious risk of COVID-19 due to malignancy or treatment. Patients with

cancer have worse outcomes with COVID-19 (Yu et al., 2021). This probably also applies to HCC patients, as they are often older, more fragile, and require multiple visits to healthcare facilities. All associations recommend ensuring continuity of care for patients with HCC by offering face-to-face visits as needed, performing follow-up screenings in a timely manner, and avoiding treatment interruptions (Boettler et al., 2020; Fix et al., 2020).

- An approximately "3-fold increased" risk for severe COVID-19 has been reported in obese patients, with a direct correlation between increased body mass index (BMI) and the proportion of patients with severe disease (Reddy, 2020). Obesity is a basic criterion in NAFLD patients. It has been reported that the severity of COVID-19 increased 6 times in obese patients with NAFLD.(van der Poorten, 2008) For this reason, individuals should definitely protect their BMI. The diet program should be followed in cooperation with the dietitian. In addition, the importance of movement should be emphasized and should be supported so that he can exercise.
- Absolute absence of contraindications should be determined before starting anticoagulants. However, if there are no contraindications, anticoagulants can be used in patients with liver cirrhosis (Harrison, 2020).
- The underlying mechanism of liver damage and its sequelae are not fully known. For this reason, it is recommended to be careful and to follow up more, especially in patients whose liver function tests do not return to normal values (Pazgan-Simon et al., 2022).
- These patients with gastrointestinal symptoms require longer hospital stays (Huang et al., 2020; Zhang et al., 2020). Therefore, the patient should be evaluated and supported psychologically.
- The use of antibiotics is still controversial and is only recommended when a coinfection is noticed. Patients should be informed about the importance of hand hygiene and maintaining social distance (Tian, Rong, Nian, & He, 2020).
- Multidisciplinary meetings should be held by teleconference to reduce risk for healthcare operators without delaying decisions (Kudo et al., 2020).
- It is necessary to pay attention to drug-drug interactions between immunosuppressive drugs and COVID-19 treatment. Patient and laboratory findings should be monitored frequently in terms of toxicity and side effects of the drugs used (Croghan, 2011; Nowicki, 2015).
- Current transmission prevention recommendations are for both droplet and airborne measures for infection control in the hospital setting.It is very

important to maintain social distance by expanding the waiting areas of patients, to wash hands frequently, to clean frequently touched surfaces, to comply with cough rules and strict infection control measures (Forns & Navasa, 2020).

- The decision to continue liver transplantation should consider resource use, including the supply of intensive care unit (ICU) beds, ventilators, personal protective equipment, and blood products. (Forns & Navasa, 2020; Organization, 2020) All donors and recipients should be tested for COVID-19 during emergency transport using a nasopharyngeal swab in approved laboratories. Also, a rapid test is highly recommended for the transplant team (Fix et al., 2020).
- Liver transplant recipients should be admitted to separate wards with strict prevention measures in place. (Health, 2020) Individualized nursing care should be offered to patients.
- The number of visitors who can see inpatients should be limited (D'Antiga, 2020; Forns & Navasa, 2020).
- In patients with chronic liver disease, possible side effects with the use of COVID-19 treatment regimens should be considered (Boettler et al., 2020).
- Heart rate, rhythm and blood pressure should be measured, vital signs should be evaluated frequently, and any changes should be determined immediately (Fitzpatrick, Quaglia, Vimalesvaran, Basso, & Dhawan, 2013).
- The patient's fluid balance should be evaluated, and signs of hypovolemia and dehydration that may develop due to decreased fluid intake should be monitored (Krag, Bendtsen, Henriksen, & Møller, 2010).
- Abdominal circumference of patients with ascites accumulation should be measured and recorded daily. In order to make measurements from the same place every day, the measurement line should be marked (Croghan, 2011; Nowicki, 2015; Özen & Enç, 2013). All fluids taken by the patient should be carefully and detailedly calculated and recorded. In the calculation of the fluid excreted by the patient, the amount of urine, the presence of watery stools, vomiting, drainage from drains and fistulas, as well as losses due to sweating should be taken into account, and breathing pattern should also be taken into account. The patient and his ECG should be monitored for signs of hyperkalemia, one of the most important electrolyte imbalances, affecting musculoskeletal and cardiac functions (Nowicki, 2015).

- The patient's body weight should be monitored every day at the same time, with the same weight and with the same clothes (Fitzpatrick et al., 2013; Nowicki, 2015; Özen & Enç, 2013). In this process, since edema and ascites may develop in patients, it should be kept in mind that body weight and albumin value alone will not be sufficient in the monitoring of nutrition. As an alternative, valid-reliable nutritional assessment methods such as nutritional risk score and malnutrition universal screening tool should be used (Ayar et al., 2016).
- There is a risk of deterioration in the integrity of the skin and mucous membranes of the patients due to the deterioration of the body's fluid balance, changes in blood values and lack of activity (Croghan, 2011). It is very important to determine the activity levels of these patients, to plan their mobility and position changes, and to regulate their nutrition for the protection of skin integrity.
- The pressure in the body parts that are at risk of developing pressure ulcers should be reduced. The moisture of the tense and dry skin due to edema should be maintained. Toxic metabolites that cannot be eliminated from the body can accumulate on the skin and cause discomfort. Therefore, the individual should be cleaned regularly. Skin color, temperature and humidity are important indicators for determining circulatory problems and should be monitored regularly (Croghan, 2011). The use of soap and adhesive tape should be avoided to avoid skin irritation. Lotion can be applied to irritated skin to minimize skin irritation (Metcalfe, 2017).
- In some liver failure, ascites accumulation and peripheral edema can be seen that restricts mobility. For these reasons, all patients should be evaluated for risk of falling (Kasper & Bettinelli, 2017). The bed borders of the patients should be removed, if the patient is agitated, soft supports should be created on these bed edges by means of blankets, and the bed brakes should be kept locked. A safe care environment should be created for the patient, he should not be left alone, the family should be informed about the importance of close follow-up and changes in behavior and consciousness (Metcalfe, 2017).
- One of the most important roles of the nurse is to educate the patient and his family, to support individuals throughout the process and to advocate for the patient. The fear, inadequacy, tense facial expression, discomfort and anxiety symptoms that occur in the patient and his family should be evaluated, a suitable environment should be created for them to express their feelings and emotional support should be provided. Patients and families need to be properly educated to prevent treatment rejection and

potential conflicts with healthcare professionals. Referring patients and family members to specialists such as psychologists, consultation-liaison psychiatry nurses, dietitians, case/situation managers, social workers or therapists can help the coping process with the current situation (Metcalfe, 2017).

CONCLUSION AND RECOMMENDATIONS

In summary, COVID-19 causes gastrointestinal and liver involvement in a wide range from direct invasion of the organism to the result of systemic immune processes. Gastrointestinal symptoms and liver function abnormalities are common during COVID-19 infection and may reflect the severity of the disease. Especially individuals with liver disease should be followed carefully in terms of early signs of the disease and diagnosis. Protecting the patient from infection, monitoring and frequent follow-up, taking measures to maintain fluid-electrolyte balance, monitoring nutrition and daily body weight, monitoring laboratory findings, evaluating skin and mucosal integrity, taking measures to prevent falls, psychosocial support for the patient and his family should provide nursing interventions such as It is to share the changes encountered in the patient follow-up with the members of the healthcare team. The nurse should plan the care with a holistic approach by understanding the patient and the process, and should combine evidence-based current information and clinical experience at every stage of treatment and care.

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Chapter 3

Oral Pigmentations

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Oral Pigmentations

The presence of pigmentation is one of the normal clinical features of the oral tissues in many people. This physiological oral pigmentation is found throughout the human race and it can be seen in the gingiva, mucous membranes, tongue, hard and soft palate and floor of the mouth (Dummett and Gupta, 1964).

The word ‘‘pigment’’ is derived from the Latin word ‘‘*pigmentum*” meaning color or coloring. Pigmented lesions are commonly found in the oral cavity (Kauzman *et al.*, 2004). The oral cavity is a mirror of the rest of the body and oral pigmentation is associated with a variety of lesions and conditions. Human oral tissues are not homogeneously colored and sometimes pigmentation can be observed. Oral pigmentation is defined as the process by which pigments are deposited in the tissues of the mouth. Oral pigmentation can be physiological, pathological or a manifestation of systemic disease. It is essential to differentiate between normal and pathological pigmentations in the oral cavity since clinicians may encounter a variety of pigmentations there (Sreeja *et al*, 2015, Roy, 2019; Thalita *et al*., 2018; Rotbeh *et al*., 2022).

Etiology of oral pigmentation

Depending on the underlying aetiology, oral pigmentation can be divided into exogenous and endogenous types. There are four endogenous pigments that contribute to the normal colour of the skin and mucous membranes: melanin, carotenoids, blood and bile pigments (reduced hemoglobin, oxygenated hemoglobin) and lipofuscin. Of these, melanin is the most abundant endogenous pigment (Roy, 2019).

Melanin

Melanin is a nonhemoglobin derived brown pigment. The word ‘‘melanin’’ comes from the Greek word, *melanos*, meaning dark (Borovansky, 2011). Melanin is produced by melanocytes in membrane-bound organelles called melanosomes. Melanocytes ogininate from the neural crest of the ectoderm and are found in the basal cell layer of the oral epithelium (Thomas and Erickson, 2008). Melanosomes contain all the enzymes and proteins required for melanin biosynthesis and the structural maturation of melanosomes.

The process of pigmentation has three phases: melanocyte activation, melanin synthesis and melanin expression (Lerner and Fitzpatrick, 1950). Sunlight, hormones and genetic constitution/ racial factors etc. control the production of chemical messengers called melanocyte stimulating hormone which initiate the activation phase. Melanocytes produce granules called melanosomes during the synthesis phase. Tyrosine, an amino acid, is converted into dehydroxyphenylalanine (DOPA)

by the enzyme tyrosinase. Next, DOPA is transformed into the secondary molecule dopaquinone by tyrosinase. Dopaquinone is converted into either dark -named as eumelanin- or light -named as pheo-melanin- melanin after a series of reactions. As the melanosomes mature intracellularly, the melanin is transferred to the keratinocytes and stored by the kerotinocytes which are the skin cells above the melanocytes in the epidermis during the expression phase. Melanin colour then eventually becomes visible on the skin surface (Feller *et al*, 2014; Madan *et al,* 2015).

Under the same physiological conditions, the number of melanocytes in the oral epithelium does not change in fair skinned and dark-skinned individuals, regardless of their race/ethnicity (Feller *et al.*, 2014). The colour of oral mucosa varies between individuals as a result of melanogenesis activity and distribution of the melanin pigment, keratinization, depth of epithelialization and vascularity. The physiological color of the oral mucosa ranges from light pink to deep bluish purple and occasionally even to blackish (Roy, 2019).

Assessment of oral pigmentation

The appearance of mucosal pigmentation can vary from focal to diffuse, and may be of physiological or pathological origin. It's important to follow a systematic approach when evaluating an “oral pigmentaion patient”. A specific diagnosis of oral pigmentation can be made with a complete history/anamnesis, clinical examination and investigations. The history/anamnesis should include the onset and other areas of lesion, change in appearance, duration, the presence of symptoms, drug/tobacco/alcohol addiction and medical, surgical and family history. A careful history/anamnesis will help to determine whether the origin of the pigmentation is exogenous or endogenous and congenital or acquired. The face, perioral region and lips should be inspected prior to the intraoral examination. The buccal mucosa should be examined first followed by the hard and soft palates, tongue, the tonsillar region and the floor of the mouth next (Powell and Rogers, 1983). The number, distribution, size, margin, colour and shape of intraoral lesions should be noted (Lenane and Powel,2000; Kauzman *at al.,* 2004). In many situations, a history/anamnesis combined with a detailed clinical examination may help to identify the likely assess cause of oral pigmentation. In an uncertain situation, a skin biopsy should be performed to evaluate the pathological findings, and required systemic investigations should be taken into consideration as well as possible referral to other specialist for further investigation (Lambertini *at al.,* 2018).

Classification systems

Classification is a method of categorizing different diseases or conditions. Pigmentation of the oral cavity has a variety of origins and different classifications are currently used. Several authors porposed different classifications. For example; Alawi classified pigmented lesions into four categories: idiopathic, endogenous, exogenous, and heme-associated pigmentation (Alawi, 2008). Thibodeau *et al.* the classification divided oral pigmentations into five subcategories, including endogenous, exogenous, drug-related, oral & perioral, and miscellaneous (Thibodeau *et al.,* 2005). Pramod defined pigmentation into two main categories: endogenous pigmentation and exogenous pigmentations (Pramod, 1998). Prabhu *et al.* classified pigmented lesions of the oral mucosa according to the pigment's source or origin of the pigment (Prabhu, 2004). Meleti *et al.* divided pigmentary changes into melanocytic and nonmelanocytic (Meleti *et al.,* 2008).

Different classification systems are important for etiology, pathogenesis and treatment planning (Peeran *at al.,* 2019) because they allow clinicians to better understand the relationships and connections between things. They also help clinicians to communicate clearly with each other.

Oral pigmentation can be broadly categorised as physiological or pathological. Pathological pigmentation can be divided into extrinsic and intrinsic types depending on the underlying aetiology (Madan *et al.,* 2015).

Physiological Pigmentation

Physiological or racial pigmentation is described as localized, symmetrical hyperpigmentation in individuals (Mirowski and Waibel, 2002). The most common cause of oral pigmentation is racial pigmentation of the oral mucosa and it is dominant group in darker skinned individuals including Blacks, Asians, South Americans and Mediterranean populations (Gaeta *et al.,* 2002.). Both children and adults can both have physiological pigmentation; there is no gender preference (Mirowski and Waibel, 2002). This pigmentation occurs within the first two decades of life, but the patient may not aware of it until much later (Kauzman, 2004) and the pigmentation may increase with age (Müller, 2010). Physiological pigmentation is determined by genes but physical, chemical and hormonal factors can increase pigmentation such as trauma, tobacco, puberty (Dummett and Gupta, 1945; Birt *et al.*, 1978). Physiological pigmentation results from increased melanin synthesis within the basal cell layer rather than an increase in the number of melanocytes. Pigmentation ranges from uniform, unilateral, bilateral, mottled, macular or patchy and light dark to brown (Madan *et al.,* 2015).

Physiological pigmentation typically occurs on the attached gingiva, followed by the buccal mucosa, lips, palate and tongue (Fig. 1). Physiological pigmentation of the gingiva typically does not affect the marginal gingiva, a good feature that is useful in differentiating this aetiology from others, such as Addison's disease (Eisen, 2000). Idiopathic, drug or tobacco induced melanosis, endocrinopathic and other systemic diseases should be considered in the differential diagnosis (Alawi, 2008).

Physiological pigmentation can be diagnosed by history and clinical examination. Although physiological pigmentation is often clinically obvious, biopsy is required if the features of the lesion are atypical. On biopsy, histological sections of pigmented lesions show that the amount of melanin has increased but the number of melanocytes in the epidermis is unchanged (Lenane and Powell, 2000). They are asymptomatic and harmless, so treatment is unnecessary. However, some patients may experience cosmetic problems as a result of these pigmentations. It may therefore be necessary to use depigmentation techniques. Surgery, cryosurgery, electrosurgery and laser surgery are among the many depigmentation techniques that have been reported in previous experimental and clinical studies. Laser treatment has more advantages than the other methods. It is simple, fast, minimally invasive, tissue selective and less traumatic for the patient (Ozbayrak *et al.,* 2000; Dumlu *et al.,* 2003, Ercalık Yalcinkaya, 2015).

Endogenous Pigmentation

Haemoglobin, haemosiderin and melanin are the most common endogenous sources of mucosal pigmentation (Alawi, 2008). Endogenous pigmentation can be associated with endocrine, syndromic, chronic inflammatory (post-traumatic/post-inflammatory pigmentation), infectious, reactive (ephelides/freckles, melanotic macules, melanoacanthomas), or neoplastic diseases (melanocytic nevi/melanocytic nevi/pigmented cellular nevi, malignant melanoma of the mouth (Sreeja *et al*., 2015).

Hypoadrenocortisim/Adrenal Insufficiency/Addison's Disease

Addison's disease results from bilateral destruction of the adrenal cortex by idiopathic, autoimmune, infectious or malignant causes. The anterior pituitary gland produces adrenocorticotropic hormone (ACTH) in response to the lack of adrenocortic hormones in the blood, and melanocyte-stimulating hormone (MSH) is induced by increased ACTH production. As a result, diffuse pigmentation of the skin and oral mucosa occurs. Hyperpigmentation of the skin and mucous membranes, which is considered pathognomonic and the most specific sign of Addison's disease, occurs in up to 92% of patients. This

pigmentation may appear up to 10 years before other symptoms. The oral pigmented macules of Addison's disease are typically blue-black or brown in colour and may be macular or streaky in configuration, and may be diffusely distributed on the tongue, gingiva, buccal mucosa and hard palate (Sreeja *at al.,* 2015). Cushing's disease, hyperthyroidism and acromegaly also show pigmentation similar to Addison's disease. This pigmentation may mimic physiological pigmentation. However, oral mucosal pigmentation in Addison's disease occurs in adulthood and systemic symptoms usually include weakness, hypotension, abdominal pain, nausea and/or vomiting, constipation and/or diarrhoea. Patients with these symptoms should be referred for a medical assessment and laboratory tests to measure plasma cortisol, ACTH and electrolyte levels in the blood. If Addison's disease is left untreated, it can be fatal. Treatment of the underlying cause as well as corticosteroid replacement therapy may be required (Kauzman *et al.,* 2004).

Post-traumatic pigmentation

Haematomas, petechiae, purpura and ecchymoses result from extravasation of blood into soft tissues and may occur spontaneously in some systemic conditions such as idiopathic thrombocytopenic purpura or following trauma (Tarakji *et al,* 2014). The colour of post-traumatic lesions, caused by the breakdown of haemoglobin into bilirubin and biliverdin, ranges from red, blue, purple, and bluish black. The colour is dependent on the length of time that the blood has been present in the extravascular space. Haemorrhagic lesions are commonly seen on the buccal mucosa, lateral surface of the tongue, lips and at the junction of the hard and soft palate where they are easily accessible to trauma (Naidu *et al.,* 2002). The clinical features of amalgam tattoos and melanotic macules can occasionally be confused with post-traumatic pigmentation, but pigmentation caused by trauma gradually returns to normal within two weeks. If haemorrhagic lesions occur in the absence of recent trauma, the patient should be screened for coagulopathies and platelet disorders.

Post-inflammatory pigmentation

Post-inflammatory hyperpigmentation can also be seen in the oral cavity, for example in oral lichen planus, which is often seen on the skin of patients with long-standing inflammatory conditions. (Mirowski and Waibel, 2002). Lichen planus is an inflammatory disorder of the skin and mucous membranes or stratified squamous epithelium. The aetiology of postinflammatory pigmentation remains unknown. Histologically, there is increased melanin synthesis and accumulation of melanin-laden macrophages in the superficial connective tissue.

This pigmentation is more common in dark-skinned individuals. Clinically, multiple areas of brown-black pigmentation are seen close to reticular or erosive lichen planus lesions; the pattern of hyperpigmentation resembles the original lesions of lichen planus, so reticulated and patchy pigmentation may be the end result of successful therapy (Gondak *at al.,*2012).

Ephelides/Freckles

Freckles are common, asymptomatic, small (less than 5 mm in diameter), well-circumscribed brown or tan patches that result from increased melanocytic melanin production rather than melanocytic dysfunction and are most commonly found on sun-exposed areas of the face and perioral skin. (Alawi, 2008). Although the pigmentation is focal in nature, the general population has many freckles. Ephelides are most common in fair-skinned individuals, followed by those with red or light blond hair. The number and intensity of ephelides tend to decrease with age. Malignant transformation has not been reported (Tarakji *et al.,* 2014). No treatment is required, but if associated with Peutz Jeghers syndrome or Addison's disease, long-term follow-up is required (Mirowski and Waibel, 2002).

Melanotic macules

Melanotic macules can be divided into two groups: labial and oral melanotic macules. The labial melanotic macule is a benign, flat, oval, well-defined, solitary pigmented lesion commonly found on the lower lip (Weathers *et al.,* 1976). Oral melanotic macules are the same lesion, flat, solitary or multiple in the oral cavity, most commonly on the gingiva, buccal mucosa and palate (Page *et al*., 1977). The aetiology is not clear, but it could be a physiological or reactive process. Both are the result of increased melanin production without an increase in the number of melanocytes. They are usually less than 1 cm in diameter, usually single but sometimes multiple lesions, have a well-defined smooth border, are homogeneous and light or dark brown in colour. The most common oral lesions of melanocytic origin are melanotic macules. They are more common in females and young adults. The lesion usually does not continue to grow once it has reached a certain size and, unlike ephelis, a melanotic macule does not darken with prolonged exposure to the sun (Alawi, 2008).

The differential diagnosis of the melanotic macules includes amalgam tattoo, melanocytic nevus, malignant melanoma, and focal ecchymosis. Benign melanocytic macules are not known to progress to melanoma. In most cases, a biopsy is needed to confirm the diagnosis and to rule out the possibility of early melanoma, especially the lesion on the palate where malignant melanoma is most

common. Once the diagnosis is confirmed, no treatment is needed, but regular monitoring may be required to assess any clinical changes (Carlos-Bregni *at al.,* 2007; Thalita, 2018; Rosebush, *et al.,* 2019).

Melanoacanthoma

Oral melanoacanthoma is a rare, reactive, benign, mixed lesion of keratinocytes and pigmented dendritic melanocytes (Mishima and Pinkus, 1960). The aetiology of melanoacanthoma is related to irritant or traumatic factors. Lesions usually occur on the buccal mucosa, which may be related to the higher incidence of trauma in this region. The size of melanoacanthomas can increase rapidly, reaching several centimetres within a few weeks, in contrast to most benign pigmented lesions. The clinical differential diagnosis should therefore include the possibility of a malignant process. Biopsy is essential, as melanoacanthomas can clinically mimic malignant melanoma (Thalita *et al.,* 2018; Rosebush *et al.,* 2019; Traves *et al.,* 2022).

Oral melanocytic nevus/ Melanocytic nevus/ Pigmented cellular nevus

Nevus cells are a variant of melanocytes which are produce melanin. Oral melanocytic nevi are rare, benign pigmented lesions, due to the focal proliferation of nevus cells either in the epithelium or in the connective tissue. nevus can be congenital called birthmark or acquired called as a mole and the majorty are accuired. Histopathologically, nevi are classified as junctional, intramucosal/intradermal and compound nevi according to the location and attachment of the nevus cell to the surface epithelium and connective tissue (Mirowski and Waibel, 2002). The location of the nevus cells also affects the colour. Deeper intramucosal and compound nevi are lighter brown than superficial nevi such as junctional nevi, which are darker brown. Spindle-shaped cells are found in the deeper part of the connective tissue in blue nevi. This nevus can be explained by the Tyndall Effect, which describes how light interacts with particles in a colloidal suspension (Sreeja *et al*., 2022). Because the blue nevus cells are far from the epithelial surface, the reflected light passes through the overlying tissue, absorbing the long wavelength colours and reflecting short wavelength colours such as blue back to the observer's eye. The most common oral nevus is the intramucosal nevus, followed by the blue nevus. The blue nevus typically occurs on the hard palate, whereas the intramucosal nevus is more likely to occur on the buccal mucosa. Oral melanocytic nevus that progresses to malignancy is extremely rare, but biopsy should be performed in undiagnosed pigmented lesions because it is difficult to differentiate clinically between a nevus

and an early lesion of melanoma, especially in the palate, and nevi can clinically mimic melanoma (Trakji *et al.,* 2014; Tavares *et al.,* 2022; Thalita *et al., 2018*).

Oral malign melanoma

Melanoma is a malignant neoplasm which is the result of the proliferation of malignant melanocytes both within the connective tissue and at the junction between the epithelium and the underlying connective tissue. Risk factors for melanoma include sun exposure, the presence of multiple nevi, immunosuppression, and a family history of melanoma (Alawi, 2008). Benign lesions such as common acquired nevus, dysplastic nevus, congenital nevus and cellular blue nevus can develop into melanoma. Malignant melanoma can occur in any site where melanocytes are present, but oral melanoma is less common than cutaneous melanoma. Melanomas include superficial spreading melanoma, lentigo maligna, nodular melanoma, acral lentiginous melanoma and mucosal lentiginous melanoma. Acral and mucosal melanomas are more likely to occur in the oral cavity (Sreeja *et al,* 2022). The most common site in the oral mucosa is the palate, followed by the gingiva, although other sites in the oral mucosa may be affected. Oral melanoma usually develops between the fourth and seventh decades of life, with a higher prevalence in men than in women (Hicks and Flaitz, 2000; Barker *et al*, 1997). Clinically, oral melanoma may present as an asymptomatic, slowly growing brown or black patch with asymmetric and irregular borders or as a rapidly growing mass characterised by pain, ulceration, bleeding and bone destruction. There are also some non-pigmented (amelanotic) oral melanomas (Kauzman *et al., 2004*). The ABCDE rule is a set of criteria for the clinical diagnosis of melanoma: Asymmetry, border irregularity, colour irregularity, diameter greater than 6 mm, elevation (Sreeja *et al.,* 2022). An early stage of oral melanoma may present as intraoral melanosis. Therefore, a wide range of clinical conditions could be considered in the differential diagnosis, such as melanocytic nevus, oral melanotic macula, amalgam tattoos, various vascular lesions, and other soft tissue neoplasms. Biopsy is always recommended for any persistent solitary pigmented lesion. Although rare, oral mucosal melanoma is a serious and often fatal disease. Radiotherapy and chemotherapy are ineffective, radical surgical excision with clear margins is required, and the prognosis is poor. Early diagnosis is the best strategy to improve the prognosis (Kauzman *et al., 2004*).

Smoking-associated melanosis or Smoker's melanosis

Smoking can cause abnormal melanin pigmentation of the oral mucosa in fair-skinned individuals and make pigmentation noticeable in darker-skinned

individuals who normally have physiological pigmentation. The mechanism of smoke-induced pigmentation is still unclear, but melanin production may increase as a biological defence against toxic substances in cigarette smoke (Kauzman *et al*., 2004), or another theory is that the heat of the smoke may induce pigmentation. Duration and amount of smoking have an effect on the intensity of pigmentation (Alawi, 2008). Due to a possible synergistic effect between the female sex hormones and smoking, melanosis in smokers is more common in women than in men. The black-brown lesions associated with smoker's melanosis usually occur on the anterior labial gingiva, followed by the buccal mucosa. Smoking-induced pigmentation does not require treatment. In most cases smoker's melanosis disappears within 3 years of stopping smoking. If the pigmentation occurs in an unexpected area or there is a change in the colour, shape or size of the pigmented lesion, a biopsy should be performed (Gondak *et al.,* 2012, Kauzman *et al.,* 2004, Meleti *et al.,* 2008).

Exogenous Pigmentation

Traumatic implantation of foreign material directly into the submucosal tissues is the most common cause of exogenously pigmented lesions. In other cases, an ingested substance may cause pigmentation by absorption and haematogenous distribution. It may also stimulate the production of melanin. Chromogenic bacteria, foods and drinks can also cause discolouration of the oral mucosa. (Alawi, 2008). Amalgam tattoos/focal argyrosis, graphite tattoos, heavy metal pigmentation, drug-induced pigmentation and hairy tounge/furred tounge are examples of exogenous pigmentation (Bunchner and Hansen, 1980; Okah and Okah, 2023).

Amalgam tattoos

Amalgam pigmentation, commonly referred to as amalgam tattooing, is a pigmented lesion on the oral mucosa (Buchner and Hansen, 1980) and this pigmentation is the most common cause of exogenous pigmentation of the oral mucosa (Mirowski and Waibel, 2002). They are iatrogenic lesions that usually result from inadvertent deposition of amalgam restorative material into the submucosal tissues during dental procedures. Clinically, the lesion is asymptomatic, flat, blue, black or dark grey in colour and most commonly occurs around restored teeth (Buchner and Hansen, 1980). In some cases, if the amalgam fragments are large enough, amalgam tattoos may be visible on radiographs due to their opaque appearance. Therefore, they can be diagnosed clinically and radiographically and no treatment is required (Fig. 2 and 3). The diagnosis of an amalgam tattoo can be difficult to differentiate from other pigmented oral

mucosal lesions such as mucosal melanoma, hemangioma, nevus, post-inflammatory pigmentation, drug-induced hyperpigmentation, smoker's melanosis and oral pigmentation associated with systemic diseases (such as Acromegaly, Albright's syndrome, Addison's disease and Nelson's syndrome), (Eisen, 2004). A diascopy examination, which is a test to determine whether a lesion is vascular, non-vascular, or haemorrhagic by applying pressure with a finger glass slide and observing colour changes, produces negative results on an amalgam tattoo, which is a test to determine whether a lesion is vascular, non-vascular, or haemorrhagic by applying pressure with a finger glass slide and observing colour changes. In case of doubt, a biopsy should be taken. Histopathologically, amalgam particles are seen as typically dark granules and solid fragments aligned along collagen fibres and around blood vessels (Buchner and Hansen, 1980; Mirowski and Waibel, 2002).

Graphite tattoos

Graphite tattoos are pigmentations that are commonly seen on the palate as a result of traumatic insertion of pencil graphite fragments. The pigmentation may be macular, focal, grey or black and is rarely seen. It can be difficult to distinguish between graphite tattoos and amalgam tattoos. Biopsy may be required to exclude the possibility of melanoma if patients with graphite tattoos do not report a history of injury There is a clear similarity between graphite particles and amalgam under the microscope (Neville *et al,* 2002, Meleti *et al*, 2008, Gondak *et al* 2012).

Heavy metal pigmentation

Lead, mercury, bismuth, silver, gold, platinum, arsenic and other heavy metals can accumulate in the blood as a result of ingestion or exposure (Mirowski and Waibel, 2002). Increasing levels of heavy metals in the blood lead to systemic and mucosal abnormalities such as heavy metal pigmentation. The aetiologies of heavy metal pigmentation are ingestion of heavy metal, occupational exposure, other common environmental sources include paints, old plumbing and seafood (Alawi,2008). Lead, mercury, bismuth and arsenic can accumulate in oral tissues if ingested in sufficiently high doses or over a long period of time. In areas of inflammation, these metal salts often extravasate from the vessels and accumulate in the tissues, usually at the gingival margin. This metallic pigmentation usually appears grey to black.

Heavy metals often diffuse linearly along the gingival margin, and the discolouration caused by bismuth and lead is known as the bismuth line and the lead line, respectively. Because inflammation of the oral tissues is reduced in patients with good oral hygiene, the incidence of pigmentation can be

significantly reduced. Oral pigmentation may be the first sign of heavy metal poisoning in some patients, so early recognition of the aetiology is crucial to avoid toxic effects (Meleti *et al,* 2008, Mirowski and Waibel, 2002).

Drug-induced pigmentation

Various drug side effects can result in oral pigmentation. There are many drugs that can cause pigmentation, including hormones, oral contraceptives, chemotherapeutics (cyclophosphamide, bleomycin, busulfan, fluorouracil and tranquillisers), antimalarials (chloroquine, clofazamine, amodiaquine), antimicrobials (minocycline), antiretrovirals (zidovudine), antifungals (ketaconazole). These include deposition of drugs or drug metabolites in dermal and epidermal layers, increased melanin deposition with or without an increase in melanocytic cells. (Kumar and Divya, 2015). Drug-induced pigmentations may appear as blue-gray or blue-black in color. The palate and gingiva are the most common sites affected. There is no reports of malignant transformation and this lesions may dissappear with drug withdrawal (Tarakji *et al.,* 2014; Okah and Okah, 2023).

Hairy tounge/Furred tounge

Hairy tongue is an acquired benign condition. The cause of hairy tongue is unclear, but it may be caused by increased keratin synthesis or decreased regular keratin desquamation (Mirowski and Waibel, 2002). The filiform papillae are elongated and hyperplastic with hyperkeratosis on the dorsal surface of the tongue (Alawi, 2008). The pigmentation of a hairy tongue may be brown, yellow, green, blue, or unpigmented (Fig. 4). According to a previous study, conducted in Turkey, the prevalence of hairy tongue ranges from 0.5% to 11.3%, the incidence of hairy tongue is higher in men than in women, and there is a positive correlation between age and hairy tongue (Avcu and Kanlı, 2003). A biopsy is not necessary as it can be diagnosed on the basis of anamnesis and clinical examination due to its distinctive features.

Legends:

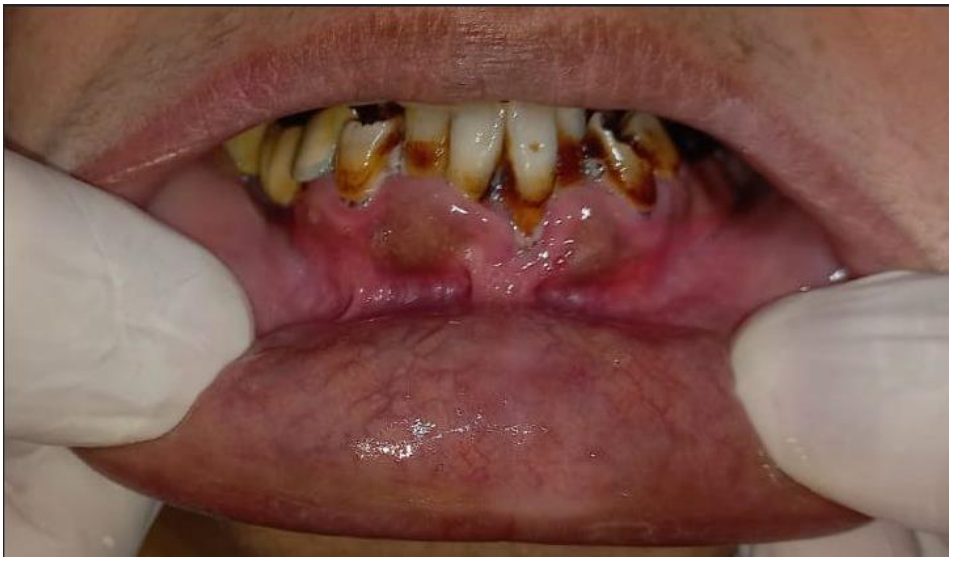

Figure 1: Physiological pigmentation on the gingiva

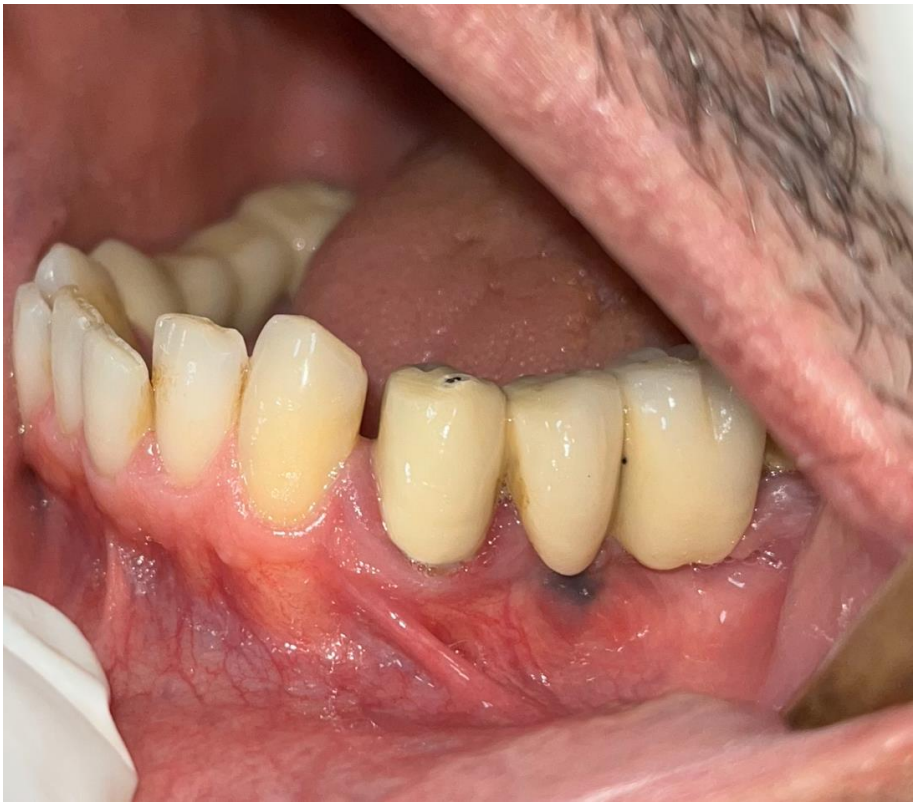

Figure 2: Clinical appearance of an amalgam tattoo.

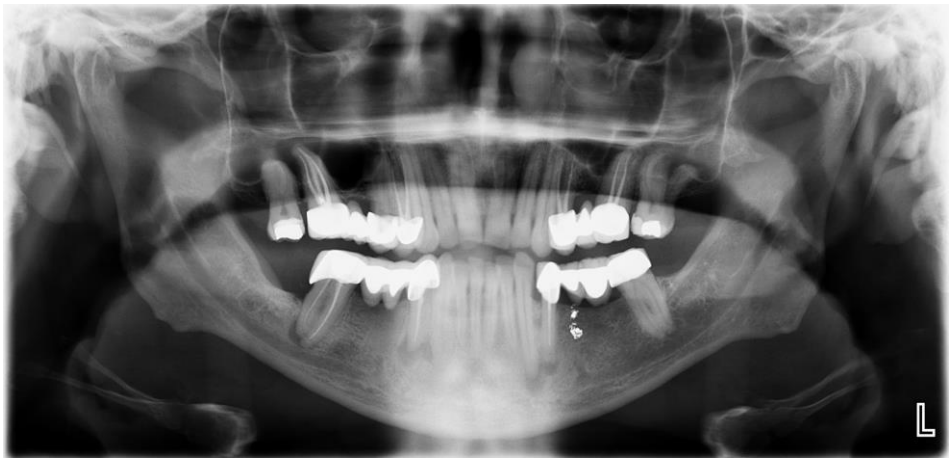

Figure 3: Radiographic findings in same patient with amalgam tattoo.

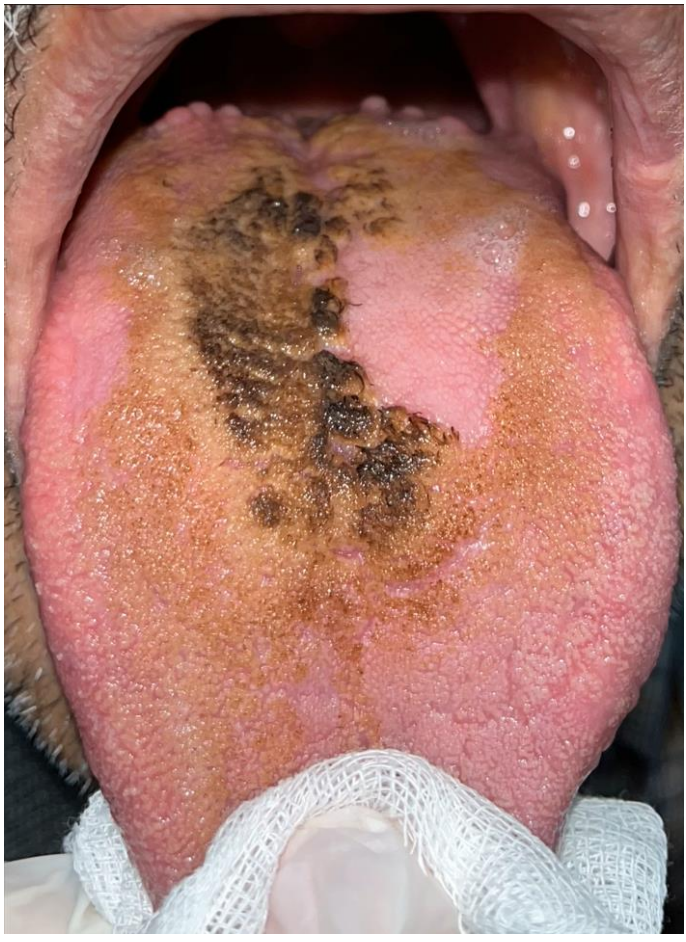

Figure 4: Hairy tongue with brown-black pigmentation.

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Chapter 4

Medications in Wound Healing: A Comprehensive Review of Current Therapies and Emerging Strategies

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1. Introduction

Wound healing is a complex biological process that involves several different stages. These stages can be broadly divided into three main phases: the inflammatory phase, the proliferative phase, and the remodelling phase (Landén, Li, & Ståhle, 2016).

The inflammatory phase is the first stage of wound healing, beginning as soon as the injury occurs. During this phase, various immune cells are recruited to the site of the wound to help control bleeding and prevent infection. These cells release signalling molecules, such as cytokines and growth factors, that help stimulate the next stage of wound healing (Muire, Mangum, & Wenke, 2020).

The proliferative phase is the second stage of wound healing, and it involves the growth and proliferation of new cells at the site of the wound. During this phase, cells called fibroblasts begin to produce collagen, a protein that helps to rebuild and strengthen the damaged tissue. Blood vessels also begin to grow into the area, bringing nutrients and oxygen to support the healing process. The final stage of wound healing is the remodeling phase, which involves the reshaping and strengthening of the new tissue that has formed. This phase can take several months or even years to complete as the body strengthens and remodels the scar tissue (Diller & Tabor, 2022).

While the body can usually heal wounds independently, several factors impede the healing process. These include poor blood flow, infections, chronic diseases, and certain medications. In these cases, medical interventions may be necessary to help support the healing process (Guo & Dipietro, 2010).

Wound healing is a fascinating and complex process that highlights the tremendous regenerative capabilities of the human body. By better understanding the different stages of wound healing and the factors that can impact this process, researchers and clinicians can work to develop new treatments and interventions that can help improve outcomes for patients with wounds of all kinds (Rodrigues, Kosaric, Bonham, & Gurtner, 2019).

2. Materials and methods

This review article discussed current and emerging strategies for wound healing medications, including growth factors and anti-inflammatory and antimicrobial agents. A comprehensive literature search was conducted using online databases such as PubMed, MEDLINE, and Cochrane Library, and relevant articles were included in this review.

The search keywords used were "wound healing," "growth factors," "anti-inflammatory agents," and "antimicrobial agents." Inclusion criteria were studies

published in English that focused on the mechanisms and effects of growth factors, anti-inflammatory agents, and antimicrobial agents in wound healing.

Studies that were excluded focused on wound healing in animals or needed to focus on the mechanisms and effects of growth factors and anti-inflammatory and antimicrobial agents in wound healing.

The literature was reviewed and summarized, and this article presented the findings. The authors have also provided their expert opinion and clinical experience in wound care.

It is essential to note that the medications discussed in this review article should only be used under the guidance of a healthcare professional. These medications should be individualized and tailored to the patient's needs and underlying conditions. The careful monitoring of the use of these medications is also necessary to avoid adverse effects on wound healing and potential complications.

This review article provides an overview of the current and emerging strategies for wound healing medications, highlighting the importance of a comprehensive and individualized approach to wound care.

3. Results and Discussion

3.1 *Wound-healing medications*

There are various medications available to promote wound healing. These medications can be broadly classified into growth factors, anti-inflammatory agents, and antimicrobial agents (Khalil, Cullen, Chambers, & McGrail, 2017).

3.1.1 *Growth Factors*

Growth factors are signaling molecules involved in various physiological processes, including cell growth, differentiation, and tissue repair.(Yun et al., 2010) In wound healing, growth factors are crucial in stimulating the proliferation and migration of cells involved in the repair process and promoting the formation of new blood vessels and extracellular matrix (ECM) proteins (Tirado-Rodriguez, Ortega, Segura-Medina, & Huerta-Yepez, 2014).

Epidermal growth factor (EGF) is one of the most significant growth factors for wound healing, as it is a potent stimulator of cell proliferation and division. EGF promotes the growth of epidermal cells and has been shown to accelerate the healing of acute and chronic wounds. In addition to its effects on cell proliferation, EGF also has anti-inflammatory properties that help to reduce swelling and redness at the site of the wound (Berlanga-Acosta et al., 2009).

Platelet-derived growth factor (PDGF) is another essential growth factor for wound healing. It is produced by platelets and other cells at the site of the wound,

and it stimulates the proliferation and migration of various types of cells, including fibroblasts and endothelial cells. Fibroblasts produce collagen, an essential component of the ECM that provides structural support to the tissue. Endothelial cells are involved in forming new blood vessels, which are necessary for delivering nutrients and oxygen to the site of the wound (Pierce, Mustoe, Altrock, Deuel, & Thomason, 1991).

Transforming growth factor-beta (TGF-beta) is a multifunctional growth factor critical to wound healing. It regulates the inflammatory response by recruiting immune cells to the site of the wound and promoting the release of other growth factors. TGF-A also stimulates the production of ECM proteins, which provide structural support to the new tissue. TGF promotes the differentiation of various cell types involved in tissue repair and regeneration (Finnson, Arany, & Philip, 2013).

Growth factors are an essential component of the wound healing process, as they help to stimulate the proliferation and differentiation of cells, promote the formation of new blood vessels, and support the production of ECM proteins. By better understanding the role of growth factors in wound healing, researchers and clinicians can work to develop new treatments and interventions that can help improve outcomes for patients with wounds of all kinds (Demidova-Rice, Hamblin, & Herman, 2012).

3.1.2 *Anti-inflammatory Agents*

Inflammation is critical to wound healing, as it helps recruit immune cells to the wound site and initiate the repair process. However, too much inflammation can harm wound healing, delaying healing and increasing the risk of infection. In addition, chronic inflammation can lead to tissue damage and impair the body's ability to heal (Eming, Krieg, & Davidson, 2007).

Anti-inflammatory agents are drugs that help to modulate the inflammatory response and promote wound healing. These drugs can be used to reduce pain and swelling associated with wounds, as well as to prevent excessive inflammation that can slow the healing process (Lin, Zhong, & Santiago, 2017).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are joint anti-inflammatory agents in wound healing. They work by inhibiting the production of prostaglandins, which are signalling molecules involved in the inflammatory response. NSAIDs can help to reduce the pain and inflammation associated with wounds. However, prolonged use of these drugs can adversely affect wound healing by inhibiting the production of growth factors and other molecules critical to the repair process (Su et al., 2010).

Corticosteroids are another type of anti-inflammatory agent used in wound healing. These drugs work by inhibiting the production of pro-inflammatory cytokines and stimulating the production of collagen and other ECM proteins. Corticosteroids can help reduce inflammation and promote wound healing. However, prolonged use of these drugs can adversely affect wound healing by impairing the immune response and increasing the risk of infection (Ahmed Shah & Saeid Amini-Nik, 2017).

Cytokine inhibitors, such as anti-TNF drugs, are a newer class of anti-inflammatory agents that have shown promise in wound healing. These drugs work by inhibiting the production of pro-inflammatory cytokines, such as tumour necrosis factor (TNF), involved in the inflammatory response. By reducing inflammation, cytokine inhibitors can help promote wound healing and prevent complications associated with excessive inflammation (Dinarello, 2010).

Using anti-inflammatory agents in wound healing is essential for modulating the inflammatory response and promoting the repair process. However, it is vital to use these drugs carefully and under the guidance of a healthcare professional, as prolonged use can have adverse effects on wound healing and increase the risk of complications (A. Shah & S. Amini-Nik, 2017).

3.1.3 *Antimicrobial Agents*

Infection is a common complication of wound healing, and it can significantly delay the healing process and increase the risk of other complications. Antimicrobial agents are drugs that can help prevent and treat infections in wounds, and they are an essential component of wound care (Bowler, Duerden, & Armstrong, 2001).

Topical antiseptics, such as povidone-iodine and chlorhexidine, are commonly used to prevent wound infection. These agents kill or inhibit the growth of bacteria and other microorganisms that can cause infections. Topical antiseptics are typically applied directly to the wound, and they are most effective when used in conjunction with other wound care measures, such as debridement and wound dressings (Atiyeh, Dibo, & Hayek, 2009).

In cases where a wound has become infected, topical and systemic antibiotics may be necessary to treat the infection. Topical antibiotics, such as mupirocin and neomycin, are applied directly to the wound, while systemic antibiotics, such as penicillin and tetracycline, are taken orally or intravenously. It is important to note that antibiotics should be limited to cases with a high risk of infection or where the wound has already become infected, as overuse of antibiotics can lead to the development of antibiotic-resistant bacteria (Bandyopadhyay, 2021).

Silver-based dressings are another type of antimicrobial agent commonly used in wound healing. These dressings contain silver ions or silver nanoparticles, which have antimicrobial properties and can help prevent and treat wound infections. Silver-based dressings are particularly effective in treating burns and other wounds at high risk of infection (Paladini & Pollini, 2019).

Overall, antimicrobial agents in wound healing are essential for preventing and treating infections. However, it is vital to use these agents carefully and under the guidance of a healthcare professional, as overuse or misuse of these agents can lead to the development of antibiotic-resistant bacteria and other complications. The use of antimicrobial agents in wound healing should be tailored to the patient's needs and the type of wound being treated (Roberts, Leaper, & Assadian, 2017).

4. Conclusion

It is important to remember that medicine alone will not heal a wound. Wound care should always include suitable dressings, regular cleaning and debriding, and good nutrition. Patients with long-term conditions like diabetes may need extra care for their underlying condition to make sure the wound heals properly.

Also, it is essential to be careful when using medications to help wounds heal since they can have harmful effects, primarily when used for a long time. For example, using corticosteroids can make it take longer for a wound to heal and make it more likely to get infected. NSAIDs, on the other hand, can slow the early stages of wound healing. Therefore, healthcare professionals should carefully monitor the use of these medications.

In conclusion, wound healing is a complicated process that must be approached from many angles for the best results. Medication can be a big part of helping a wound heal, but it should only be used after carefully assessing the patient's needs and underlying conditions. By using a comprehensive and individualized approach to wound care, healthcare professionals can help patients achieve optimal wound healing and improved quality of life.

Conflicts of Interest

The authors declare that there is no conflict of interests.

Statement contribution of the author

This study's analysis and writing were made by the authors.

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Chapter 5

Crosstalk between Circadian Meal Timing System and Gut Microbiota

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1. Introduction

Environmental rhythms in daily and seasonal light patterns, food availability, and temperature are predictable, and humans can anticipate these environmental events by periodically and predictably changing their internal conditions (Lemmer 2015). Daily rhythms are not simply a response to the 24-hour changes in the physical environment as the Earth rotates on its axis, but arise from the body's temporal system (Vitaterna et al. 2011). This time system; the circadian clock, or circadian rhythm, is a natural rhythm that occurs when an organism rotates on the earth to adapt to periodic changes in the environment. When the environment changes, the body can readjust its circadian clock by sensing external signals (mainly light), ensuring that the organism "does the right thing" at the right time (Zhou et al. 2019).

The central clock is located in the suprachiasmatic nucleus of the hypothalamus and the peripheral clocks in most mammalian peripheral cells. Circadian rhythms can be driven or adjusted by environmental cues to synchronize the body with external cues known as zeitgebers (Voigt, Forsyth et al. 2016). The central clock is entrained by light/dark cycles, while nutrient signals are the dominant factors in the entrainment of peripheral clocks that determine the active/resting phases of the cell (Zhou et al. 2019; Oike 2017). It has been reported that the circadian rhythm of the host regulates the circadian rhythm of the gut microbiota, and feeding behaviour significantly affects the intestinal circadian rhythm (Voigt, Summa et al. 2016). Nutritional factors, including micronutrients and macronutrients, have the greatest influence on the shape and formation of the human gut microbiota (Zhang et al. 2018). In addition, disturbed eating habits, such as eating irregular meals, can lead to homeostatic imbalances that can lead to obesity and even lifestyle diseases. Recent nutritional studies in chronobiology, termed "chrononutrition," have revealed a molecular link between energy homeostasis and meal timing (Oike et al. 2014). Manipulation of gut microbiota composition through dietary changes and meal timing has emerged as a potentially effective “pharmaconutrition strategy” to correct dysbiosis and host metabolic disorders (Zeb et al. 2023)

2. The effects of meal timing zeitgeber on metabolism via circadian timing system

The circadian rhythm is controlled at the cellular level by a molecular network of molecular clocks in all cells of the body and is based on the CLOCK transcriptional-translational feedback loop of clock genes (circadian locomotor output cycles, kaput) and BMAL1 (brain and muscle arnt like protein 1). (Kohsaka and Bass 2007; Bass and Takahashi 2011). CLOCK and BMAL1

have been identified in almost all human organs and tissues and individually regulate the timing of physiological processes in different parts of the body. The primary regulator of the circadian rhythm is the suprachiasmatic nucleus (SCN), which is located in the hypothalamus of the brain and coordinates anabolic and catabolic processes in peripheral tissues with daily sleep-wake and fasting cycles. In addition to photogenic inputs, peripheral tissues are also sensitive to other factors such as food (quality, quantity and timing) and physical activity (Stenvers et al. 2019). For example, the timing of nutrient availability strongly regulates circadian clocks in the gut and liver, and these clocks are also affected by dietary composition (eg, a high-fat or high-sugar diet) (Mattson et al. 2014; Mendoza 2007; Burgess and Molina 2014).

2.1. Meal timing and energy metabolism

Changes in the level or activity of nicotinamide adenine dinucleotide (NAD) and sirtuins, depending on the energy state of the cell, affect the circadian clock. Sirt1 is a key regulator and promoter of clock gene production and provides a biological link between metabolic regulation and circadian rhythms. Also, the hepatic NADH cycle links nutritional status to total body energy through the circadian regulation of Sirt1. However, AMP-activated protein kinase (AMPK) phosphorylates CRY (cryptochromic circadian regulator) and promotes deterioration of cellular energy status during fasting, which affects the circadian system. This is because periods of eating and fasting increase the robustness or amplitude of the circadian oscillation of the activator and repressor components. To ensure the coordinated control of anabolic and catabolic forms of metabolism according to the activity/rest cycle, circadian oscillation and feeding/fasting signals are synergistically combined. This is achieved by ensuring that the daily oscillator is in sync with the feed/fast signals (Zeb et al. 2023).

Circadian rhythms can cause energy imbalances and regulate energy metabolism, but energy intake and activity can also influence the timing of clock genes and their local tissue activity (Ruddick-Collins et al. 2020). To ensure accurate synchronization of the central and peripheral clocks, the timing of meals must be coordinated with the body's circadian rhythms, because eating is even more important than what you eat (Asher and Sassone-Corsi 2015; Kessler and Pivovarova-Ramich 2019; Parr et al. 2020).

Unpredictable meal times can disrupt the circadian alignment of extra-organ metabolic processes and disrupt energy homeostasis. Disrupted systemic cooperation between clocks may be the most critical factor in energy metabolism induced by abnormal nutrition (Oike et al. 2014). In studies using

mice that mimic human eating habits, breakfast is usually the most effective meal time to determine the phase of the liver clock because breakfast is eaten after the longest fasting period of the day (Hirao et al. 2010). Thus, late dinner or midnight snacks change the timing of hunger and significantly change the phase of peripheral clocks (Kuroda et al. 2012). Strong indications show that it is better to maintain the rhythm of day and night sleep than to eat at night (Stenvers et al. 2012). Night eating was one of the eating behaviours that were often assessed in the evening for habitual night meals (Ishihara et al. 1985), consuming more calories at dinner (Muñoz et al. 2017) and at bedtime (Suh et al. 2017). Night eating syndrome (NES), defined as $\geq$ 25% of daily energy intake after dinner and/or eating $\geq$ 2 nights per week, provides a model for understanding the potential effects of meal timing (Allison et al. 2010).). NES patients often have elevated cortisol levels and decreased or delayed melatonin levels, often with no delay in sleep time compared to those who eat regularly. In addition, insulin and glucose levels are often elevated in these individuals, and the synchronization between glucose and insulin is usually somewhat altered and lost (Birketvedt et al. 2014).

Another hypothesis is that meal timing that is not synchronized with light/dark signals can lead to higher caloric intake due to impairment of satiety mechanisms mediated by leptin and ghrelin (Mazzoccoli et al. 2012). Unusual timing of meals also causes overeating, partly due to insufficient satiety. Because circadian clocks regulate the expression of appetite-inhibiting leptin (Abellan et al. 2011), the circadian rhythm leads to a decrease in serum leptin during the day (Scheer et al. 2009). Indeed, some studies have shown that a weakened feeding rhythm increases overall feeding (Bray et al. 2013; Hariri and Thibault 2011; Yoshida et al. 2012). In particular, leptin levels decrease during short sleep and energy consumption increases (Stern et al. 2014; St-Onge 2013).

One of the mechanisms that influence the circadian clock for meal timing is the change in resting energy expenditure. Feeding time can affect energy expenditure/basal thermogenesis because the body's core temperature is regulated by circadian clocks. For example, Rev-erbα is a circadian clock that controls the rhythmic expression of uncoupling protein 1 (UcP1), a key factor in brown adipose tissue thermogenesis (Chaix et al. 2018). The diurnal regulation of body temperature means that thermogenesis varies throughout the day. Indeed, diet-induced thermogenesis induces diurnal variations in humans, being greatest in the morning, followed by the afternoon and night (Romon et al. 1993; Bo et al. 2015; Fukuda and Morita 2017). Such diurnal thermogenesis can reasonably explain the increase in body weight in people who skip breakfast. A randomized crossover study evaluating the effects of either an early or late

lunch (3.5 hours apart) over 2 weeks in 32 women found that premeal, premeal, and postprandial energy expenditure was corrected in the late eaters. Respiratory quotient and morning-afternoon cortisol profiles were altered. The difference was due to a homeostatic effect of meal timing, with temperature increases occurring after a meal in both the early and late lunch groups (Bandin et al. 2015).

Light conditions also affect both thermogenesis and metabolism. Because continuous light suppresses central circadian rhythms, irregular feeding behavior, sleep/wake cycles, and energy homeostasis, including thermogenesis, can result. In addition, a change in lighting conditions or feeding time affects metabolism, body temperature and weight within a few days (Scheer et al. 2009). These immediate effects are probably due to a desynchronization between internal clocks, similar to jet lag. Chronic jet lag, including shift work, inevitably increases the risk of metabolic disorders. Hepatic clocks migrate rapidly with food signals, with the liver thought to adapt to new meal times in approximately 3 days, while kidney, heart, pancreas, and lung functions take longer (Stokkan et al. 2001; Damiola et al. 2000). It has been shown that the balance between food and hunger interval is an important factor in determining the phase of the liver clock.

2.2. Relation between chrononutrition, time-restricted feeding and circadian ryhmicity

Chrononutrition has been proposed as a means to adjust macro/micronutrient food composition or meal timing to human circadian rhythms to influence whole-body physiology and metabolism and improve overall health. In addition, eating habits are influenced by circadian rhythm, including the timing of eating and the irregularity, inconsistency and frequency of eating in mealtime situations (Pot et al. 2014). At the biological level, feeding schedules are primarily dictated by an innate timing mechanism. At the behavioural level, when eating occurs at regular and predictable times, the circadian clock activates nutrient sensing pathways to act synergistically to maintain nutrient homeostasis. However, when feeding occurs at random times, these same feeding responsive pathways provide “phase shift” feedback to the circadian clock, so that food is expected at a new feeding time on subsequent days (Chaix et al. 2019). Such circadian disruption acutely affects the remodeling of circadian gene expression or, in most cases; both are commonly found in animal models of obesity and metabolic dysregulation. Thus, input time is the dominant factor in determining the phase of peripheral circadian clocks. The general effect of different nutritional challenges on serum and skeletal muscle

metabolism was a clear reconnection of morning and evening metabolic profiles in response to both time and type of nutritional challenge (Sato et al. 2018).

The concept of time-restricted feeding (TRF) was born in connection with tarring rhythms and crown feeding. In TRF, the daily duration of eating (ie the time between the first and last energy consumption) is reduced from the usual 12-14 hours a day to the "eating window" of 10 hours a day. It's a new diet tool that advises people to shorten their daily eating window without changing calories or diet quality. In addition, TRF restores circadian rhythms and leads to pleiotropic metabolic benefits in animal models (Kessler and Pivovarova-Ramich 2019; Chaix et al. 2014; Delahaye et al. 2018; Gill et al. 2015; Hatori et al. 2012). Time- restricted eating and optional consumption of food for a certain period of time or a balanced breakfast can strongly drag and thereby strengthen the circadian clocks of peripheral tissues, while eating at unusual times or with fatty foods weakens these clocks (De Cabo and Mattson 2019; Di Francesco et al. 2018). Time-restricted feeding per day for a week completely changes the phase of circadian expression of the clock and clock-controlled genes in peripheral tissues of nocturnal rodents, while the central clock that dominates light/dark cycles remains unchanged (Stokkan et al. 2001; Damiola and others 2000; Hara et al 2001). The benefit of TRF against metabolic diseases is related to several temporal changes in physiology and metabolism in different organs. In the liver, TRF reprograms the metabolic flow through gluconeogenesis, directing pyruvate metabolism to the TCA cycle and glucose-6P metabolism through the pentose phosphate pathway. These two pathways contribute to increased nucleotide production. TRF also increases the expression of Cyp7A, which redirects cholesterol to bile acid production. TRF also increases the activity of brown fat, increases fatty acid ß-oxidation and decreases hepatic glucose. In white adipose tissue, TRF reduces macrophage infiltration and the resulting inflammation. In Drosophila, TRF has significant positive effects on heart health and improves sleep (Longo and Panda 2016; Panda 2016). Clock-deficient mice with food restricted to 9-10 h/day were protected against glucose intolerance and insulin resistance without changes in activity or energy consumption (Scheer et al. 2009).

Gill and Panda (2015) were the first to report that TRF in obese humans produced moderate weight loss after subjects reduced their eating window from >14 to ~10 hours per day for 16 weeks. Although participants in this study were not asked to change the quality or quantity of their diet, the food diaries showed a 20 percent reduction in energy intake. A randomized, 5-week isoenergetic controlled feeding trial with early TRF (08:00-15:00) versus a controlled 12-hour feeding window in overweight and obese (BMI 25-50 kg/m^2) adult men

with elevated HbA1c that TRF increased beta-cell function, reduced blood pressure and oxidative stress, and improved 24-h glucose balance (Sutton et al. 2018). Parr et al. determined that TRF (8 hours per day, meals at 10:00, 13:00 and 17:00) compared to extended feeding (15 hours per day, meals at 07:00, 14:00 and 21:00) improved nocturnal and postprandial glycemic control in overweight and obese subjects (Parr et al. . 2020).

It has been shown that TRF can protect mice against obesity, hyperinsulinemia, fatty liver, and inflammation when fed a high-fat diet. Rodents fed ad libitum with high fat showed an altered circadian rhythm compared to TRF rodents. In addition, daily periods of fasting and feeding trigger alternative activation of fasting-responsive cAMP response element-binding protein (CREB) and AMP kinase and feeding-responsive insulin-dependent mammalian target of rapamycin (mTOR) pathways involved in metabolic homeostasis (Hatori et al. al (2012). These results can be explained by the significant cross-talk and close interaction between cellular clocks and fed/fast state-induced signaling. For example, we know that fasting, like the ketogenic diet, induces the phosphorylation of AMPK, a key factor in mitochondrial biogenesis and function. On the other hand, the fed state stimulates the mechanistic target of rapamycin (mTOR) pathway, promoting anabolic processes during times of increased energy availability, which can disrupt the AMPK pathway.

In general, the regular availability of food (regular mealtimes) affects the release of various signals from the gut. It has been suggested that signals from the gut inform the dorsomedial hypothalamus (DMH) about food availability. Thus, DMH can influence other tissues and regulate food anticipation, digestion and absorption. Although circadian genes expressed in the gut play an important role, there is evidence that food itself is an important regulator of nutrient flow through clock function (Paoli et al. 2019).

3. Communication between the meal timing and gut microbiota

Gut microbiota and the circadian clock share a regulatory relationship that plays an important role in metabolic health (Parkar et al. 2019). The circadian clock influences the composition of the gut microbiota, and conversely, the gut microbiota can also regulate the circadian rhythm, indicating a two-way communication between the gut microbiota and the circadian clock. On the other hand, the intestine has its own oscillator, which is mainly regulated by nutrition (Tognini et al. 2017; Yoshida et al. 2015). It has previously been observed that there are daily variations in the composition and function of the intestinal microbiota itself, the regulation of which is regulated by the eating

rhythms of the host and the types of food consumed (Malago 2015; Liang et al. 2015). Based on the results so far, meal timing is important for our health and controls our body clock (Oda 2015). A growing body of evidence suggests that meal timing is an important factor in metabolic regulation and that the circadian clock is closely related to metabolic functions (Kessler and Pivovarova-Ramich 2019). Thus, it is evident that meal times can have a strong influence on the dialogue between the timing system and the gut microbiota.

Looking more closely at the interaction between microbiota and circadian rhythm at the molecular level, it is most important to focus on the modulatory role of gut microbiota between feeding time and host circadian rhythms. If the light/dark cycle is considered a timing factor of the central biological clock in mammals, mealtime can be considered a timing factor of the circadian rhythm of the mammalian gut and gut microbiota. It is known that the gut microbiota is not only a passive system involved in feeding time and circadian interaction, but also actively regulates circadian rhythms through various components such as SCFA and bile acids. The SCN clock provides temporal information to the clocks of peripheral organs and systems, including muscle and adipose tissue, the cardiovascular system, the liver, and the gut microbiome, as shown in Figure 1. Peripheral clocks respond to signals such as neurohumoral changes induced by fasting/feeding periods, including hormones (eg, ghrelin, growth hormone, and cortisol). The normal circadian rhythm and healthy gut microbiota are presented on the left side of Figure 1. Ghrelin, growth hormone, cortisol and melatonin were shown to be non-rhythmic in germ-free mice (Weger et al. 2019). Ghrelin levels were shown to be negatively correlated with Bifidobacterium, Lactobacillus and Blautia coccoides-Eubacterium rectale and positively with Bacteroides and Prevotella abundance (Queipo-Ortuno et al. 2013). Intestinal epithelial cells that alter gut barrier function have been shown to activate enteroendocrine cells with a circadian rhythm, and dendritic cell modulation that alters the immune system is one of the well-known examples of gut microbiota-host communication. In addition, SCFAs (propionate, butyrate, acetate) and bile acids also alter circadian rhythms. In studies (Leone et al. 2015; Tahara et al. 2018), oral administration of SCFAs caused significant phase changes in PER2 and BMAL1 rhythms in peripheral tissues. Unconjugated bile acids have been shown to regulate circadian rhythms and alter the expression of circadian clock genes in peripheral tissues (Govindarajan et al. 2016). Interestingly, feeding during the inactive phase causes similar changes in overall bile acid composition (Eggink et al. 2017). In addition to these described molecular mechanisms, cells and cytokines of the immune system exhibit a circadian rhythm in response to the gut microbiome

(Labrecque and Cermakian 2015). Unwanted changes in gut microbiota or circadian rhythm are associated with low-grade sterile inflammation in the body (Voigt Forsyth et al. 2016).

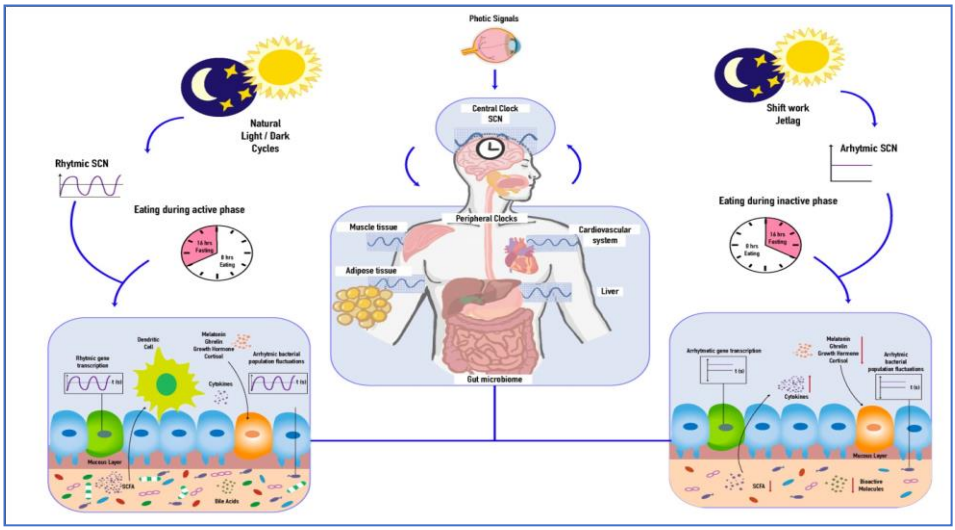

Figure 1. Molecular pathways among meal timing, gut microbiota, and the circadian system (*Illustrated by Iren Gokgoz modified from Teichman et al. 2020*)

In recent years, the importance of circadian rhythms, a critical factor in physiological processes related to energy metabolism and energy balance (EB), and the possible health effects of disruption of these rhythms on the gut microbiome have been emphasized. It discusses the effects of strong desynchronization protocols as drivers of diurnal variation, as well as the more subtle effects of changing meal times, where the extent of diurnal disruption may be less obvious. A large number of metabolic processes, including the expression of many energy-regulating endocrine hormones through related biomarkers; for example, cortisol, leptin, ghrelin, and other energy-regulating neuroendocrine factors show temporal rhythms driven by both the time of day and food intake. Hormonal signals transmit messages to the periphery of the hypothalamic arcuate nucleus (ARC) and energy regulatory centers, where the temporal expression of receptors enables effective signaling. In the ARC, neuropeptide Y (NPY)/agouti-related protein (AgRP) and proopiomelanocortin (POMC)/cocaine-amphetamine-related transcript (CART) neurons express corresponding neuropeptides, increasing or decreasing appetite and decreasing or increasing energy metabolism, and energy consumption accordingly.

Mealtime and activity can also affect the timing and amplitude of peripheral clock genes and thus the timing of hormone secretion. Uncoupling energy intake (EI)/energy expenditure (EE) and the SCN can lead to desynchronization of circadian rhythms with either a misaligned or suppressed circadian rhythm (Collado et al. 2018; Papadopoulou et al. 2020).

A growing body of evidence supports the negative effects of circadian rhythms on health, and there is strong evidence in mouse models that diet-induced circadian rhythms lead to various metabolic consequences through dysbiosis of the gut microbiome in response to both acute and chronic feeding time fluctuations (Ruddick-Collins and others 2020). The rhythmic changes shown by the intestinal microbiota are regulated by the host organism, especially the feeding times of individuals and the change in microbial activity depending on the availability of the nutritional element (Voigt, Summa et al. 2016). Regular feeding-fasting cycles, inevitably determined by sleep-wake rhythms, represent the dominant synchronization signals of peripheral clocks, triggering a series of molecular transport pathways capable of realizing the circadian routine (Schmidt 2014; Jung et al. 2011). In contrast, interrupted feeding schedules can completely uncouple peripheral clock oscillators from the suprachiasmatic nucleus, strengthening the argument that diet-modulated metabolic signals reach and signal the SCN and modulate specific output pathways of the clock (Branecky et al. 2015; Gabel et al. 2018). Thus, meal times are a dominant factor in the temporal organization of microbiome activity. Abnormal gut microbiota, circadian rhythms, and dysbiosis occurred when rhythmic feeding times were disrupted, such as the absence of the host's genetic molecular clock and time-shifted jet lag. If physiological adaptations to circadian disturbances are not accompanied by adaptations of gut microbes to circadian patterns, this may have metabolic consequences for the host in terms of the efficiency of energy recovery and utilization (Nobs et al. 2019). Since many components of food can alter the composition and function of gut microbes, it is possible that manipulating the quality, quantity, or timing of food can manipulate the gut microbiota and ultimately influence and mitigate some of the metabolic consequences of modern lifestyle problems such as sleep disorders and heart rhythm disorders. Manipulation of daily rhythms of gut microbial abundance and activity may therefore allow a chrononutrition-based approach to enhance host circadian rhythms and metabolic homeostasis (Parkar et al. 2019).

The timing of meals and the eating window are now becoming as important as the composition of the diet to promote the rhythmicity of the microbiome (Parkar et al. 2019). Feeding restricted to the active dark phase induced a cyclic

rhythm in the mouse gut microbiome, with Firmicutes peaking during feeding and decreasing during daily fasting with a peak-to-trough ratio of 3:1. Bacteroidetes and Verrucomicrobia peaked during daily fasting, probably due to their better ability to obtain food from intestinal mucosal glycan (Zarrinpar et al. 2014). The internal circadian clock of intestinal epithelial cells influences daily production of glucocorticoids under the control of the pituitary-adrenal axis, and this rhythm is influenced by the state of the microbiota. In addition, a change in the microbiota can cause disruption of the circadian rhythm by corticosteroids, which affects nutrient absorption. In addition, the composition of the microbiota varies during the day, which can be disturbed by several conditions, such as jet lag or a high-fat diet (Voigt, Forsyth et al. 2014). TRF-induced changes in gut microbiota were more significant in mice treated with daily 16-hour fasting, with Ruminococcaceae and Alistipes and A. muciniphila numbers compared to controls (Li et al. 2020).

TRF also reduced Lactococcus spp. compared to an ad libitum high-fat diet, which showed that Lactococcus spp. Both species must be obesogenic. TRF also restored the abundance of Clostridia and Ruminococcaceae (e.g., Oscillibacter) during the active phase, but not cyclic rhythms comparable to those observed with the standard diet (Zarrinpar et al. 2014). Indeed, microbial rhythms, such as those generated by TRF, may have greater metabolic consequences for the host than microbial abundance. Similarly, the duration of TRF-induced overnight fasting in humans was found to be proportional to faecal propionate, which is diverted to gluconeogenesis in the liver (Louis et al. 2007; Kaczmarek et al. 2017). In addition, disruption of the circadian rhythm also increases the permeability of the intestinal epithelial barrier (Summa et al. 2013). In addition, gut bacteria affect physiological sleep regulation and the sleep response to microorganisms by causing an increase in the concentration of cytokines (eg, IL-1), which increases the permeability of the intestinal epithelium (Maslanik et al. 2012). Poroyko et al. (2016) showed that Lachnospiraceae and Ruminococcaceae species were more abundant in chronically sleep-deprived mice.

The contribution of Lachnospiraceae bacteria to metabolic diseases has also been shown in studies with bacteria-free ob/ob mice. In germ-free mice, colonization with Lachnospiraceae strain AJ110941 resulted in rearrangement of the metabolic phenotype, increased fasting blood glucose, increased liver fat content and mesenteric adipose tissue mass, and decreased plasma insulin levels and HOMA values. (Kameyama and Itoh, 2014). Thais et al. (2014), two individuals whose circadian rhythm was disrupted by jet lag, the day before a jet lag-inducing trip; stool samples were collected during jet lag and after

recovery from jet lag (ie, two weeks after jet lag). Mice transplanted with stool samples taken during jet lag showed increased body weight and high fasting blood sugar levels. Another study also showed that chronic diurnal variability induces obesity by causing dysbiosis in the intestinal microbiota (Schoenfeld et al. 2015). In short, it can be stated that feeding during the day and in a limited time window has a positive effect on the changes in the intestinal microbiota and leads to the improvement of systemic inflammation, metabolic disorders and obesity (Paoli et al. 2019).

However, the intestinal microbiota is not only affected by the time of eating, but also by the composition of the meal. In a study in mice, eating a high-fat diet reduced diurnal fluctuations in the abundance of bacteria in the gut microbiome. In particular, members of the Lachnospiraceae family, which are short-chain fatty acid-producing bacteria, suffer from this disease. In contrast, bacteria such as H_2S-producing bacteria (sulfate-reducing bacteria) were found to show no circadian rhythm before the procedure, while mice have a circadian rhythm after a high-fat diet. Nutritional interventions in mice fed a high-fat diet have been shown to partially restore the circadian rhythm of gut bacteria when the intervention occurs only at night (similar to a time-restricted diet). The study concluded that consumption of a fatty diet suppresses circadian rhythms in the functioning of the intestinal microbiome, and under conditions of consumption of a high fat diet, diurnal fluctuations in the production of short chain fatty acids are excluded (Leone et al. al. 2015). Therefore, meal timing has been reported to induce functional changes not only in gut microbiota abundance, but also in functional variations of gut microbiota. Therefore, it is thought that the observed health effects related to dietary habits, such as time-restricted diet and meal frequency, may also be related to the gut microbiota.

Table 1 summarizes the effects of TRF patterns on gut microbiota and lists the possible health benefits of TRF in the study. In conclusion, these findings summarize the role of the gut microbiota in regulating circadian rhythms in health and disease. When human studies are examined, it is seen that the intervention duration of time-restricted diet models varies from one week to three months (Remely et al. 2020; Ozkul et al. 2019; Gabel et al. 2020; Zeb et al. 2020a and 2020b). According to the results of these studies, time restricted feeding did not significantly alter the diversity or overall composition of the gut microbiome. Time restricted feeding could impact the main phyla of gut bacteria such as Prevotellaceae and Bacteroideaceae (Zeb et al. 2020b). However, these changes varied between studies. For instance, Gabel et al. (2020) was found no significantly alteration on the diversity or overall composition of the gut microbiome. In two human studies (Remely et al. 2020;

Ozkul et al. 2019), in which the time-restricted feeding model intervention duration were different, *Akkermansia muciniphila* increased similarly to each other. *Akkermansia muciniphila* has attracted growing interest for its health-promotion. These results are consistent with the results of the mice studies including (Li et al. 2020; Beli et al. 2018). This effect result from the reduction of metabolic endotoxemia by modulating gut barrier integrity positively (Polat and Ekici 2019). Therefore, with the help of gut microbiota analyzes to be made at different times during the study period, evaluating the effects of the intervention duration of time-restricted diet models will provide more efficient outputs. In addition, studies on more homogeneous and similar human samples will be important in order to understand whether the metabolic outputs including decreasing in liver triglycerides (Li et al. 2020), plasma lipopolysaccharide levels (Liu et al. 2020), gastrointestinal symptoms (Remely et al. 2020), adiposity (Merwe et al. 2020) and increasing in glucose tolerance (Beli et al. 2018) and prevention of metabolic diseases (Zeb et al. 2020b) obtained from the results of these studies are results mediated by gut microbiota or the metabolic effects of time restricted feeding models.

Table 1. An overview of the researchs about the effects of TRF patterns on gut microbiota

TRF Patterns	Intervention Duration	Study Model	TRF Effects on Gut Microbiota	Health Benefits	Reference
16 hours fasting in a day	1 month	Mice	Increase in Akkermansia; Decrease in Alistipes and Ruminococcaceae	Decrease in liver triglycerides	Li et al. 2020
Intermittent fasting	7 months	Diabetic mice	Increase in Lactobacillus; Decrease in Oscillospira, Bacteroides and Akkermansia	Increase in glucose tolerance	Beli et al. 2018
Intermittent fasting	28 days	Diabetic mice	Increase in Lactobacillus and Odoribacter. Decrease in Enterococcus, Streptococcus, and Enterococcaceae	Decrease in Plasma lipopolysaccharide levels	Liu et al. 2020
A fasting pattern followed by probiotic use	1 week	Humans	Increase in *Feacalibacterium prausnitzii*, Bifidobacterium and *Akkermansia muciniphila*	Decrease in gastrointestinal symptoms	Remely et al. 2020
17 hours fasting in a day	29 days	Humans	Increase in *Bacteroides fragilis* and *Akkermansia muciniphila*	Decrease in fasting blood glucose and total cholesterol levels	Özkul et al. 2019
A fasting pattern	Every other day	Multiple sclerosis mice	Increase in Lactobacillaceae, Bacteroidaceae, Prevotellaceae and *Bifidobacterium pseudolongum*	Decrease in leptin	Cignarella et al. 2018
A fasting pattern	Every other day	Mice	Increase in Firmicutes	Selective upregulation of beige cells	Li et al. 2017
High fat and 6 hour-time restricted feeding	6 weeks	Mice	Increase in Ruminococcus, Christensenellaceae, Clostridiales, Coprococcus, Lactococcus, Desulfovibrio Decrease in Bilophila	Decrease in adiposity according to body composition	Merwe et al. 2020

Fasting mimicking diet	4 days	Mice with intestinal bowel disease	Increase in Lactobacillaceae and Bifidobacteriaceae	Decrease in intestinal inflammation	Rangan et al. 2019
16 hours fasting in a day	12 weeks	Humans with obesity	Not significantly alteration on the diversity or overall composition of the gut microbiome	Decrease in body weight	Gabel et al. 2020
16 hours fasting in a day	25 days	Healthy humans	Increase in Prevotlla_9, Faecalibacterium, and Dialister	TRF-associated gut microbiota alteration and its key roles in various metabolic processes	Zeb et al. 2020a
16 hours fasting in a day	25 days	Healthy males	Increase in microbial richness; enrichment of Prevotellaceae and Bacteroideaceae.	May be a remedy for the prevention of metabolic diseases related to dyslipidemia	Zeb et al. 2020b
8 hours fasting in a day	12 weeks	14 adults with obesity	No significant changes in the abundance of microbiota	No significant changes	Guo et al. 2021
8 hours fasting in a day	12 weeks	24 adults with obesity	Increase in Lachnospiraceae, Parasutterella, and Romboutsia	Upregulation of butyric acid-producing Lachnospiraceae provides a positive health effect	Su et al. 2021
Ramadan time-restricted feeding	4 weeks	30 healthy males	Increase in microbial diversity and butyric-acid-producing Lachnospiraceae	Improvement of lipid profile and body weight in humans,	Khan et al., 2022
Ramadan time-restricted feeding	29 days	9 healthy adults	Increase in Butyricicoccus, Bacteroides, Faecalibacterium, Roseburia, Allobaculum, Eubacterium, Dialister, and Erysipelotrichi	Improvement in insulin sensitivity	Xie et al., 2022
17 hours in a day	29 days	9 healthy adults	Increase in Akkermansia muciniphila, Faecalibacterium prausnitzii, Bifidobacterium spp., Lactobacillus spp.,	Better metabolic conditions related to hepatic lipid metabolism	Ye at al. 2020

			Bacteroides fragilis group, and Enterobacteriaceae		
16 hours in a day	5 weeks	82 healthy adults	Increase in gut microbial diversity	Regulation of circadian clock gene expression	Asher et al. 2008

Not only the composition of the food has a negative effect on the microbiota, but also the time of the meals: consuming food outside the normal nutritional phase (eating in the light in rodents and eating late in the evening in humans) can interrupt the meal normal functioning of the peripheral and central clock (Asher and Sassone-Corsi 2015). Since TRF strategies can differ according to different daily fasting hours, a recent study investigated the effects of 12-, 16-, and 20-h daily fasting for one month on the gut microbiota of mice (Li et al. 2020).

Conclusions

Food ingredients have a key effect on the intestinal microbiota, influencing its composition in terms of abundance and diversity. It has been demonstrated that the intestinal microbiota plays an important role in non-infectious diseases, as it actively participates in the maintenance of intestinal homeostasis by influencing nutrient metabolism, the intestinal barrier and the immune system. The diet/microbiome interaction currently supports the implementation of personalized nutrition, and microbiota composition is a key factor influencing response to nutritional interventions, which will soon consider the initial stratification of individuals based on their microbiota. In recent years, in addition to quality and quantity, time has become an important factor for metabolism and intestinal health. The evidence collected so far is encouraging, and the use of a chrono-nutritional approach can be useful to prevent adverse health effects of changes in the intestinal microbiota, especially in pathological individuals already characterized by intestinal dysbiosis. This new knowledge can lead to the development of new strategies, such as chrononutrition methods, to change the microbiota and treat or prevent these diseases.

Therefore, chrononutrition methods to optimize metabolism by timing food intake to acrophases of metabolic rhythms are thought to be a focal topic in the future to identify metabolic characteristics unique to each individual in response to different nutritional interventions practitioners who help treat chronic diseases such as obesity and type 2 diabetes. Smart nutrition consists of "5 W and 1 H" meals that tell who eats what, when, why and where and how to eat, which can be adopted by creating an individual diet after a microbiota analysis

and restores a healthy gut microbiota. Although there is little evidence to explain the relationship between microbiota and meal timing, data promise that maintaining the correct meal phase of an individual's circadian typology and extending the fasting period by reducing meal frequency can have a positive effect on the gut microbiome.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Chapter 6

Acupuncture Treatment in Fibromyalgia

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INTRODUCTION

Fibromyalgia syndrome (FMS); it is a chronic pain syndrome with symptoms such as extensive fatigue, musculoskeletal pain, sleep disorder, irritable bowel syndrome, chronic headache, depression, anxiety, restless legs syndrome, temporomandibular joint dysfunction, irritable bladder syndrome and cognitive dysfunction [1]. It is reported to affect 0.5-5% of the population and is common in women with a rate of 9/1 [2, 3].

PATHOGENESIS

The pathogenesis of fibromyalgia is still not fully understood. There is no laboratory test or imaging method used for diagnosis and diagnosis is based on clinical evaluation. Therefore, some authors report that the diagnosis of FMS should be a diagnosis of exclusion [4]. Apart from biological stress causes such as physical trauma, infection, deterioration in muscle microcirculation, sleep disorders, abnormalities in central pain mechanisms, impaired immune and autonomic functions, some forms of psychological stress are assumed to be involved in the pathogenesis [5].

Many studies have been considered on the pathogenesis of FMS in the past years, and these include peripheral and central changes. Peripheral inflammation, called neurogenic inflammation has a significant contribution in FMS. Neurogenic inflammation process; contains a variety of neuropeptides, chemokines, and cytokines that activate both the inherited and adaptive immune systems [6]. There are nociceptors that lower the threshold level against external stimuli such as pain, heat, cold, electricity and sound, and this explains an increased sensitivity to pain [7]. These findings support the emergence of peripheral sensitization in this syndrome. In addition, C fiber hyperexcitability and a decrease in intraepidermal nerve fibers have been reported in FMS patients [8, 9]. Small fibril dysfunction may explain the dysesthesia in FMS patients [10]. Small fiber polyneuropathy findings were found in the biopsies of patients with FMS. Small fiber polyneuropathy develops with the contribution of neuroinflammatory mediators. These studies show that FMS pain has a neuropathic component [11-13].

Although a wide spectrum of pathogenetic mechanisms involving many systems are emphasized in FMS, central nervous system involvement is critical. Patients with FMS have a pain-specific accelerated brain processing, referred to as the “neurological pain signature” [14]. Despite decreased cortical and subcortical gray matter density in these patients, increased brain glial activation has been reported [15]. Impaired opioid function, plus augmented excitatory neurotransmitter (substance-P, glutamate, and others) and diminished inhibitory

neurotransmitter (GABA) levels; they cause central sensitization by changing the nervous system communication in this syndrome [16].

It has been reported that pain in FMS originates from the central system and there is a dysfunction in the pain perception-regulation system. This dysfunction is shown as the cause of hyperalgesia and allodynia seen in patients. Excitatory transmitters for instance calcitonin gene-related peptide (CGRP), glutamate, substance P, are responsible for central sensitization and neuronal hyperactivity, and inhibitory neurotransmitters such as norepinephrine and serotonin are responsible for pain modulation. Thanks to the increasing number of studies examining the relationship between CGRP and pain, the anti-CGRP monoclonal antibody developed in recent years of which is important as a potential treatment for patients with chronic pain syndrome [17, 18].

In another study investigating the relationship between tension-type headache (GBA) FMS syndrome and CGRP: While there are results suggesting that CGRP may play a role in the etiology of GBA, no significant relationship was found between them and FMS [19].

Calcitonin gene-related peptide (CGRP), localized in A delta and C nerve fibers, is a 37 amino acid peptide [20]. One of the excitatory neurotransmitters, CGRP is responsible for pain transmission and central sensitization. Besides CGRP, CGRP receptors are also an important factor in peripheral and central sensitization. A functional CGRP receptor requires three components; the receptor activity modifying protein1 (RAMP1), the calcitonin receptor-like receptor (CLR), and receptor component protein (RCP) [21]. In a study that compared the levels of CGRP and CGRP receptor proteins in healthy controls and fibromyalgia patients; While RCP, CLR and CGRP levels were found to be significantly higher in patients with FMS compared to healthy controls, no statistically significant difference was found between the two groups in RAMP1 levels [22]. Consequently, more research is needed to elucidate the pathogenesis of FMS.

In patients with FMS, lower serum and CSF (Cerebral Spinal Fluid) serotonin and noradrenaline levels, and 5-hydroxy-indolacetic acid levels in the cerebrospinal fluid were found to be lower than controls. These reductions in the inhibitory system cause central sensitization and, accordingly, pain and hyperalgesia. Serotonin is also responsible for deep sleep and pain perception. Therefore, low plasma serotonin levels cause insomnia in patients with FMS [23, 24].

Hypothalamo-pituitary axis disorder was found in patients with FMS. It may be associated with HPA axis dysfunction, nocturnal sympathetic hyperactivity, irritable bowel syndrome, and widespread pain [25.]

DIAGNOSIS

The American College of Rheumatology (ACR) 1990 diagnostic criteria have been used over the years in the diagnosis of FMS. These criteria are based on the sensitive point examination. According to this; FMS is diagnosed when as a minimum 11 of 18 tender points have pain on palpation for more than 3 months. In order to diagnose FMS according to the ACR 1990 Criteria, the patient must first have widespread pain. To be able to say widespread pain; pain in the right and left halves of the body, upper back and, lower and also axial skeletal pain in the cervical spine or rib cage or thoracic spine or lumbar region. Secondary, at least 11 of the 18 tender points must have pain on palpation. Where sensitive points should be; Bilateral suboccipital muscle insertions in the occiput, bilateral in the lower cervical region, anterior part of the C5-7 intertransverse regions, midpoint of the bilateral upper border in the trapezius muscle, bilateral origos in the supraspinatus muscle, region near the middle border on the spina scapula, bilateral second costochondral junction lateral to the upper surfaces, bilateral lateral 2 cm distal to the epicondyles, anterior fold of the muscle in the bilateral upper quadrant of the hip in the gluteal region, posterior to the bilateral trochanteric process in the greater trochanter, and the medial fat pad proximal to the bilateral knee joint line [26].

Evaluation according to the ACR 2010 criteria is made by the Symptom Severity Scale (SSS) and the Widespread Pain Index (WPI). Any other disease with an WPI score of 7 or greater than 7 and an SSS score of 5 or 5, or a WPI score of 3-6 and an SSS score of 9 or 9, with symptoms persisting for more than 3 months, as well as any other disease that may explain these complaints patients who do not have FMS are diagnosed. In addition, somatic symptoms are also taken into account. In this context, muscle pain, fatigue, memory problems, waking up tired and cognitive functions, irritable bowel syndrome, abdominal pain, headache, numbness, dry mouth, drowsiness, depression, constipation, insomnia, irritability are evaluated. A score between 0-3 can be obtained for each question; 0=absent, 1=mild, 2=moderate, 3=severe [27, 28.]

The ACR 1990 criteria have a specificity of 81.1% and a sensitivity of 88.4%. However, ACR published new FMS diagnostic criteria in 2010 because of the lack of tender point sensitivity in 25% of the patients and the inability to use tender points in the follow-up of the disease, and cognitive dysfunction and sleep disturbance are not among these criteria [29.] In the ACR 2010 criteria, there is no tender point examination, but non-pain symptoms for instance cognitive dysfunction, fatigue, and sleep disturbance are evaluated. The aim here is to emphasize the importance of non-pain symptoms, to measure the severity of the disease objectively, to follow up the cases that have not yet fulfilled the 1990

ACR criteria, and to evaluate the response to treatment. The Wide spread Pain Index gives the number of areas where the patient has felt pain during the previous week. Scoring is made using WPI, fatigue severity, waking up tired, symptom severity including cognitive problems (Symptom Severity-SS) in 2010 ACR criteria . The number of other somatic symptoms associated with the disease is also assessed and graded. The 2010 ACR criteria count the number of painful areas present in WPI without taking into account their distribution in the body, and this seems to be a limitation. In 2016, a new regulation was brought to these criteria, and the areas evaluated by WPI were divided into 5 regions in order to exclude regional pain disorder and ensure the generalization of pain (multi-site pain). Pain in 4 out of 5 sites in fibromyalgia is essential for diagnosis [29- 31].

The 5 regions in which pain was evaluated with the widespread pain scale were determined as, the axial region, the upper right region, the upper left region, the lower right region, and the lower left region. Upper left area; left shoulder girdle, left chin, left forearm is the left arm. Upper right area; right shoulder, right jaw, right forearm and right arm. The axial region is the chest, abdomen, back, neck, and waist. The lower left area is the left leg, left hip, left thigh, and the lower right area is right leg, the right hip, and right thigh. Accordingly, the widespread pain index (WPI) is scored between 0-19 for 19 regions [30, 31].

The symptom severity scale (SSS) is scored between 0-12. Fatigue, awakening from rest, cognitive disorders and somatic symptoms are questioned. For the first three symptoms;

0 = no complaints

1 = mild complaints (usually intermittent or mild)

2 = moderate complaints (usually present and/or moderate)

3 = severe complaints (life-disturbing problems, persistent, common).

For the somatic symptoms, symptoms that bothered the patient during the previous 6 months are asked:

1= Headaches (0–1)

2= Pain or cramps in the lower abdomen (0–1)

3= Depression (0–1)

Accordingly, the following three conditions are necessary to diagnose a patient with FMS.

- Symptom severity (SS) scale score 5 or greater than 5 or diffuse pain index (WPI) greater than or equal to 7

- Symptom severity (SS) scale score of 9 or greater and widespread pain index (WPI) 4-6

- General pain: Must be in at least 4 out of 5 areas
- Symptoms must persist for at least 3 months. Fibromyalgia diagnosis is valid regardless of other diagnoses [29-32].

TREATMENT METHODS IN FIBROMYALGI

Pharmacological Treatment

- Paracetamol and Tramadol, a weak opioid
- Tricyclic antidepressants
- Serotonin and noradrenaline reuptake inhibitors (SNRIs)
- Selective serotonin reuptake inhibitors (SSRIs)
- Anticonvulsants: Gabapentin and Pregabalin

Tricyclic antidepressants inhibit serotonin and noradrenaline reuptake in the central nervous system. Amitriptyline, a tricyclic antidepressant, was found to be effective in FMS symptoms in randomized controlled studies, and it was reported that 25-50% of patients had moderate improvement in pain severity and sleep disturbance [33]. Although it is the most commonly prescribed drug in FMS, it is not FDA-approved. It has a moderate effect on pain and sleep quality in FMS. Although cyclobenzaprine is a TSA in nature, it is classified as a muscle relaxant. It also has a mild antidepressant effect. In patients with mild and moderate FMS, 10 mg may be recommended at bedtime [34, 35].

SSRIs are better tolerated than TSAs, they are not as effective as TSAs on pain, fatigue and sleep disturbance in FMS. Therefore, their use in FMS is mostly on the treatment of depression [36-38].

SNRIs are drugs that inhibit serotonin and noradrenaline reuptake. Duloxetine and Milnacipran are FDA-approved for use in FMS. They act by inhibiting the reuptake of serotonin and noradrenaline, which have an effect on cognitive functions, sleep, concentration and pain inhibition [39.]

Duloxetine is also used in diabetic peripheral neuropathy, chronic pain due to osteoarthritis, major depression, general anxiety disorders, urinary incontinence and chronic low back pain. It has FDA approval for use in depression, diabetic peripheral neuropathy and FMS [40].

Anticonvulsant drugs are also known to have analgesic properties. The most commonly used drugs for this purpose are Pregabalin and Gabapentin. Pregabalin is a gamma amino butyric acid (GABA) analogue. It reduces the release of neurotransmitters that play a role in pain, such as Glutamate and Substance-P. It has FDA approval for the treatment of FMS [41].

The mechanism of action of Gabapentin is not fully known. However, it is known that it increases GABA synthesis in all glial structures in a dose-

dependent manner. Gabapentin has been reported to reduce pain, increase sleep quality and quantity, and improve quality of life in FMS [42].

Non-pharmacological Treatment

- Exercise:-Aerobic exercise, strengthening exercises, stretching exercises
- Physical therapy agents
- Education
- Cognitive behavioral therapy
- Complementary medicine methods (acupuncture, Thai-Chi, homeopathy, phyto-therapy etc)

The European Union of Rheumatology (EULAR) recommends that the patient diagnosed with FMS should first be given education about the disease and exercise. Initiation of pharmacological treatment is emphasized if the patient has severe pain, cognitive dysfunction and sleep disorders [43]. Exercise studies have shown that patients with FMS have low cardiovascular endurance, decreased muscle strength and endurance, as well as physical deconditioning [44]. Suggested exercises in FMS; aerobic exercises are stretching, relaxation and in-water exercises. The aim is to improve posture, reduce stress, increase endurance, and increase cardiovascular endurance [45].

In FMS, moderate to high intensity aerobic exercises (dancing, cycling, swimming etc). It has been reported to be effective in increasing pain and aerobic capacity [46]. A meta-analysis of 34 studies and 2276 patients found positive effects of aerobic exercise on general well-being, physical function, and pain [47, 48]. According to the results of another study investigating the effectiveness of in-water exercises, it was reported that in-water exercises were more effective on pain, stiffness, muscle strength and general well-being than the non-exercise group [49].

ACUPUNCTURE

Acupuncture is a 3000-year-old complementary medicine method applied all over the world, especially in China and Far East countries. Its main philosophy is based on the balance and harmony between the energy flows in the whole universe. According to the philosophy of acupuncture, the blockage of the energy flow in the body causes disease. The purpose of acupuncture is to remove this blockage and bring the body back into balance. Acupuncture has analgesic, homeostatic, autoimmune, sedative, psychological, and motor functions improving effects. Acupuncture is a treatment method applied by placing fine needles on special acupuncture points on the skin and sometimes

manipulating them to achieve therapeutic effect. It has become increasingly popular all over the world, especially in chronic pain management [50, 51].

Methods used in practice; traditional dry needling, Chinese needle acupuncture, electroacupuncture, laser acupuncture, and mechanical acupressure heat acupuncture (moxibustion) [52]. Needles placed on special acupuncture points on the skin target the whole skin surface, soft tissue or specific well-defined points of the body. These are called head, ear, and hand acupuncture. It is thought that these acupuncture points are related to each other via meridians and their collaterals. Once inserted, needles can be manipulated by hand, heat, or electrical stimulation. It is thought that with the stimulation of the needles, the balance of the body is rearranged and the flow of energy or Qi returns to normal. Balanced energy also ensures optimal health and homeostasis [53].

Studies on the analgesic mechanism of acupuncture are increasing. The mechanism of acupuncture analgesia includes the regulation of pain-modulating pathways and various biochemical contents of the central nervous system. According to this theory, by manipulating or stimulating an acupuncture needle placed on the acupuncture point on the muscle or skin; nerve fibers such as A-delta and C fibers in the skin and muscle are stimulated. The signals from here are transmitted to the spinal cord. This creates activation in the hypothalamus arcuate nucleus, brainstem periaqueductal gray area, and spinal cord, which are the endogenous-pain-modulated system at the site. Eventually, the endogenous opiate system becomes active and the perception of central pain and the sensation of painful stimuli decrease [54-56].

According to the theory of Traditional Chinese Medicine (TCM), there are 12 pairs of main meridians and 8 extra meridians in the human body, which correspond to organs. Although meridians bear the same name as organs in the body, their anatomy and physiology in western medicine do not overlap. Because, according to TCT, organs are functional systems rather than anatomical structures. The 12 main meridians are lung, heart, pericardium, small intestine, large intestine, liver, gall bladder, bladder, stomach, kidney, triple warmer and spleen [57, 58]. Each organ has a left and right pair of meridians with acupuncture points. Meridians run both on the surface and deep of the body and are in contact with each other and with organs. Meridians are responsible for regulating the relevant organ or system. It is also accepted that meridians can control pain throughout their course. The emergence of analgesia as a result of stimulation of an acupuncture point has been associated with inhibition of neural activity in the brainstem reticular formation and dorsal periaqueductal gray area, and it has been observed that acupuncture analgesia

may lose its effect after administration of betaendorphin antiserum into the third ventricle and hypophysectomy [59]. By inserting the acupuncture needle into the body, free nerve endings are stimulated and thus the release of endogenous opioids, which are known to have a role in pain control [60]. It is stated that enkephalins, one of the endogenous opioids whose levels increase in the central nervous system and plasma with the application of acupuncture, play a role in regulating the mental and psychological state. It is known that enkephalins have antidepressant, anticonvulsive and anti-anxiety effects. In addition to endogenous opioids, an increase in serotonin levels in the central nervous system has been observed with acupuncture practice [61].

Acupuncture increases local blood flow [62]. In addition, recent studies report that acupuncture also improves neuropathic pain and pain catastrophizing properties in FMS patients [63, 64]. The most common use of acupuncture in humans is chronic pain [65].

The effectiveness of acupuncture in fibromyalgia is measured with different scales. These are the Fibromyalgia severity scale (FSS), the Fibromyalgia Impact Questionnaire (FEAS) and the visual analog scale (VAS). Karatay et al. in a randomized and placebo-controlled study on the effects of acupuncture treatment on serotonin and Substance P levels and fibromyalgia symptoms, in both true acupuncture and pseudo/placebo acupuncture groups; At the end of 1 month, he reported positive results in terms of quality of life, number of tender points, pain, fatigue and depression. Evaluation of the results in this study was made by physical examination, VAS, FEAS, Back depression scale. The positive effect in the study did not exceed 7 months. While serum serotonin levels were increased in patients who underwent real acupuncture, substance-P levels were found to be decreased. While no change was found in Substance P levels in sham acupuncture, serum serotonin levels increased. In addition, the FEAS score did not change in the pseudo-acupuncture group [66].

In a systematic review study comparing complementary and alternative treatment methods for instance homeopathy, osteopathy, acupuncture, aromatherapy, herbal therapy, chiropractic, reflexology and hypnotherapy, acupuncture was reported to be the most effective method [67]. Yuksel et al. reported that there was no statistical difference between true acupuncture and transctaneous electrical nerve stimulation (TENS) in VAS pain score, fatigue, and FEAS score. TENS and real acupuncture increase EEG inhibitory activity and also reduce pain [68].

The literature supports the effectiveness of coenzyme Q10, alpha-lipoic acid, vitamin D and tryptophan in the treatment of FMS. Migratens, a nutraceutic product, consists of these ingredients. In a study comparing acupuncture and

Migratens, acupuncture treatment statistically significantly reduced pain at 1, 3, and 6 months and improved quality of life [69]. There are several studies reporting varying results comparing acupuncture versus placebo therapy in fibromyalgia. While there are studies reporting that there is no significant difference between placebo treatment and acupuncture treatment, there are also studies that favor acupuncture over placebo [70, 71]. Vas et al. investigated the efficacy of acupuncture in 153 FMS patients. They reported that acupuncture treatment, which was applied in addition to the drug treatments that the patients were currently using, provided a greater improvement in pain intensity compared to the placebo acupuncture group, and the effect of this treatment lasted for 1 year [72]. Almutairi et al. in a meta-analysis conducted by FMS patients, acupuncture, intravenous lidocaine and diet, physiotherapy and pseudo/placebo treatments were compared and it was found that acupuncture reduced pain and depression and increased quality of life. Only a positive effect of physiotherapy on quality of life was found, and no superiority of iv lidocaine and diet over placebo treatment was reported [73]. Minakawa Y et al. investigated the effectiveness of scalp electroacupuncture in addition to conventional electroacupuncture applied to 4 extremities in a nonrandomized study of patients with FMS with persistent drug-resistant symptoms. They reported that the combination of conventional electroacupuncture with scalp electroacupuncture effectively reduced pain, improved quality of life, and reduced the drug dose of pregabalin in patients with FMS [74].

In another study, the effectiveness of conventional body acupuncture was investigated in patients with severe FMS who received standard drug therapy but did not respond to treatment. Patients who used 300 mg pregabalin and 60 mg duloxetine for at least 3 months but did not achieve remission were included in the study. Patients' LIV 3, LI 14, SP6, ST36, CV6, CV12, EX HN3 (Yin Tang) and CV 2O points were pinned. Double acupuncture points are needled bilaterally. The point selections were made according to the TCM principles and accordingly; LIV3+LI14 that activates Qi, ST36+SP6+CV6+CV12 that strengthens Qi and blood, CV20 that raises Qi, and Shen (Yin-Tang) that calms it were chosen. After eight weeks of treatment, acupuncture has been reported to be effective in catastrophizing pain and neuropathic pain properties in FMS [75].

Kim J. et al. as a result of a meta-analysis on real acupuncture and pseudo acupuncture in FMS; It has been reported that real acupuncture is effective in reducing pain, improving sleep quality and general condition in the short term compared to sham acupuncture in patients with FMS, but has no effect on fatigue due to FMS [76].

In a published survey study, patients with FMS were questioned about their satisfaction with pharmacological and non-pharmacological treatments and acupuncture; It has been reported to provide the highest level of satisfaction compared to diet, physiotherapy, exercise, psychotherapy and pharmacological treatments [77].

FMS treatment requires a multidisciplinary approach. As the first approach, education, exercise and psychological treatment and pharmacological initial treatments are performed. However, there may be difficulties in tolerating pharmacological treatments due to their side effects. A few of the patients continue with the initial option for one year from the start of pharmacological treatment. Treatment compliance of patients with FMS is also poor. Data on treatment conducted in the USA have shown that the concept of patient tolerability is limited as well as patient satisfaction [77, 78]. Polypharmacy is also a problem in these patients. A survey of FMS patients' perspectives on treatments investigated the self-reported outcomes and efficacy of pharmacological and non-pharmacological treatment use. Results show high acceptability rates for non-pharmacological treatments with lower side effects, despite similar degrees of efficacy [79]. It is seen that pain thresholds are reduced with acupuncture treatment in FMS patients. It is also noteworthy that anxiety, depression, fatigue, and sleep disorders also decrease in addition to pain [80]. There is moderate evidence that pain and stiffness improve with acupuncture treatment. On the other hand, the evidence is moderate that there is no difference between acupuncture and sham acupuncture in reducing pain or fatigue or improving sleep or general well-being. There has also been evidence that electroacupuncture is better at reducing pain and stiffness, as well as improving fatigue, sleep, and general well-being compared to manual acupuncture. It was observed that the effect lasted for up to one month but did not persist at the six-month follow-up. In this study, it was stated that acupuncture appears to be safe and patients with FMS may reflect using Electroacupuncture alone or in combination with medication and exercise [54].

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Chapter 7

Pairwise Granger Causality Tests Of New Cases In Covid-19 Pandemic Between Countries

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1. Introduction

The Covid-19 pandemic, which emerged in Wuhan, China in 2019 and affected the whole world, not only showed how unprepared all humanity is in many issues, but also revealed that nothing will be the same as before. Due to the ongoing epidemic, countries had to bring innovations and regulations in many areas such as health systems, education systems, working orders, transportation sectors, retail and service sectors, etc. At this stage, many fundamental changes had to be brought forward, perhaps thanks to the pandemic, with the thought that crises also create opportunities.

Some of the issues that today's world is advantageous in the Covid-19 pandemic were the developing technological infrastructure, laboratory studies and data collection technologies. The epidemic data that emerged in many countries are collected correctly and made ready for analysis. The data used in this study consists of daily Covid-19 data, which includes the countries whose data are recorded daily in the world. Due to the difference in the incidence of Covid-19 cases in the selected countries, 01.05.2020 has been taken as the start date of pandemic. Covid-19 data is taken from "https://ourworldindata.org/coronavirus[1]".

Daily Covid-19 cases differ from country to country. The number of recorded cases is quite high in some countries. A few questions can be asked about these high case numbers: First; Are there more cases due to overpopulation? Second; Are data records being logged correctly? Third; Are adequate measures being taken for increasing Covid-19 cases? Different answers can be given to these questions. This study focuses especially on the interaction between the selected (57) countries. For the analysis, daily Covid-19 data[2] of the selected countries are recorded properly from five different continents are selected. By taking the ratio of daily Covid-19 cases to country population density, population density is removed from the data and daily covid case comparison between countries is provided.

In the study; First of all, correlation values between daily new covid case rates by countries are calculated. In the second step; with the Hierarchical Cluster Analysis, countries are classified according to their correlation values. In the third step; In the clustering results, which is the most significant among these classifications, the cluster of countries in which four groups are separated was taken. In the fourth step; Causality analyzes of countries within each group were obtained using Pairwise Granger Causality Tests.

[1] Access Date: 11.12.2021.

[2] Lost records in Covid-19 case data are obtained from https://www.worldometers.info/coronavirus/.

The study consists of four parts. In the second part, explanations about the method used are given. In the third section, the results are given and explained in the accompanying tables. In the last section, the results obtained and the interaction of the Covid-19 pandemic between countries are evaluated.

2. Data and Methodology

Considering the general evaluation of causality, some basic definitions of causality can be given as follows:

- A relationship in a time sequence between occurrences, processes, or entities, where one always comes after the other.
- A connection between actual events, processes, or things and things that don't come from experiments.
- A connection between data from related time series that are subject to different conditions.
- A relationship between variables in which one has the efficiency of producing or modifying the other.
- A relationship between an idea and an experience.
- A relationship between an event or process and itself.
- A relationship between variables, one without which the other cannot occur.
- A relationship between an event, process or entity and its cause or explanation.

Hierarchical clustering is a bottom-up (agglomerative) clustering method. It starts by treating each element as an individual cluster, then gradually merges them into larger clusters. In particular, it selects the closest pair of clusters in each phase of hierarchical clustering and merges them into a new parent cluster. After $N-1$ repetitions, the method is repeated until only one cluster remains where N is the number of objects. A tree structure plot called a dendrogram can be used to describe the result of hierarchical clustering. (Xiao et.al. 2012)

The Pearson's correlation is utilized to measure the similarity between distinct row and column vectors. The Pearson's correlation coefficient r_{xy} between any two n-dimensional row and column vectors x and y can be calculate by Eq. 1.

$$Corr_{xy} = r_{xy} = \frac{n\sum_{i=1}^{n} x_i y_i - \left(\sum_{i=1}^{n} x_i\right)\left(\sum_{i=1}^{n} y_i\right)}{\sqrt{n\sum_{i=1}^{n} x_i^2 - \left(\sum_{i=1}^{n} x_i\right)^2}\sqrt{n\sum_{i=1}^{n} y_i^2 - \left(\sum_{i=1}^{n} y_i\right)^2}}. \quad (1)$$

The distance d between the row and column vectors x and y was determined as 1 minus their correlation coefficient since "distance" is more commonly used to show dissimilarity for clustering research than "similarity" given in Eq.2.

$$d_{xy} = 1 - r_{xy} = 1 - \frac{S_{xy}}{S_x S_y}. \quad (2)$$

Where S_{xy} represents the sample covariance, S_x and S_y represent the standard deviations of the row and column vectors x and y. The interpretation of the Eq. 2 is that the closer two vectors are, the shorter their distance will be. As the correlation increases to 1, the distance will approach zero.

There is another distance measurement called cophenetic distance D_{rs} defined as intercluster distance between two clusters r and s determined to merged into a new cluster at a joint of the dendrogram in addition to their original distance d_{xy} for any two vectors x and y given in Eq.2.

The cophenetic distance can be calculated many ways of which single, complete, and average linkage are used frequently given below; respectively

$$D_{rs} = \min\left\{d_{xy} : x \in r,\ y \in s\right\} \quad (3)$$

$$D_{rs} = \max\left\{d_{xy} : x \in r,\ y \in s\right\} \quad (4)$$

$$D_{rs} = \frac{\sum_{y=1}^{N_s}\sum_{x=1}^{N_r} d_{xy}}{N_s . N_r}. \quad (5)$$

Because it yields better cophenetic correlations than the other approaches and because it has a higher tolerance for outliers than the complete linkage, the average linkage strategy was employed in this study to determine cophenetic distance. The cophenetic correlation, which is defined as the correlation between

the original and cophenetic distances, assesses how well the dendrogram illustrates the pattern of similarities or differences among clusters. The outcome of the cophenetic correlation demonstrates the caliber of the clustering analysis.

3. Empirical Results

This section contains the fundamental results of the analysis. In order to be able to compare new Covid-19 cases by country, it would be more accurate to compare the covid rates depending on the populations by country, since the frequency of new Covid-19 cases varies according to the population of the country. In the study, the ratio of daily new cases to the population is taken for the analysis and the effect of population density is purified from the number of cases for comparing the daily new covid cases by country. The aim is to find out casual effect of the daily new covid cases between countries. The purpose is to cluster for identifying relatively homogeneous groups of the countries based on correlations on daily new covid rates relative to country populations by hierarchical cluster analysis. The country groups obtained as a result of the clustering are given in Table 1.

Table 1. The Sets of the Countries

1		**2**	**3**	**4**
AUSTRIA	SWEDEN	MEXICO	ARGENTINA	COLOMBIA
BELGIUM	UNITED KINGDOM	GUATEMALA	BRAZIL	KYRGYZSTAN
BULGARIA	CANADA	CUBA	CHILE	SOUTHAFRICA
CZECHIA	UNITED STATES	JAMAICA	PERU	TUNISIA
DENMARK	AUSTRALIA	VENEZUELA	PARAGUAY	UGANDA
FINLAND	NEW ZEALAND	IRAN	INDIA	ZIMBABWE
FRANCE	ARMENIA	JAPAN	PAKISTAN	ALGERIA
GERMANY	AZERBAIJAN	PHILIPPINES	SAUDIARABIA	**7 Countries**
ITALY	GEORGIA	SOUTHKOREA	EGYPT	
NETHERLANDS	ISREAL	THAILAND	**9 Countries**	
NORWAY	TURKEY	MALAYSIA		
RUSSIA	NIGERIA	ANGOLA		
SPAIN		LIBYA		
25 Countries		KENYA		
		ETHIOPIA		
		MOROCCA		
		16 Countries		

As seen in Table-1; 27 of the 57 countries surveyed are in the first group; 16 of them are in the second group, 9 of them are in the third group and 7 of them are in the fourth group.

Granger causality test has an important role in time series analysis (Granger, 1969). It is a statistical hypothesis test to determine whether the time series is useful in estimating other time series using this test. The causality between two variables in the time series examined using the Granger causality test is investigated. The probabilistic explanation of causality is tried to be revealed by using the method. By the help of Granger causality test, cause and effect can be examined. Granger-causality represents a particular type of causality related to precedence. Granger-causality test can also be used as part of a strategy to determine whether variables are weakly, strongly, super exogenous or not. Granger Causality tests among the countries in the first group is given in the Table 2.

Table 2. Granger Causality Test Results of the Countries in the First Group
(X: Country A does not Granger Cause Country B)

Pairwise Granger Causality Tests
Date: 12/21/21 Time: 20:43
Sample: 5/01/2020 11/12/2021
Lags: 2

	BELGIUM	AUSTRIA	BULGARIA	CZECHIA	DENMARK	FINLAND	FRANCE	GERMANY	ITALY	NETHERLANDS	NORWAY	RUSSIA	SPAIN	SWEDEN	UK	CANADA	USA	AUSTRALIA	N. ZEALAND	ARMENIA	AZERBAIJAN	GEORGIA	ISREAL	TURKEY	NIGERIA
BELGIUM		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AUSTRIA	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BULGARIA	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CZECHIA	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DENMARK	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FINLAND	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FRANCE	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
GERMANY	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ITALY	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NETHERLANDS	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NORWAY	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
RUSSIA	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
SPAIN	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
SWEDEN	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
UK	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X

CANADA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
USA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
AUSTRALIA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
N. ZEALAND	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
ARMENIA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
AZERBAIJAN	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
GEORGIA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
ISREAL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
TURKEY	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
NIGERIA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Granger Causality tests among countries in the second group are given in Table 3.

Table 3. Granger Causality Test Results of the Countries in the Second Group

(X: Country A does not Granger Cause Country B)

Pairwise Granger Causality Tests
Date: 12/21/21 Time: 20:43
Sample: 5/01/2020 11/12/2021
Lags: 2

	MEXICO	GUATEMALA	CUBA	JAMAICA	VENEZUELA	IRAN	JAPAN	PHILIPPINES	SOUTHKOREA	THAILAND	MALAYSIA	ANGOLA	LIBYA	KENYA	ETHIOPIA	MOROCCA	MEXICO	GUATEMALA	CUBA
MEXICO		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
GUATEMALA	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CUBA	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
JAMAICA	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VENEZUELA	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
IRAN	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
JAPAN	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
PHILIPPINES	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
SOUTHKOREA	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
THAILAND	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
MALAYSIA	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
ANGOLA	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
LIBYA	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
KENYA	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
ETHIOPIA	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
MOROCCA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
MEXICO	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X

GUATEMALA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
CUBA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Granger Causality tests among countries in the third group are given in Table 4.

Table 4. Granger Causality Test Results of the Countries in the Third Group

(X: Country A does not Granger Cause Country B)

Pairwise Granger Causality Tests
Date: 12/21/21 Time: 20:48
Sample: 5/01/2020 11/12/2021
Lags: 2

	ARGENTINA	BRAZIL	CHILE	PERU	PARAGUAY	INDIA	PAKISTAN	SAUDIARABIA	EGYPT	SAUDIARABIA	EGYPT	ARGENTINA	BRAZIL	CHILE	PERU	PARAGUAY
ARGENTINA		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BRAZIL	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CHILE	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
PERU	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
PARAGUAY	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
INDIA	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
PAKISTAN	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
SAUDIARABIA	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
EGYPT	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
ARGENTINA	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
BRAZIL	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
CHILE	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
PERU	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
PARAGUAY	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X

Granger Causality Test Results of the Countries in the Fourth Group are given in Table 5

Table 5. Granger Causality Test Results of the Countries in the Fourth Group

(X: Country A does not Granger Cause Country B)

Pairwise Granger Causality Tests
Date: 12/21/21 Time: 20:50
Sample: 5/01/2020 11/12/2021
Lags: 2

	COLOMBIA	KYRGYZSTAN	SOUTHAFRICA	TUNISIA	UGANDA	ZIMBABWE	ZIMBABWE	ALGERIA
COLOMBIA		X	X	X	X	X	X	X
KYRGYZSTAN	X		X	X	X	X	X	X

SOUTHAFRICA	X	X		X	X	X	X	X
TUNISIA	X	X	X		X	X	X	X
UGANDA	X	X	X	X		X	X	X
ZIMBABWE	X	X	X	X	X		X	X
ALGERIA	X	X	X	X	X	X	x	

As a result of the tests carried out to analyze the increases in the Covid-19 epidemic and the spread, it is seen that the increases in the countries are not the cause of each other.

4. Conclusion

Since the Covid-19 pandemic first appeared, the priority has been given to stop the spread of the pandemic. In the second stage, medical solutions have begun to develop against the disease. Many academic studies have also been carried out on the subject, including many different approaches. In this study, first of all, countries are divided into groups. Thus, similar countries in terms of population densities are evaluated among themselves. In the second step of the study, Granger Causality tests among countries provide information about the interaction between countries.

References

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Xiao Liu, Xiao-Hong Zhu, Peihua Qiu, and Wei Chen (2012). A Correlation-Matrix-Based Hierarchical Clustering Method for Functional Connectivity Analysis, J Neurosci Methods. 2012 October 15; 211(1): 94–102. doi:10.1016/j.jneumeth.2012.08.016.

Appendix-A

Pairwise Granger Causality Tests
Date: 12/21/21 Time: 12:44
Sample: 5/01/2020 11/12/2021
Lags: 1

Null Hypothesis:	Obs	F-Statistic	Prob.
BELGIUM does not Granger Cause AUSTRIA	560	11.4644	0.0008
AUSTRIA does not Granger Cause BELGIUM		0.76635	0.3817
BULGARIA does not Granger Cause AUSTRIA	560	129.859	3.E-27
AUSTRIA does not Granger Cause BULGARIA		35.2304	5.E-09
CZECHIA does not Granger Cause AUSTRIA	560	9.17427	0.0026
AUSTRIA does not Granger Cause CZECHIA		0.64909	0.4208
DENMARK does not Granger Cause AUSTRIA	560	5.04499	0.0251
AUSTRIA does not Granger Cause DENMARK		21.4144	5.E-06
FINLAND does not Granger Cause AUSTRIA	560	2.19964	0.1386
AUSTRIA does not Granger Cause FINLAND		11.5407	0.0007
FRANCE does not Granger Cause AUSTRIA	560	0.19743	0.6570
AUSTRIA does not Granger Cause FRANCE		12.6299	0.0004
GERMANY does not Granger Cause AUSTRIA	560	26.3802	4.E-07
AUSTRIA does not Granger Cause GERMANY		41.9823	2.E-10
ITALY does not Granger Cause AUSTRIA	560	4.99845	0.0258
AUSTRIA does not Granger Cause ITALY		3.54596	0.0602
NETHERLANDS does not Granger Cause AUSTRIA	560	0.79686	0.3724
AUSTRIA does not Granger Cause NETHERLANDS		14.3222	0.0002
NORWAY does not Granger Cause AUSTRIA	560	51.5373	2.E-12
AUSTRIA does not Granger Cause NORWAY		6.87026	0.0090
RUSSIA does not Granger Cause AUSTRIA	560	5.37197	0.0208
AUSTRIA does not Granger Cause RUSSIA		6.86844	0.0090
SPAIN does not Granger Cause AUSTRIA	560	0.60807	0.4358
AUSTRIA does not Granger Cause SPAIN		0.73122	0.3929
SWEDEN does not Granger Cause AUSTRIA	560	0.71253	0.3990
AUSTRIA does not Granger Cause SWEDEN		1.39934	0.2373
UNITEDKINGDOM does not Granger Cause AUSTRIA	560	2.32125	0.1282
AUSTRIA does not Granger Cause UNITEDKINGDOM		0.17221	0.6783
CANADA does not Granger Cause AUSTRIA	560	1.06234	0.3031
AUSTRIA does not Granger Cause CANADA		15.9197	7.E-05
UNITEDSTATES does not Granger Cause AUSTRIA	560	0.51948	0.4714
AUSTRIA does not Granger Cause UNITEDSTATES		10.7754	0.0011
AUSTRALIA does not Granger Cause AUSTRIA	560	3.45723	0.0635
AUSTRIA does not Granger Cause AUSTRALIA		1.02089	0.3127
NEWZEALAND does not Granger Cause AUSTRIA	560	18.3582	2.E-05
AUSTRIA does not Granger Cause NEWZEALAND		5.20866	0.0229
ARMENIA does not Granger Cause AUSTRIA	560	0.35213	0.5531
AUSTRIA does not Granger Cause ARMENIA		6.74544	0.0096
AZERBAIJAN does not Granger Cause AUSTRIA	560	0.26132	0.6094
AUSTRIA does not Granger Cause AZERBAIJAN		6.15975	0.0134
GEORGIA does not Granger Cause AUSTRIA	560	7.50281	0.0064
AUSTRIA does not Granger Cause GEORGIA		6.24519	0.0127
ISREAL does not Granger Cause AUSTRIA	560	0.26116	0.6095
AUSTRIA does not Granger Cause ISREAL		0.61459	0.4334
TURKEY does not Granger Cause AUSTRIA	560	0.33994	0.5601
AUSTRIA does not Granger Cause TURKEY		1.68800	0.1944
NIGERIA does not Granger Cause AUSTRIA	560	0.35960	0.5490
AUSTRIA does not Granger Cause NIGERIA		0.84872	0.3573
BULGARIA does not Granger Cause BELGIUM	560	53.1878	1.E-12
BELGIUM does not Granger Cause BULGARIA		8.41871	0.0039

CZECHIA does not Granger Cause BELGIUM	560	14.1811	0.0002
BELGIUM does not Granger Cause CZECHIA		5.1E-05	0.9943
DENMARK does not Granger Cause BELGIUM	560	1.23140	0.2676
BELGIUM does not Granger Cause DENMARK		5.64695	0.0178
FINLAND does not Granger Cause BELGIUM	560	1.88974	0.1698
BELGIUM does not Granger Cause FINLAND		1.72037	0.1902
FRANCE does not Granger Cause BELGIUM	560	0.18416	0.6680
BELGIUM does not Granger Cause FRANCE		32.3284	2.E-08
GERMANY does not Granger Cause BELGIUM	560	7.96850	0.0049
BELGIUM does not Granger Cause GERMANY		5.63574	0.0179
ITALY does not Granger Cause BELGIUM	560	0.44468	0.5051
BELGIUM does not Granger Cause ITALY		12.5403	0.0004
NETHERLANDS does not Granger Cause BELGIUM	560	5.10174	0.0243
BELGIUM does not Granger Cause NETHERLANDS		12.3230	0.0005
NORWAY does not Granger Cause BELGIUM	560	14.0929	0.0002
BELGIUM does not Granger Cause NORWAY		1.73843	0.1879
RUSSIA does not Granger Cause BELGIUM	560	2.64173	0.1047
BELGIUM does not Granger Cause RUSSIA		12.8514	0.0004
SPAIN does not Granger Cause BELGIUM	560	2.02146	0.1556
BELGIUM does not Granger Cause SPAIN		0.15959	0.6897
SWEDEN does not Granger Cause BELGIUM	560	5.06709	0.0248
BELGIUM does not Granger Cause SWEDEN		0.67617	0.4113
UNITEDKINGDOM does not Granger Cause BELGIUM	560	1.69721	0.1932
BELGIUM does not Granger Cause UNITEDKINGDOM		0.01011	0.9199
CANADA does not Granger Cause BELGIUM	560	3.79312	0.0520
BELGIUM does not Granger Cause CANADA		4.16985	0.0416
UNITEDSTATES does not Granger Cause BELGIUM	560	0.22278	0.6371
BELGIUM does not Granger Cause UNITEDSTATES		0.61916	0.4317
AUSTRALIA does not Granger Cause BELGIUM	560	1.19884	0.2740
BELGIUM does not Granger Cause AUSTRALIA		1.06920	0.3016
NEWZEALAND does not Granger Cause BELGIUM	560	6.33324	0.0121
BELGIUM does not Granger Cause NEWZEALAND		2.95037	0.0864
ARMENIA does not Granger Cause BELGIUM	560	0.02151	0.8834
BELGIUM does not Granger Cause ARMENIA		21.4223	5.E-06
AZERBAIJAN does not Granger Cause BELGIUM	560	0.00490	0.9442
BELGIUM does not Granger Cause AZERBAIJAN		0.41036	0.5220
GEORGIA does not Granger Cause BELGIUM	560	3.13511	0.0772
BELGIUM does not Granger Cause GEORGIA		1.40051	0.2371
ISREAL does not Granger Cause BELGIUM	560	0.41185	0.5213
BELGIUM does not Granger Cause ISREAL		2.06134	0.1516
TURKEY does not Granger Cause BELGIUM	560	1.65197	0.1992
BELGIUM does not Granger Cause TURKEY		1.14852	0.2843
NIGERIA does not Granger Cause BELGIUM	560	1.07065	0.3012
BELGIUM does not Granger Cause NIGERIA		3.77934	0.0524
CZECHIA does not Granger Cause BULGARIA	560	0.35168	0.5534
BULGARIA does not Granger Cause CZECHIA		43.2565	1.E-10
DENMARK does not Granger Cause BULGARIA	560	5.09548	0.0244
BULGARIA does not Granger Cause DENMARK		18.2728	2.E-05
FINLAND does not Granger Cause BULGARIA	560	14.1294	0.0002
BULGARIA does not Granger Cause FINLAND		65.6647	3.E-15
FRANCE does not Granger Cause BULGARIA	560	1.48392	0.2237
BULGARIA does not Granger Cause FRANCE		70.1333	5.E-16
GERMANY does not Granger Cause BULGARIA	560	0.16068	0.6887
BULGARIA does not Granger Cause GERMANY		98.4469	2.E-21

ITALY does not Granger Cause BULGARIA	560	10.4234	0.0013
BULGARIA does not Granger Cause ITALY		88.0464	2.E-19
NETHERLANDS does not Granger Cause BULGARIA	560	11.1379	0.0009
BULGARIA does not Granger Cause NETHERLANDS		47.9720	1.E-11
NORWAY does not Granger Cause BULGARIA	560	16.2034	6.E-05
BULGARIA does not Granger Cause NORWAY		0.58836	0.4434
RUSSIA does not Granger Cause BULGARIA	560	17.1212	4.E-05
BULGARIA does not Granger Cause RUSSIA		5.15157	0.0236
SPAIN does not Granger Cause BULGARIA	560	1.93266	0.1650
BULGARIA does not Granger Cause SPAIN		1.93740	0.1645
SWEDEN does not Granger Cause BULGARIA	560	1.28742	0.2570
BULGARIA does not Granger Cause SWEDEN		16.8590	5.E-05
UNITEDKINGDOM does not Granger Cause BULGARIA	560	4.09619	0.0435
BULGARIA does not Granger Cause UNITEDKINGDOM		0.67225	0.4126
CANADA does not Granger Cause BULGARIA	560	5.23507	0.0225
BULGARIA does not Granger Cause CANADA		0.02684	0.8699
UNITEDSTATES does not Granger Cause BULGARIA	560	0.24045	0.6241
BULGARIA does not Granger Cause UNITEDSTATES		0.17665	0.6744
AUSTRALIA does not Granger Cause BULGARIA	560	9.58666	0.0021
BULGARIA does not Granger Cause AUSTRALIA		0.84635	0.3580
NEWZEALAND does not Granger Cause BULGARIA	560	19.9951	9.E-06
BULGARIA does not Granger Cause NEWZEALAND		15.0925	0.0001
ARMENIA does not Granger Cause BULGARIA	560	20.4227	8.E-06
BULGARIA does not Granger Cause ARMENIA		233.056	3.E-44
AZERBAIJAN does not Granger Cause BULGARIA	560	18.0626	3.E-05
BULGARIA does not Granger Cause AZERBAIJAN		98.2285	2.E-21
GEORGIA does not Granger Cause BULGARIA	560	6.97375	0.0085
BULGARIA does not Granger Cause GEORGIA		70.6258	4.E-16
ISREAL does not Granger Cause BULGARIA	560	0.16068	0.6887
BULGARIA does not Granger Cause ISREAL		2.51649	0.1132
TURKEY does not Granger Cause BULGARIA	560	12.1822	0.0005
BULGARIA does not Granger Cause TURKEY		7.26496	0.0072
NIGERIA does not Granger Cause BULGARIA	560	7.14781	0.0077
BULGARIA does not Granger Cause NIGERIA		1.01543	0.3140
DENMARK does not Granger Cause CZECHIA	560	6.16270	0.0133
CZECHIA does not Granger Cause DENMARK		2.43305	0.1194
FINLAND does not Granger Cause CZECHIA	560	0.03932	0.8429
CZECHIA does not Granger Cause FINLAND		4.08845	0.0437
FRANCE does not Granger Cause CZECHIA	560	5.60390	0.0183
CZECHIA does not Granger Cause FRANCE		37.9495	1.E-09
GERMANY does not Granger Cause CZECHIA	560	4.37676	0.0369
CZECHIA does not Granger Cause GERMANY		3.76029	0.0530
ITALY does not Granger Cause CZECHIA	560	0.06061	0.8056
CZECHIA does not Granger Cause ITALY		45.6618	4.E-11
NETHERLANDS does not Granger Cause CZECHIA	560	5.10090	0.0243
CZECHIA does not Granger Cause NETHERLANDS		21.3717	5.E-06
NORWAY does not Granger Cause CZECHIA	560	16.5979	5.E-05
CZECHIA does not Granger Cause NORWAY		0.39617	0.5293
RUSSIA does not Granger Cause CZECHIA	560	2.89754	0.0893
CZECHIA does not Granger Cause RUSSIA		0.65459	0.4188
SPAIN does not Granger Cause CZECHIA	560	8.10979	0.0046
CZECHIA does not Granger Cause SPAIN		0.10359	0.7477
SWEDEN does not Granger Cause CZECHIA	560	13.5118	0.0003
CZECHIA does not Granger Cause SWEDEN		1.56800	0.2110

UNITEDKINGDOM does not Granger Cause CZECHIA	560	2.27355	0.1322
CZECHIA does not Granger Cause UNITEDKINGDOM		0.00727	0.9321
CANADA does not Granger Cause CZECHIA	560	16.6333	5.E-05
CZECHIA does not Granger Cause CANADA		6.88917	0.0089
UNITEDSTATES does not Granger Cause CZECHIA	560	3.85929	0.0500
CZECHIA does not Granger Cause UNITEDSTATES		7.74427	0.0056
AUSTRALIA does not Granger Cause CZECHIA	560	0.47080	0.4929
CZECHIA does not Granger Cause AUSTRALIA		0.66794	0.4141
NEWZEALAND does not Granger Cause CZECHIA	560	0.36004	0.5487
CZECHIA does not Granger Cause NEWZEALAND		0.67362	0.4121
ARMENIA does not Granger Cause CZECHIA	560	1.79384	0.1810
CZECHIA does not Granger Cause ARMENIA		14.0112	0.0002
AZERBAIJAN does not Granger Cause CZECHIA	560	0.72242	0.3957
CZECHIA does not Granger Cause AZERBAIJAN		0.00475	0.9451
GEORGIA does not Granger Cause CZECHIA	560	0.09435	0.7588
CZECHIA does not Granger Cause GEORGIA		2.00551	0.1573
ISREAL does not Granger Cause CZECHIA	560	4.34379	0.0376
CZECHIA does not Granger Cause ISREAL		0.45844	0.4986
TURKEY does not Granger Cause CZECHIA	560	0.16913	0.6810
CZECHIA does not Granger Cause TURKEY		2.33774	0.1268
NIGERIA does not Granger Cause CZECHIA	560	0.64179	0.4234
CZECHIA does not Granger Cause NIGERIA		0.00122	0.9721
FINLAND does not Granger Cause DENMARK	560	4.68653	0.0308
DENMARK does not Granger Cause FINLAND		6.95460	0.0086
FRANCE does not Granger Cause DENMARK	560	1.09772	0.2952
DENMARK does not Granger Cause FRANCE		4.62242	0.0320
GERMANY does not Granger Cause DENMARK	560	30.7641	5.E-08
DENMARK does not Granger Cause GERMANY		48.7601	8.E-12
ITALY does not Granger Cause DENMARK	560	0.37644	0.5398
DENMARK does not Granger Cause ITALY		2.80151	0.0947
NETHERLANDS does not Granger Cause DENMARK	560	23.5302	2.E-06
DENMARK does not Granger Cause NETHERLANDS		19.1944	1.E-05
NORWAY does not Granger Cause DENMARK	560	14.9758	0.0001
DENMARK does not Granger Cause NORWAY		5.96026	0.0149
RUSSIA does not Granger Cause DENMARK	560	22.5370	3.E-06
DENMARK does not Granger Cause RUSSIA		0.51976	0.4712
SPAIN does not Granger Cause DENMARK	560	0.02290	0.8798
DENMARK does not Granger Cause SPAIN		0.52052	0.4709
SWEDEN does not Granger Cause DENMARK	560	3.07852	0.0799
DENMARK does not Granger Cause SWEDEN		4.63455	0.0318
UNITEDKINGDOM does not Granger Cause DENMARK	560	3.66312	0.0561
DENMARK does not Granger Cause UNITEDKINGDOM		6.87817	0.0090
CANADA does not Granger Cause DENMARK	560	4.27360	0.0392
DENMARK does not Granger Cause CANADA		19.5490	1.E-05
UNITEDSTATES does not Granger Cause DENMARK	560	3.07207	0.0802
DENMARK does not Granger Cause UNITEDSTATES		31.3648	3.E-08
AUSTRALIA does not Granger Cause DENMARK	560	1.32735	0.2498
DENMARK does not Granger Cause AUSTRALIA		0.17859	0.6727
NEWZEALAND does not Granger Cause DENMARK	560	12.7607	0.0004
DENMARK does not Granger Cause NEWZEALAND		3.94378	0.0475
ARMENIA does not Granger Cause DENMARK	560	5.09696	0.0244
DENMARK does not Granger Cause ARMENIA		2.09987	0.1479
AZERBAIJAN does not Granger Cause DENMARK	560	11.3770	0.0008
DENMARK does not Granger Cause AZERBAIJAN		3.57199	0.0593

GEORGIA does not Granger Cause DENMARK	560	21.1634	5.E-06
DENMARK does not Granger Cause GEORGIA		8.03577	0.0048
ISREAL does not Granger Cause DENMARK	560	0.47233	0.4922
DENMARK does not Granger Cause ISREAL		0.82590	0.3639
TURKEY does not Granger Cause DENMARK	560	7.33011	0.0070
DENMARK does not Granger Cause TURKEY		4.01039	0.0457
NIGERIA does not Granger Cause DENMARK	560	1.65724	0.1985
DENMARK does not Granger Cause NIGERIA		1.78625	0.1819
FRANCE does not Granger Cause FINLAND	560	1.19699	0.2744
FINLAND does not Granger Cause FRANCE		5.40715	0.0204
GERMANY does not Granger Cause FINLAND	560	11.9160	0.0006
FINLAND does not Granger Cause GERMANY		4.78758	0.0291
ITALY does not Granger Cause FINLAND	560	1.73741	0.1880
FINLAND does not Granger Cause ITALY		0.05900	0.8082
NETHERLANDS does not Granger Cause FINLAND	560	5.37950	0.0207
FINLAND does not Granger Cause NETHERLANDS		9.61999	0.0020
NORWAY does not Granger Cause FINLAND	560	75.2110	5.E-17
FINLAND does not Granger Cause NORWAY		10.3028	0.0014
RUSSIA does not Granger Cause FINLAND	560	22.8564	2.E-06
FINLAND does not Granger Cause RUSSIA		2.01404	0.1564
SPAIN does not Granger Cause FINLAND	560	3.71725	0.0544
FINLAND does not Granger Cause SPAIN		2.23470	0.1355
SWEDEN does not Granger Cause FINLAND	560	9.94587	0.0017
FINLAND does not Granger Cause SWEDEN		1.28462	0.2575
UNITEDKINGDOM does not Granger Cause FINLAND	560	13.1221	0.0003
FINLAND does not Granger Cause UNITEDKINGDOM		0.05520	0.8143
CANADA does not Granger Cause FINLAND	560	9.13712	0.0026
FINLAND does not Granger Cause CANADA		7.28782	0.0072
UNITEDSTATES does not Granger Cause FINLAND	560	9.52790	0.0021
FINLAND does not Granger Cause UNITEDSTATES		10.5320	0.0012
AUSTRALIA does not Granger Cause FINLAND	560	7.20028	0.0075
FINLAND does not Granger Cause AUSTRALIA		1.99507	0.1584
NEWZEALAND does not Granger Cause FINLAND	560	11.6694	0.0007
FINLAND does not Granger Cause NEWZEALAND		5.96093	0.0149
ARMENIA does not Granger Cause FINLAND	560	0.07974	0.7778
FINLAND does not Granger Cause ARMENIA		2.05173	0.1526
AZERBAIJAN does not Granger Cause FINLAND	560	4.57061	0.0330
FINLAND does not Granger Cause AZERBAIJAN		5.96063	0.0149
GEORGIA does not Granger Cause FINLAND	560	20.0723	9.E-06
FINLAND does not Granger Cause GEORGIA		2.24576	0.1345
ISREAL does not Granger Cause FINLAND	560	9.53096	0.0021
FINLAND does not Granger Cause ISREAL		3.04609	0.0815
TURKEY does not Granger Cause FINLAND	560	19.1995	1.E-05
FINLAND does not Granger Cause TURKEY		0.84684	0.3578
GERMANY does not Granger Cause FRANCE	560	29.6337	8.E-08
FRANCE does not Granger Cause GERMANY		0.06983	0.7917
ITALY does not Granger Cause FRANCE	560	47.3558	2.E-11
FRANCE does not Granger Cause ITALY		1.43291	0.2318
NETHERLANDS does not Granger Cause FRANCE	560	29.9112	7.E-08
FRANCE does not Granger Cause NETHERLANDS		2.7E-06	0.9987
NORWAY does not Granger Cause FRANCE	560	28.6680	1.E-07
FRANCE does not Granger Cause NORWAY		0.34938	0.5547
RUSSIA does not Granger Cause FRANCE	560	0.10340	0.7479
FRANCE does not Granger Cause RUSSIA		2.04027	0.1537

SPAIN does not Granger Cause FRANCE	560	37.5396	2.E-09
FRANCE does not Granger Cause SPAIN		0.07362	0.7862
SWEDEN does not Granger Cause FRANCE	560	61.6509	2.E-14
FRANCE does not Granger Cause SWEDEN		4.16992	0.0416
UNITEDKINGDOM does not Granger Cause FRANCE	560	1.21445	0.2709
FRANCE does not Granger Cause UNITEDKINGDOM		0.05737	0.8108
CANADA does not Granger Cause FRANCE	560	47.6683	1.E-11
FRANCE does not Granger Cause CANADA		25.8727	5.E-07
UNITEDSTATES does not Granger Cause FRANCE	560	15.6051	9.E-05
FRANCE does not Granger Cause UNITEDSTATES		3.97450	0.0467
AUSTRALIA does not Granger Cause FRANCE	560	4.52876	0.0338
FRANCE does not Granger Cause AUSTRALIA		0.00234	0.9614
NEWZEALAND does not Granger Cause FRANCE	560	1.37596	0.2413
FRANCE does not Granger Cause NEWZEALAND		0.16684	0.6831
ARMENIA does not Granger Cause FRANCE	560	5.99794	0.0146
FRANCE does not Granger Cause ARMENIA		0.90431	0.3420
AZERBAIJAN does not Granger Cause FRANCE	560	0.58779	0.4436
FRANCE does not Granger Cause AZERBAIJAN		2.32002	0.1283
GEORGIA does not Granger Cause FRANCE	560	0.68751	0.4074
FRANCE does not Granger Cause GEORGIA		4.64631	0.0315
ISREAL does not Granger Cause FRANCE	560	2.89195	0.0896
FRANCE does not Granger Cause ISREAL		0.10191	0.7497
TURKEY does not Granger Cause FRANCE	560	11.8623	0.0006
FRANCE does not Granger Cause TURKEY		1.76240	0.1849
NIGERIA does not Granger Cause FRANCE	560	0.10458	0.7465
FRANCE does not Granger Cause NIGERIA		1.38616	0.2396
ITALY does not Granger Cause GERMANY	560	9.88904	0.0018
GERMANY does not Granger Cause ITALY		39.5283	7.E-10
NETHERLANDS does not Granger Cause GERMANY	560	40.0165	5.E-10
GERMANY does not Granger Cause NETHERLANDS		76.9610	2.E-17
NORWAY does not Granger Cause GERMANY	560	68.5620	9.E-16
GERMANY does not Granger Cause NORWAY		0.25664	0.6126
RUSSIA does not Granger Cause GERMANY	560	23.6150	2.E-06
GERMANY does not Granger Cause RUSSIA		11.7781	0.0006
SPAIN does not Granger Cause GERMANY	560	0.92542	0.3365
GERMANY does not Granger Cause SPAIN		0.00027	0.9869
SWEDEN does not Granger Cause GERMANY	560	19.9173	1.E-05
GERMANY does not Granger Cause SWEDEN		0.89733	0.3439
UNITEDKINGDOM does not Granger Cause GERMANY	560	9.18441	0.0026
GERMANY does not Granger Cause UNITEDKINGDOM		5.80348	0.0163
CANADA does not Granger Cause GERMANY	560	80.9165	4.E-18
GERMANY does not Granger Cause CANADA		33.5193	1.E-08
UNITEDSTATES does not Granger Cause GERMANY	560	17.4885	3.E-05
GERMANY does not Granger Cause UNITEDSTATES		18.1487	2.E-05
AUSTRALIA does not Granger Cause GERMANY	560	1.62831	0.2025
GERMANY does not Granger Cause AUSTRALIA		0.17215	0.6784
NEWZEALAND does not Granger Cause GERMANY	560	11.5859	0.0007
GERMANY does not Granger Cause NEWZEALAND		5.04676	0.0251
ARMENIA does not Granger Cause GERMANY	560	3.45457	0.0636
GERMANY does not Granger Cause ARMENIA		34.6376	7.E-09
AZERBAIJAN does not Granger Cause GERMANY	560	12.8945	0.0004
GERMANY does not Granger Cause AZERBAIJAN		10.5725	0.0012
GEORGIA does not Granger Cause GERMANY	560	7.66650	0.0058
GERMANY does not Granger Cause GEORGIA		1.01255	0.3147

ISREAL does not Granger Cause GERMANY	560	0.34205	0.5589
GERMANY does not Granger Cause ISREAL		0.70930	0.4000
TURKEY does not Granger Cause GERMANY	560	28.8762	1.E-07
GERMANY does not Granger Cause TURKEY		3.80689	0.0515
NIGERIA does not Granger Cause GERMANY	560	0.58914	0.4431
GERMANY does not Granger Cause NIGERIA		0.03767	0.8462
NETHERLANDS does not Granger Cause ITALY	560	1.89653	0.1690
ITALY does not Granger Cause NETHERLANDS		0.03711	0.8473
NORWAY does not Granger Cause ITALY	560	21.0460	6.E-06
ITALY does not Granger Cause NORWAY		0.25111	0.6165
RUSSIA does not Granger Cause ITALY	560	0.14027	0.7082
ITALY does not Granger Cause RUSSIA		0.03322	0.8554
SPAIN does not Granger Cause ITALY	560	19.9521	1.E-05
ITALY does not Granger Cause SPAIN		2.4E-06	0.9988
SWEDEN does not Granger Cause ITALY	560	69.5982	6.E-16
ITALY does not Granger Cause SWEDEN		5.34844	0.0211
UNITEDKINGDOM does not Granger Cause ITALY	560	1.10857	0.2929
ITALY does not Granger Cause UNITEDKINGDOM		1.66787	0.1971
CANADA does not Granger Cause ITALY	560	15.2252	0.0001
ITALY does not Granger Cause CANADA		33.7433	1.E-08
UNITEDSTATES does not Granger Cause ITALY	560	9.64075	0.0020
ITALY does not Granger Cause UNITEDSTATES		16.6268	5.E-05
AUSTRALIA does not Granger Cause ITALY	560	0.46677	0.4948
ITALY does not Granger Cause AUSTRALIA		0.57114	0.4501
NEWZEALAND does not Granger Cause ITALY	560	0.01338	0.9080
ITALY does not Granger Cause NEWZEALAND		0.37264	0.5418
ARMENIA does not Granger Cause ITALY	560	0.10726	0.7434
ITALY does not Granger Cause ARMENIA		0.22558	0.6350
AZERBAIJAN does not Granger Cause ITALY	560	2.01701	0.1561
ITALY does not Granger Cause AZERBAIJAN		1.16495	0.2809
GEORGIA does not Granger Cause ITALY	560	0.10922	0.7412
ITALY does not Granger Cause GEORGIA		0.08104	0.7760
ISREAL does not Granger Cause ITALY	560	2.60605	0.1070
ITALY does not Granger Cause ISREAL		0.09803	0.7543
TURKEY does not Granger Cause ITALY	560	0.02465	0.8753
ITALY does not Granger Cause TURKEY		0.68790	0.4072
NIGERIA does not Granger Cause ITALY	560	0.41957	0.5174
ITALY does not Granger Cause NIGERIA		0.10914	0.7413
NORWAY does not Granger Cause NETHERLANDS	560	17.5970	3.E-05
NETHERLANDS does not Granger Cause NORWAY		4.00333	0.0459
RUSSIA does not Granger Cause NETHERLANDS	560	6.31452	0.0123
NETHERLANDS does not Granger Cause RUSSIA		0.27624	0.5994
SPAIN does not Granger Cause NETHERLANDS	560	0.44832	0.5034
NETHERLANDS does not Granger Cause SPAIN		2.89823	0.0892
SWEDEN does not Granger Cause NETHERLANDS	560	21.3419	5.E-06
NETHERLANDS does not Granger Cause SWEDEN		7.02454	0.0083
UNITEDKINGDOM does not Granger Cause NETHERLANDS	560	1.37857	0.2408
NETHERLANDS does not Granger Cause UNITEDKINGDOM		0.56302	0.4534
CANADA does not Granger Cause NETHERLANDS	560	0.11071	0.7395
NETHERLANDS does not Granger Cause CANADA		27.2777	2.E-07
UNITEDSTATES does not Granger Cause NETHERLANDS	560	0.19231	0.6612
NETHERLANDS does not Granger Cause UNITEDSTATES		7.72232	0.0056
AUSTRALIA does not Granger Cause NETHERLANDS	560	2.17634	0.1407
NETHERLANDS does not Granger Cause AUSTRALIA		0.77342	0.3795

NEWZEALAND does not Granger Cause NETHERLANDS	560	12.9755	0.0003
NETHERLANDS does not Granger Cause NEWZEALAND		1.13386	0.2874
ARMENIA does not Granger Cause NETHERLANDS	560	8.14416	0.0045
NETHERLANDS does not Granger Cause ARMENIA		0.88802	0.3464
AZERBAIJAN does not Granger Cause NETHERLANDS	560	7.49678	0.0064
NETHERLANDS does not Granger Cause AZERBAIJAN		0.43236	0.5111
GEORGIA does not Granger Cause NETHERLANDS	560	13.7232	0.0002
NETHERLANDS does not Granger Cause GEORGIA		2.10045	0.1478
ISREAL does not Granger Cause NETHERLANDS	560	0.13899	0.7094
NETHERLANDS does not Granger Cause ISREAL		0.34360	0.5580
TURKEY does not Granger Cause NETHERLANDS	560	6.64991	0.0102
NETHERLANDS does not Granger Cause TURKEY		0.87602	0.3497
NIGERIA does not Granger Cause NETHERLANDS	560	0.08653	0.7687
NETHERLANDS does not Granger Cause NIGERIA		0.06867	0.7934
RUSSIA does not Granger Cause NORWAY	560	11.7059	0.0007
NORWAY does not Granger Cause RUSSIA		1.28586	0.2573
SPAIN does not Granger Cause NORWAY	560	2.50050	0.1144
NORWAY does not Granger Cause SPAIN		0.45140	0.5020
SWEDEN does not Granger Cause NORWAY	560	2.74517	0.0981
NORWAY does not Granger Cause SWEDEN		6.99105	0.0084
UNITEDKINGDOM does not Granger Cause NORWAY	560	5.06507	0.0248
NORWAY does not Granger Cause UNITEDKINGDOM		1.48376	0.2237
CANADA does not Granger Cause NORWAY	560	0.01301	0.9092
NORWAY does not Granger Cause CANADA		1.70613	0.1920
UNITEDSTATES does not Granger Cause NORWAY	560	3.37822	0.0666
NORWAY does not Granger Cause UNITEDSTATES		4.76821	0.0294
AUSTRALIA does not Granger Cause NORWAY	560	5.06070	0.0249
NORWAY does not Granger Cause AUSTRALIA		9.70498	0.0019
NEWZEALAND does not Granger Cause NORWAY	560	23.1814	2.E-06
NORWAY does not Granger Cause NEWZEALAND		15.3198	0.0001
ARMENIA does not Granger Cause NORWAY	560	0.48666	0.4857
NORWAY does not Granger Cause ARMENIA		29.9687	7.E-08
AZERBAIJAN does not Granger Cause NORWAY	560	7.68548	0.0058
NORWAY does not Granger Cause AZERBAIJAN		29.4995	8.E-08
GEORGIA does not Granger Cause NORWAY	560	1.72169	0.1900
NORWAY does not Granger Cause GEORGIA		28.4929	1.E-07
ISREAL does not Granger Cause NORWAY	560	2.95622	0.0861
NORWAY does not Granger Cause ISREAL		2.94359	0.0868
TURKEY does not Granger Cause NORWAY	560	5.18256	0.0232
NORWAY does not Granger Cause TURKEY		2.93959	0.0870
NIGERIA does not Granger Cause NORWAY	560	1.14026	0.2861
NORWAY does not Granger Cause NIGERIA		0.67191	0.4127
SPAIN does not Granger Cause RUSSIA	560	1.25433	0.2632
RUSSIA does not Granger Cause SPAIN		1.65830	0.1984
SWEDEN does not Granger Cause RUSSIA	560	0.32652	0.5679
RUSSIA does not Granger Cause SWEDEN		0.45369	0.5009
UNITEDKINGDOM does not Granger Cause RUSSIA	560	0.45778	0.4989
RUSSIA does not Granger Cause UNITEDKINGDOM		10.6884	0.0011
CANADA does not Granger Cause RUSSIA	560	0.95642	0.3285
RUSSIA does not Granger Cause CANADA		3.98883	0.0463
UNITEDSTATES does not Granger Cause RUSSIA	560	0.45232	0.5015
RUSSIA does not Granger Cause UNITEDSTATES		24.4456	1.E-06
AUSTRALIA does not Granger Cause RUSSIA	560	10.8577	0.0010

RUSSIA does not Granger Cause AUSTRALIA		0.09636	0.7564
NEWZEALAND does not Granger Cause RUSSIA	560	3.44604	0.0639
RUSSIA does not Granger Cause NEWZEALAND		12.9349	0.0004
ARMENIA does not Granger Cause RUSSIA	560	36.7015	3.E-09
RUSSIA does not Granger Cause ARMENIA		3.99228	0.0462
AZERBAIJAN does not Granger Cause RUSSIA	560	1.59028	0.2078
RUSSIA does not Granger Cause AZERBAIJAN		5.60076	0.0183
GEORGIA does not Granger Cause RUSSIA	560	22.2746	3.E-06
RUSSIA does not Granger Cause GEORGIA		43.2927	1.E-10
ISREAL does not Granger Cause RUSSIA	560	2.90453	0.0889
RUSSIA does not Granger Cause ISREAL		1.39562	0.2380
TURKEY does not Granger Cause RUSSIA	560	0.39851	0.5281
RUSSIA does not Granger Cause TURKEY		0.42423	0.5151
NIGERIA does not Granger Cause RUSSIA	560	9.50831	0.0021
RUSSIA does not Granger Cause NIGERIA		1.81645	0.1783
SWEDEN does not Granger Cause SPAIN	560	0.08190	0.7748
SPAIN does not Granger Cause SWEDEN		0.52728	0.4681
UNITEDKINGDOM does not Granger Cause SPAIN	560	4.06170	0.0443
SPAIN does not Granger Cause UNITEDKINGDOM		0.04361	0.8347
CANADA does not Granger Cause SPAIN	560	0.51964	0.4713
SPAIN does not Granger Cause CANADA		0.37322	0.5415
UNITEDSTATES does not Granger Cause SPAIN	560	0.03648	0.8486
SPAIN does not Granger Cause UNITEDSTATES		9.42257	0.0022
AUSTRALIA does not Granger Cause SPAIN	560	3.33922	0.0682
SPAIN does not Granger Cause AUSTRALIA		0.11234	0.7376
NEWZEALAND does not Granger Cause SPAIN	560	0.51889	0.4716
SPAIN does not Granger Cause NEWZEALAND		0.65969	0.4170
ARMENIA does not Granger Cause SPAIN	560	0.64472	0.4223
SPAIN does not Granger Cause ARMENIA		0.63127	0.4272
AZERBAIJAN does not Granger Cause SPAIN	560	0.80534	0.3699
SPAIN does not Granger Cause AZERBAIJAN		0.66987	0.4134
GEORGIA does not Granger Cause SPAIN	560	0.55005	0.4586
SPAIN does not Granger Cause GEORGIA		1.87365	0.1716
ISREAL does not Granger Cause SPAIN	560	3.23398	0.0727
SPAIN does not Granger Cause ISREAL		2.99428	0.0841
TURKEY does not Granger Cause SPAIN	560	0.52774	0.4679
SPAIN does not Granger Cause TURKEY		0.16077	0.6886
NIGERIA does not Granger Cause SPAIN	560	0.00460	0.9460
SPAIN does not Granger Cause NIGERIA		23.5429	2.E-06
UNITEDKINGDOM does not Granger Cause SWEDEN	560	0.03005	0.8624
SWEDEN does not Granger Cause UNITEDKINGDOM		1.26459	0.2613
CANADA does not Granger Cause SWEDEN	560	76.2764	3.E-17
SWEDEN does not Granger Cause CANADA		39.1484	8.E-10
UNITEDSTATES does not Granger Cause SWEDEN	560	0.86553	0.3526
SWEDEN does not Granger Cause UNITEDSTATES		11.3266	0.0008
AUSTRALIA does not Granger Cause SWEDEN	560	3.69296	0.0552
SWEDEN does not Granger Cause AUSTRALIA		0.20979	0.6471
NEWZEALAND does not Granger Cause SWEDEN	560	0.88174	0.3481
SWEDEN does not Granger Cause NEWZEALAND		0.12536	0.7234
ARMENIA does not Granger Cause SWEDEN	560	2.25622	0.1336
SWEDEN does not Granger Cause ARMENIA		8.02205	0.0048
AZERBAIJAN does not Granger Cause SWEDEN	560	1.60752	0.2054
SWEDEN does not Granger Cause AZERBAIJAN		6.80803	0.0093
GEORGIA does not Granger Cause SWEDEN	560	0.94036	0.3326

SWEDEN does not Granger Cause GEORGIA		0.92847	0.3357
ISREAL does not Granger Cause SWEDEN	560	0.06152	0.8042
SWEDEN does not Granger Cause ISREAL		1.11139	0.2922
TURKEY does not Granger Cause SWEDEN	560	7.89678	0.0051
SWEDEN does not Granger Cause TURKEY		3.50901	0.0616
NIGERIA does not Granger Cause SWEDEN	560	0.59164	0.4421
SWEDEN does not Granger Cause NIGERIA		2.16187	0.1420
CANADA does not Granger Cause UNITEDKINGDOM	560	0.35685	0.5505
UNITEDKINGDOM does not Granger Cause CANADA		2.56055	0.1101
UNITEDSTATES does not Granger Cause UNITEDKINGDOM	560	0.45300	0.5012
UNITEDKINGDOM does not Granger Cause UNITEDSTATES		27.0928	3.E-07
AUSTRALIA does not Granger Cause UNITEDKINGDOM	560	0.93515	0.3339
UNITEDKINGDOM does not Granger Cause AUSTRALIA		1.13570	0.2870
NEWZEALAND does not Granger Cause UNITEDKINGDOM	560	0.11482	0.7348
UNITEDKINGDOM does not Granger Cause NEWZEALAND		5.27251	0.0220
ARMENIA does not Granger Cause UNITEDKINGDOM	560	0.48264	0.4875
UNITEDKINGDOM does not Granger Cause ARMENIA		2.70912	0.1003
AZERBAIJAN does not Granger Cause UNITEDKINGDOM	560	3.14817	0.0766
UNITEDKINGDOM does not Granger Cause AZERBAIJAN		1.78215	0.1824
GEORGIA does not Granger Cause UNITEDKINGDOM	560	12.0330	0.0006
UNITEDKINGDOM does not Granger Cause GEORGIA		18.4070	2.E-05
ISREAL does not Granger Cause UNITEDKINGDOM	560	3.53658	0.0606
UNITEDKINGDOM does not Granger Cause ISREAL		10.6408	0.0012
TURKEY does not Granger Cause UNITEDKINGDOM	560	0.97951	0.3228
UNITEDKINGDOM does not Granger Cause TURKEY		0.02463	0.8754
NIGERIA does not Granger Cause UNITEDKINGDOM	560	1.17438	0.2790
UNITEDKINGDOM does not Granger Cause NIGERIA		7.98465	0.0049
UNITEDSTATES does not Granger Cause CANADA	560	1.09071	0.2968
CANADA does not Granger Cause UNITEDSTATES		1.82026	0.1778
AUSTRALIA does not Granger Cause CANADA	560	0.46895	0.4938
CANADA does not Granger Cause AUSTRALIA		0.04002	0.8415
NEWZEALAND does not Granger Cause CANADA	560	0.52703	0.4682
CANADA does not Granger Cause NEWZEALAND		0.96033	0.3275
ARMENIA does not Granger Cause CANADA	560	6.73552	0.0097
CANADA does not Granger Cause ARMENIA		10.1503	0.0015
AZERBAIJAN does not Granger Cause CANADA	560	34.1727	9.E-09
CANADA does not Granger Cause AZERBAIJAN		23.7759	1.E-06
GEORGIA does not Granger Cause CANADA	560	7.06092	0.0081
CANADA does not Granger Cause GEORGIA		31.7831	3.E-08
ISREAL does not Granger Cause CANADA	560	1.24541	0.2649
CANADA does not Granger Cause ISREAL		0.64372	0.4227
TURKEY does not Granger Cause CANADA	560	36.9380	2.E-09
CANADA does not Granger Cause TURKEY		0.43910	0.5078
NIGERIA does not Granger Cause CANADA	560	0.12318	0.7257
CANADA does not Granger Cause NIGERIA		4.70446	0.0305
AUSTRALIA does not Granger Cause UNITEDSTATES	560	0.31490	0.5749
UNITEDSTATES does not Granger Cause AUSTRALIA		0.68643	0.4077
NEWZEALAND does not Granger Cause UNITEDSTATES	560	1.81904	0.1780
UNITEDSTATES does not Granger Cause NEWZEALAND		2.40779	0.1213
ARMENIA does not Granger Cause UNITEDSTATES	560	2.74734	0.0980
UNITEDSTATES does not Granger Cause ARMENIA		12.7252	0.0004
AZERBAIJAN does not Granger Cause UNITEDSTATES	560	35.2093	5.E-09
UNITEDSTATES does not Granger Cause AZERBAIJAN		39.2843	7.E-10
GEORGIA does not Granger Cause UNITEDSTATES	560	21.1516	5.E-06

UNITEDSTATES does not Granger Cause GEORGIA		62.1430	2.E-14
ISREAL does not Granger Cause UNITEDSTATES	560	20.6324	7.E-06
UNITEDSTATES does not Granger Cause ISREAL		13.3862	0.0003
TURKEY does not Granger Cause UNITEDSTATES	560	4.60045	0.0324
UNITEDSTATES does not Granger Cause TURKEY		0.09091	0.7631
NIGERIA does not Granger Cause UNITEDSTATES	560	9.92687	0.0017
UNITEDSTATES does not Granger Cause NIGERIA		27.9871	2.E-07
NEWZEALAND does not Granger Cause AUSTRALIA	560	0.10804	0.7425
AUSTRALIA does not Granger Cause NEWZEALAND		17.8098	3.E-05
ARMENIA does not Granger Cause AUSTRALIA	560	3.40486	0.0655
AUSTRALIA does not Granger Cause ARMENIA		7.93115	0.0050
AZERBAIJAN does not Granger Cause AUSTRALIA	560	1.26607	0.2610
AUSTRALIA does not Granger Cause AZERBAIJAN		1.15052	0.2839
GEORGIA does not Granger Cause AUSTRALIA	560	5.20058	0.0230
AUSTRALIA does not Granger Cause GEORGIA		6.78805	0.0094
ISREAL does not Granger Cause AUSTRALIA	560	8.00741	0.0048
AUSTRALIA does not Granger Cause ISREAL		1.05399	0.3050
TURKEY does not Granger Cause AUSTRALIA	560	1.34209	0.2472
AUSTRALIA does not Granger Cause TURKEY		0.13278	0.7157
NIGERIA does not Granger Cause AUSTRALIA	560	0.09552	0.7574
AUSTRALIA does not Granger Cause NIGERIA		0.39490	0.5300
ARMENIA does not Granger Cause NEWZEALAND	560	5.96119	0.0149
NEWZEALAND does not Granger Cause ARMENIA		2.52409	0.1127
AZERBAIJAN does not Granger Cause NEWZEALAND	560	2.61155	0.1067
NEWZEALAND does not Granger Cause AZERBAIJAN		0.89615	0.3442
GEORGIA does not Granger Cause NEWZEALAND	560	17.4777	3.E-05
NEWZEALAND does not Granger Cause GEORGIA		2.97871	0.0849
ISREAL does not Granger Cause NEWZEALAND	560	0.24546	0.6205
NEWZEALAND does not Granger Cause ISREAL		0.01025	0.9194
TURKEY does not Granger Cause NEWZEALAND	560	2.67749	0.1023
NEWZEALAND does not Granger Cause TURKEY		0.03356	0.8547
NIGERIA does not Granger Cause NEWZEALAND	560	0.00580	0.9393
NEWZEALAND does not Granger Cause NIGERIA		1.00748	0.3159
AZERBAIJAN does not Granger Cause ARMENIA	560	0.39543	0.5297
ARMENIA does not Granger Cause AZERBAIJAN		0.18111	0.6706
GEORGIA does not Granger Cause ARMENIA	560	7.19085	0.0075
ARMENIA does not Granger Cause GEORGIA		0.12601	0.7227
ISREAL does not Granger Cause ARMENIA	560	0.01127	0.9155
ARMENIA does not Granger Cause ISREAL		4.44890	0.0354
TURKEY does not Granger Cause ARMENIA	560	2.93491	0.0872
ARMENIA does not Granger Cause TURKEY		0.00455	0.9463
NIGERIA does not Granger Cause ARMENIA	560	0.80777	0.3692
ARMENIA does not Granger Cause NIGERIA		4.85548	0.0280
GEORGIA does not Granger Cause AZERBAIJAN	560	15.6642	9.E-05
AZERBAIJAN does not Granger Cause GEORGIA		0.37862	0.5386
ISREAL does not Granger Cause AZERBAIJAN	560	1.41795	0.2342
AZERBAIJAN does not Granger Cause ISREAL		2.70596	0.1005
TURKEY does not Granger Cause AZERBAIJAN	560	10.8197	0.0011
AZERBAIJAN does not Granger Cause TURKEY		1.09549	0.2957
NIGERIA does not Granger Cause AZERBAIJAN	560	0.15180	0.6970
AZERBAIJAN does not Granger Cause NIGERIA		0.01048	0.9185
ISREAL does not Granger Cause GEORGIA	560	1.70792	0.1918
GEORGIA does not Granger Cause ISREAL		1.24198	0.2656
TURKEY does not Granger Cause GEORGIA	560	9.65189	0.0020

GEORGIA does not Granger Cause TURKEY		2.69348	0.1013
NIGERIA does not Granger Cause GEORGIA	560	1.67942	0.1955
GEORGIA does not Granger Cause NIGERIA		0.04610	0.8301
TURKEY does not Granger Cause ISREAL	560	0.01126	0.9155
ISREAL does not Granger Cause TURKEY		0.00664	0.9351
NIGERIA does not Granger Cause ISREAL	560	14.1119	0.0002
ISREAL does not Granger Cause NIGERIA		30.4857	5.E-08
NIGERIA does not Granger Cause TURKEY	560	3.89679	0.0489
TURKEY does not Granger Cause NIGERIA		0.36462	0.5462

Appendix B

Pairwise Granger Causality Tests
Date: 12/21/21 Time: 20:43
Sample: 5/01/2020 11/12/2021
Lags: 2

Null Hypothesis:	Obs	F-Statistic	Prob.
GUATEMALA does not Granger Cause MEXICO	559	44.0702	2.E-18
MEXICO does not Granger Cause GUATEMALA		0.52039	0.5946
CUBA does not Granger Cause MEXICO	559	11.8577	9.E-06
MEXICO does not Granger Cause CUBA		3.07507	0.0470
JAMAICA does not Granger Cause MEXICO	559	1.40156	0.2471
MEXICO does not Granger Cause JAMAICA		15.7186	2.E-07
VENEZUELA does not Granger Cause MEXICO	559	1.93868	0.1449
MEXICO does not Granger Cause VENEZUELA		0.36244	0.6961
IRAN does not Granger Cause MEXICO	559	18.4478	2.E-08
MEXICO does not Granger Cause IRAN		4.06236	0.0177
JAPAN does not Granger Cause MEXICO	559	15.7141	2.E-07
MEXICO does not Granger Cause JAPAN		15.0892	4.E-07
PHILIPPINES does not Granger Cause MEXICO	559	2.12398	0.1205
MEXICO does not Granger Cause PHILIPPINES		13.4903	2.E-06
SOUTHKOREA does not Granger Cause MEXICO	559	30.1475	4.E-13
MEXICO does not Granger Cause SOUTHKOREA		16.4225	1.E-07
THAILAND does not Granger Cause MEXICO	559	7.48703	0.0006
MEXICO does not Granger Cause THAILAND		4.43844	0.0122
MALAYSIA does not Granger Cause MEXICO	559	10.9915	2.E-05
MEXICO does not Granger Cause MALAYSIA		11.4288	1.E-05
ANGOLA does not Granger Cause MEXICO	559	8.64797	0.0002
MEXICO does not Granger Cause ANGOLA		0.70943	0.4924
LIBYA does not Granger Cause MEXICO	559	23.3889	2.E-10
MEXICO does not Granger Cause LIBYA		14.5098	7.E-07
KENYA does not Granger Cause MEXICO	559	11.8630	9.E-06
MEXICO does not Granger Cause KENYA		2.15978	0.1163
ETHIOPIA does not Granger Cause MEXICO	559	4.03904	0.0181
MEXICO does not Granger Cause ETHIOPIA		4.12237	0.0167
MOROCCA does not Granger Cause MEXICO	559	32.3328	5.E-14
MEXICO does not Granger Cause MOROCCA		5.77852	0.0033
CUBA does not Granger Cause GUATEMALA	559	124.482	2.E-45
GUATEMALA does not Granger Cause CUBA		4.81779	0.0084
JAMAICA does not Granger Cause GUATEMALA	559	11.5044	1.E-05
GUATEMALA does not Granger Cause JAMAICA		32.5028	4.E-14
VENEZUELA does not Granger Cause GUATEMALA	559	16.4294	1.E-07
GUATEMALA does not Granger Cause VENEZUELA		4.00441	0.0188
IRAN does not Granger Cause GUATEMALA	559	101.855	2.E-38
GUATEMALA does not Granger Cause IRAN		19.6176	6.E-09
JAPAN does not Granger Cause GUATEMALA	559	34.5993	7.E-15
GUATEMALA does not Granger Cause JAPAN		78.2536	1.E-30
PHILIPPINES does not Granger Cause GUATEMALA	559	38.8625	2.E-16
GUATEMALA does not Granger Cause PHILIPPINES		63.3494	2.E-25
SOUTHKOREA does not Granger Cause GUATEMALA	559	40.7403	3.E-17
GUATEMALA does not Granger Cause SOUTHKOREA		24.5863	6.E-11
THAILAND does not Granger Cause GUATEMALA	559	80.4275	2.E-31
GUATEMALA does not Granger Cause THAILAND		25.2162	3.E-11
MALAYSIA does not Granger Cause GUATEMALA	559	100.170	7.E-38
GUATEMALA does not Granger Cause MALAYSIA		36.8590	9.E-16
ANGOLA does not Granger Cause GUATEMALA	559	16.1167	2.E-07
GUATEMALA does not Granger Cause ANGOLA		0.17314	0.8411

LIBYA does not Granger Cause GUATEMALA	559	53.8699	4.E-22
GUATEMALA does not Granger Cause LIBYA		20.3553	3.E-09
KENYA does not Granger Cause GUATEMALA	559	0.30834	0.7348
GUATEMALA does not Granger Cause KENYA		17.9726	3.E-08
ETHIOPIA does not Granger Cause GUATEMALA	559	1.86840	0.1553
GUATEMALA does not Granger Cause ETHIOPIA		14.1968	1.E-06
MOROCCA does not Granger Cause GUATEMALA	559	5.04341	0.0068
GUATEMALA does not Granger Cause MOROCCA		43.0009	4.E-18
JAMAICA does not Granger Cause CUBA	559	6.92488	0.0011
CUBA does not Granger Cause JAMAICA		7.67222	0.0005
VENEZUELA does not Granger Cause CUBA	559	0.92983	0.3952
CUBA does not Granger Cause VENEZUELA		4.40163	0.0127
IRAN does not Granger Cause CUBA	559	10.2587	4.E-05
CUBA does not Granger Cause IRAN		9.51565	9.E-05
JAPAN does not Granger Cause CUBA	559	1.44839	0.2358
CUBA does not Granger Cause JAPAN		5.73060	0.0034
PHILIPPINES does not Granger Cause CUBA	559	7.17608	0.0008
CUBA does not Granger Cause PHILIPPINES		10.1831	5.E-05
SOUTHKOREA does not Granger Cause CUBA	559	1.22263	0.2952
CUBA does not Granger Cause SOUTHKOREA		13.8557	1.E-06
THAILAND does not Granger Cause CUBA	559	5.27085	0.0054
CUBA does not Granger Cause THAILAND		11.5670	1.E-05
MALAYSIA does not Granger Cause CUBA	559	1.03350	0.3564
CUBA does not Granger Cause MALAYSIA		18.9040	1.E-08
ANGOLA does not Granger Cause CUBA	559	2.91285	0.0552
CUBA does not Granger Cause ANGOLA		8.93927	0.0002
LIBYA does not Granger Cause CUBA	559	2.73606	0.0657
CUBA does not Granger Cause LIBYA		7.59618	0.0006
KENYA does not Granger Cause CUBA	559	1.88871	0.1522
CUBA does not Granger Cause KENYA		1.76438	0.1723
ETHIOPIA does not Granger Cause CUBA	559	3.10549	0.0456
CUBA does not Granger Cause ETHIOPIA		0.87447	0.4177
MOROCCA does not Granger Cause CUBA	559	1.20830	0.2995
CUBA does not Granger Cause MOROCCA		10.4168	4.E-05
VENEZUELA does not Granger Cause JAMAICA	559	0.54598	0.5796
JAMAICA does not Granger Cause VENEZUELA		9.14187	0.0001
IRAN does not Granger Cause JAMAICA	559	12.9516	3.E-06
JAMAICA does not Granger Cause IRAN		2.14915	0.1176
JAPAN does not Granger Cause JAMAICA	559	18.0405	3.E-08
JAMAICA does not Granger Cause JAPAN		0.39916	0.6711
PHILIPPINES does not Granger Cause JAMAICA	559	14.8930	5.E-07
JAMAICA does not Granger Cause PHILIPPINES		3.87038	0.0214
SOUTHKOREA does not Granger Cause JAMAICA	559	7.16802	0.0008
JAMAICA does not Granger Cause SOUTHKOREA		1.63571	0.1958
THAILAND does not Granger Cause JAMAICA	559	6.11054	0.0024
JAMAICA does not Granger Cause THAILAND		4.97436	0.0072
MALAYSIA does not Granger Cause JAMAICA	559	8.75376	0.0002
JAMAICA does not Granger Cause MALAYSIA		3.53302	0.0299
ANGOLA does not Granger Cause JAMAICA	559	1.38372	0.2515
JAMAICA does not Granger Cause ANGOLA		2.97728	0.0517
LIBYA does not Granger Cause JAMAICA	559	3.36873	0.0351
JAMAICA does not Granger Cause LIBYA		2.44081	0.0880
KENYA does not Granger Cause JAMAICA	559	7.84675	0.0004
JAMAICA does not Granger Cause KENYA		5.12261	0.0062

ETHIOPIA does not Granger Cause JAMAICA	559	7.64342	0.0005
JAMAICA does not Granger Cause ETHIOPIA		10.7625	3.E-05
MOROCCA does not Granger Cause JAMAICA	559	12.3398	6.E-06
JAMAICA does not Granger Cause MOROCCA		2.34832	0.0965
IRAN does not Granger Cause VENEZUELA	559	3.87538	0.0213
VENEZUELA does not Granger Cause IRAN		5.49262	0.0043
JAPAN does not Granger Cause VENEZUELA	559	1.74191	0.1761
VENEZUELA does not Granger Cause JAPAN		3.77077	0.0236
PHILIPPINES does not Granger Cause VENEZUELA	559	6.98967	0.0010
VENEZUELA does not Granger Cause PHILIPPINES		2.99016	0.0511
SOUTHKOREA does not Granger Cause VENEZUELA	559	7.27206	0.0008
VENEZUELA does not Granger Cause SOUTHKOREA		0.55296	0.5756
THAILAND does not Granger Cause VENEZUELA	559	4.60221	0.0104
VENEZUELA does not Granger Cause THAILAND		0.49719	0.6085
MALAYSIA does not Granger Cause VENEZUELA	559	5.90472	0.0029
VENEZUELA does not Granger Cause MALAYSIA		4.08417	0.0173
ANGOLA does not Granger Cause VENEZUELA	559	3.45431	0.0323
VENEZUELA does not Granger Cause ANGOLA		8.97827	0.0001
LIBYA does not Granger Cause VENEZUELA	559	1.22696	0.2940
VENEZUELA does not Granger Cause LIBYA		1.47799	0.2290
KENYA does not Granger Cause VENEZUELA	559	2.02415	0.1331
VENEZUELA does not Granger Cause KENYA		0.09703	0.9075
ETHIOPIA does not Granger Cause VENEZUELA	559	2.44311	0.0878
VENEZUELA does not Granger Cause ETHIOPIA		1.08184	0.3397
MOROCCA does not Granger Cause VENEZUELA	559	0.00944	0.9906
VENEZUELA does not Granger Cause MOROCCA		0.05400	0.9474
JAPAN does not Granger Cause IRAN	559	10.0551	5.E-05
IRAN does not Granger Cause JAPAN		38.1308	3.E-16
PHILIPPINES does not Granger Cause IRAN	559	9.54570	8.E-05
IRAN does not Granger Cause PHILIPPINES		16.3332	1.E-07
SOUTHKOREA does not Granger Cause IRAN	559	7.89444	0.0004
IRAN does not Granger Cause SOUTHKOREA		41.6311	1.E-17
THAILAND does not Granger Cause IRAN	559	4.85889	0.0081
IRAN does not Granger Cause THAILAND		9.61289	8.E-05
MALAYSIA does not Granger Cause IRAN	559	7.84738	0.0004
IRAN does not Granger Cause MALAYSIA		28.1111	2.E-12
ANGOLA does not Granger Cause IRAN	559	11.4435	1.E-05
IRAN does not Granger Cause ANGOLA		22.1179	6.E-10
LIBYA does not Granger Cause IRAN	559	27.1684	6.E-12
IRAN does not Granger Cause LIBYA		45.5704	5.E-19
KENYA does not Granger Cause IRAN	559	7.48145	0.0006
IRAN does not Granger Cause KENYA		26.8643	7.E-12
ETHIOPIA does not Granger Cause IRAN	559	1.04761	0.3515
IRAN does not Granger Cause ETHIOPIA		9.71852	7.E-05
MOROCCA does not Granger Cause IRAN	559	6.87063	0.0011
IRAN does not Granger Cause MOROCCA		16.8959	8.E-08
PHILIPPINES does not Granger Cause JAPAN	559	0.11813	0.8886
JAPAN does not Granger Cause PHILIPPINES		24.1248	9.E-11
SOUTHKOREA does not Granger Cause JAPAN	559	29.0751	1.E-12
JAPAN does not Granger Cause SOUTHKOREA		23.6781	1.E-10
THAILAND does not Granger Cause JAPAN	559	3.91812	0.0204
JAPAN does not Granger Cause THAILAND		17.7047	4.E-08
MALAYSIA does not Granger Cause JAPAN	559	2.98894	0.0512
JAPAN does not Granger Cause MALAYSIA		10.6997	3.E-05

ANGOLA does not Granger Cause JAPAN	559	12.9998	3.E-06
JAPAN does not Granger Cause ANGOLA		3.50975	0.0306
LIBYA does not Granger Cause JAPAN	559	29.0482	1.E-12
JAPAN does not Granger Cause LIBYA		5.47843	0.0044
KENYA does not Granger Cause JAPAN	559	18.5875	2.E-08
JAPAN does not Granger Cause KENYA		0.23082	0.7940
ETHIOPIA does not Granger Cause JAPAN	559	7.19371	0.0008
JAPAN does not Granger Cause ETHIOPIA		1.55593	0.2119
MOROCCA does not Granger Cause JAPAN	559	23.7313	1.E-10
JAPAN does not Granger Cause MOROCCA		0.42160	0.6562
SOUTHKOREA does not Granger Cause PHILIPPINES	559	7.80097	0.0005
PHILIPPINES does not Granger Cause SOUTHKOREA		1.66920	0.1893
THAILAND does not Granger Cause PHILIPPINES	559	7.13596	0.0009
PHILIPPINES does not Granger Cause THAILAND		1.43246	0.2396
MALAYSIA does not Granger Cause PHILIPPINES	559	24.5624	6.E-11
PHILIPPINES does not Granger Cause MALAYSIA		6.78762	0.0012
ANGOLA does not Granger Cause PHILIPPINES	559	6.16766	0.0022
PHILIPPINES does not Granger Cause ANGOLA		16.4862	1.E-07
LIBYA does not Granger Cause PHILIPPINES	559	2.24305	0.1071
PHILIPPINES does not Granger Cause LIBYA		0.34648	0.7073
KENYA does not Granger Cause PHILIPPINES	559	16.5168	1.E-07
PHILIPPINES does not Granger Cause KENYA		0.08042	0.9227
ETHIOPIA does not Granger Cause PHILIPPINES	559	9.42352	9.E-05
PHILIPPINES does not Granger Cause ETHIOPIA		4.42011	0.0125
MOROCCA does not Granger Cause PHILIPPINES	559	9.35448	0.0001
PHILIPPINES does not Granger Cause MOROCCA		0.40552	0.6668
THAILAND does not Granger Cause SOUTHKOREA	559	6.88137	0.0011
SOUTHKOREA does not Granger Cause THAILAND		3.99027	0.0190
MALAYSIA does not Granger Cause SOUTHKOREA	559	17.5215	4.E-08
SOUTHKOREA does not Granger Cause MALAYSIA		28.6506	1.E-12
ANGOLA does not Granger Cause SOUTHKOREA	559	12.2074	6.E-06
SOUTHKOREA does not Granger Cause ANGOLA		3.10668	0.0455
LIBYA does not Granger Cause SOUTHKOREA	559	22.6115	4.E-10
SOUTHKOREA does not Granger Cause LIBYA		4.03556	0.0182
KENYA does not Granger Cause SOUTHKOREA	559	3.37981	0.0348
SOUTHKOREA does not Granger Cause KENYA		16.5617	1.E-07
ETHIOPIA does not Granger Cause SOUTHKOREA	559	0.94686	0.3886
SOUTHKOREA does not Granger Cause ETHIOPIA		12.4044	5.E-06
MOROCCA does not Granger Cause SOUTHKOREA	559	15.7778	2.E-07
SOUTHKOREA does not Granger Cause MOROCCA		17.8276	3.E-08
MALAYSIA does not Granger Cause THAILAND	559	13.4614	2.E-06
THAILAND does not Granger Cause MALAYSIA		3.48908	0.0312
ANGOLA does not Granger Cause THAILAND	559	20.6893	2.E-09
THAILAND does not Granger Cause ANGOLA		4.16988	0.0159
LIBYA does not Granger Cause THAILAND	559	3.55228	0.0293
THAILAND does not Granger Cause LIBYA		5.13542	0.0062
KENYA does not Granger Cause THAILAND	559	5.83903	0.0031
THAILAND does not Granger Cause KENYA		0.60031	0.5490
ETHIOPIA does not Granger Cause THAILAND	559	2.94093	0.0536
THAILAND does not Granger Cause ETHIOPIA		0.06502	0.9371
MOROCCA does not Granger Cause THAILAND	559	12.1851	7.E-06
THAILAND does not Granger Cause MOROCCA		2.22955	0.1085
ANGOLA does not Granger Cause MALAYSIA	559	17.3980	5.E-08
MALAYSIA does not Granger Cause ANGOLA		3.96453	0.0195

LIBYA does not Granger Cause MALAYSIA	559	14.2442	9.E-07
MALAYSIA does not Granger Cause LIBYA		6.82789	0.0012
KENYA does not Granger Cause MALAYSIA	559	13.9921	1.E-06
MALAYSIA does not Granger Cause KENYA		0.71622	0.4890
ETHIOPIA does not Granger Cause MALAYSIA	559	12.3573	6.E-06
MALAYSIA does not Granger Cause ETHIOPIA		0.05209	0.9492
MOROCCA does not Granger Cause MALAYSIA	559	14.7183	6.E-07
MALAYSIA does not Granger Cause MOROCCA		1.02256	0.3604
LIBYA does not Granger Cause ANGOLA	559	4.96025	0.0073
ANGOLA does not Granger Cause LIBYA		1.54358	0.2145
KENYA does not Granger Cause ANGOLA	559	0.82290	0.4397
ANGOLA does not Granger Cause KENYA		9.04978	0.0001
ETHIOPIA does not Granger Cause ANGOLA	559	1.19689	0.3029
ANGOLA does not Granger Cause ETHIOPIA		17.8370	3.E-08
MOROCCA does not Granger Cause ANGOLA	559	3.17982	0.0424
ANGOLA does not Granger Cause MOROCCA		16.6523	9.E-08
KENYA does not Granger Cause LIBYA	559	7.72064	0.0005
LIBYA does not Granger Cause KENYA		18.9064	1.E-08
ETHIOPIA does not Granger Cause LIBYA	559	1.00246	0.3676
LIBYA does not Granger Cause ETHIOPIA		4.54815	0.0110
MOROCCA does not Granger Cause LIBYA	559	9.33974	0.0001
LIBYA does not Granger Cause MOROCCA		53.9299	4.E-22
ETHIOPIA does not Granger Cause KENYA	559	3.17563	0.0425
KENYA does not Granger Cause ETHIOPIA		7.68379	0.0005
MOROCCA does not Granger Cause KENYA	559	6.99053	0.0010
KENYA does not Granger Cause MOROCCA		9.51658	9.E-05
MOROCCA does not Granger Cause ETHIOPIA	559	3.77450	0.0235
ETHIOPIA does not Granger Cause MOROCCA		2.15899	0.1164

Appendix C

Pairwise Granger Causality Tests
Date: 12/21/21 Time: 20:48
Sample: 5/01/2020 11/12/2021
Lags: 2

Null Hypothesis:	Obs	F-Statistic	Prob.
BRAZIL does not Granger Cause ARGENTINA	559	18.5712	2.E-08
ARGENTINA does not Granger Cause BRAZIL		105.265	2.E-39
CHILE does not Granger Cause ARGENTINA	559	5.02499	0.0069
ARGENTINA does not Granger Cause CHILE		13.3853	2.E-06
PERU does not Granger Cause ARGENTINA	559	0.70817	0.4930
ARGENTINA does not Granger Cause PERU		21.1418	1.E-09
PARAGUAY does not Granger Cause ARGENTINA	559	20.5037	3.E-09
ARGENTINA does not Granger Cause PARAGUAY		16.2907	1.E-07
INDIA does not Granger Cause ARGENTINA	559	36.4544	1.E-15
ARGENTINA does not Granger Cause INDIA		77.1634	3.E-30
PAKISTAN does not Granger Cause ARGENTINA	559	0.34207	0.7104
ARGENTINA does not Granger Cause PAKISTAN		10.3996	4.E-05
SAUDIARABIA does not Granger Cause ARGENTINA	559	1.16035	0.3141
ARGENTINA does not Granger Cause SAUDIARABIA		1.31669	0.2689
EGYPT does not Granger Cause ARGENTINA	559	0.06200	0.9399
ARGENTINA does not Granger Cause EGYPT		2.46946	0.0856
CHILE does not Granger Cause BRAZIL	559	11.0120	2.E-05
BRAZIL does not Granger Cause CHILE		50.4101	8.E-21
PERU does not Granger Cause BRAZIL	559	5.96113	0.0027
BRAZIL does not Granger Cause PERU		18.7465	1.E-08
PARAGUAY does not Granger Cause BRAZIL	559	78.4996	1.E-30
BRAZIL does not Granger Cause PARAGUAY		9.18757	0.0001
INDIA does not Granger Cause BRAZIL	559	8.94140	0.0002
BRAZIL does not Granger Cause INDIA		27.3533	5.E-12
PAKISTAN does not Granger Cause BRAZIL	559	1.15975	0.3143
BRAZIL does not Granger Cause PAKISTAN		10.6432	3.E-05
SAUDIARABIA does not Granger Cause BRAZIL	559	6.47050	0.0017
BRAZIL does not Granger Cause SAUDIARABIA		2.02853	0.1325
EGYPT does not Granger Cause BRAZIL	559	1.28062	0.2787
BRAZIL does not Granger Cause EGYPT		2.54044	0.0798
PERU does not Granger Cause CHILE	559	16.1232	2.E-07
CHILE does not Granger Cause PERU		0.75768	0.4692
PARAGUAY does not Granger Cause CHILE	559	21.4462	1.E-09
CHILE does not Granger Cause PARAGUAY		6.21812	0.0021
INDIA does not Granger Cause CHILE	559	16.7594	9.E-08
CHILE does not Granger Cause INDIA		1.66293	0.1905
PAKISTAN does not Granger Cause CHILE	559	2.76453	0.0639
CHILE does not Granger Cause PAKISTAN		0.00135	0.9986
SAUDIARABIA does not Granger Cause CHILE	559	1.26042	0.2843
CHILE does not Granger Cause SAUDIARABIA		3.20059	0.0415
EGYPT does not Granger Cause CHILE	559	6.57494	0.0015
CHILE does not Granger Cause EGYPT		5.18485	0.0059
PARAGUAY does not Granger Cause PERU	559	8.60893	0.0002
PERU does not Granger Cause PARAGUAY		0.33891	0.7127
INDIA does not Granger Cause PERU	559	11.9524	8.E-06
PERU does not Granger Cause INDIA		3.01860	0.0497
PAKISTAN does not Granger Cause PERU	559	0.75283	0.4715
PERU does not Granger Cause PAKISTAN		0.06677	0.9354
SAUDIARABIA does not Granger Cause PERU	559	0.34036	0.7117
PERU does not Granger Cause SAUDIARABIA		2.28445	0.1028

EGYPT does not Granger Cause PERU	559	0.53939	0.5834
PERU does not Granger Cause EGYPT		0.44089	0.6437
INDIA does not Granger Cause PARAGUAY	559	6.70256	0.0013
PARAGUAY does not Granger Cause INDIA		36.3867	1.E-15
PAKISTAN does not Granger Cause PARAGUAY	559	0.22170	0.8012
PARAGUAY does not Granger Cause PAKISTAN		5.54473	0.0041
SAUDIARABIA does not Granger Cause PARAGUAY	559	1.18717	0.3059
PARAGUAY does not Granger Cause SAUDIARABIA		0.60957	0.5440
EGYPT does not Granger Cause PARAGUAY	559	0.47034	0.6250
PARAGUAY does not Granger Cause EGYPT		0.63021	0.5329
PAKISTAN does not Granger Cause INDIA	559	3.55034	0.0294
INDIA does not Granger Cause PAKISTAN		9.91581	6.E-05
SAUDIARABIA does not Granger Cause INDIA	559	5.36097	0.0049
INDIA does not Granger Cause SAUDIARABIA		0.75585	0.4701
EGYPT does not Granger Cause INDIA	559	0.19993	0.8188
INDIA does not Granger Cause EGYPT		0.21810	0.8041
SAUDIARABIA does not Granger Cause PAKISTAN	559	1.31566	0.2691
PAKISTAN does not Granger Cause SAUDIARABIA		4.84365	0.0082
EGYPT does not Granger Cause PAKISTAN	559	2.96632	0.0523
PAKISTAN does not Granger Cause EGYPT		1.71690	0.1806
EGYPT does not Granger Cause SAUDIARABIA	559	4.92578	0.0076
SAUDIARABIA does not Granger Cause EGYPT		0.73230	0.4813

Appendix D

Pairwise Granger Causality Tests
Date: 12/21/21 Time: 20:50
Sample: 5/01/2020 11/12/2021
Lags: 2

Null Hypothesis:	Obs	F-Statistic	Prob.
KYRGYZSTAN does not Granger Cause COLOMBIA	559	1.31887	0.2683
COLOMBIA does not Granger Cause KYRGYZSTAN		5.25391	0.0055
SOUTHAFRICA does not Granger Cause COLOMBIA	559	10.4436	4.E-05
COLOMBIA does not Granger Cause SOUTHAFRICA		3.58243	0.0285
TUNISIA does not Granger Cause COLOMBIA	559	2.39362	0.0922
COLOMBIA does not Granger Cause TUNISIA		7.46908	0.0006
UGANDA does not Granger Cause COLOMBIA	559	0.01065	0.9894
COLOMBIA does not Granger Cause UGANDA		18.7558	1.E-08
ZIMBABWE does not Granger Cause COLOMBIA	559	4.94401	0.0074
COLOMBIA does not Granger Cause ZIMBABWE		7.29156	0.0007
ALGERIA does not Granger Cause COLOMBIA	559	2.78808	0.0624
COLOMBIA does not Granger Cause ALGERIA		3.40604	0.0339
SOUTHAFRICA does not Granger Cause KYRGYZSTAN	559	0.97465	0.3780
KYRGYZSTAN does not Granger Cause SOUTHAFRICA		6.94932	0.0010
TUNISIA does not Granger Cause KYRGYZSTAN	559	3.45101	0.0324
KYRGYZSTAN does not Granger Cause TUNISIA		8.91901	0.0002
UGANDA does not Granger Cause KYRGYZSTAN	559	3.37712	0.0349
KYRGYZSTAN does not Granger Cause UGANDA		1.89145	0.1518
ZIMBABWE does not Granger Cause KYRGYZSTAN	559	1.25860	0.2849
KYRGYZSTAN does not Granger Cause ZIMBABWE		11.6461	1.E-05
ALGERIA does not Granger Cause KYRGYZSTAN	559	3.02468	0.0494
KYRGYZSTAN does not Granger Cause ALGERIA		23.7256	1.E-10
TUNISIA does not Granger Cause SOUTHAFRICA	559	0.91785	0.4000
SOUTHAFRICA does not Granger Cause TUNISIA		6.68581	0.0014
UGANDA does not Granger Cause SOUTHAFRICA	559	1.62492	0.1979
SOUTHAFRICA does not Granger Cause UGANDA		18.0569	3.E-08
ZIMBABWE does not Granger Cause SOUTHAFRICA	559	69.2220	1.E-27
SOUTHAFRICA does not Granger Cause ZIMBABWE		11.7101	1.E-05
ALGERIA does not Granger Cause SOUTHAFRICA	559	8.77431	0.0002
SOUTHAFRICA does not Granger Cause ALGERIA		1.87059	0.1550
UGANDA does not Granger Cause TUNISIA	559	4.49202	0.0116
TUNISIA does not Granger Cause UGANDA		2.48112	0.0846
ZIMBABWE does not Granger Cause TUNISIA	559	34.0147	1.E-14
TUNISIA does not Granger Cause ZIMBABWE		8.92552	0.0002
ALGERIA does not Granger Cause TUNISIA	559	1.44094	0.2376
TUNISIA does not Granger Cause ALGERIA		5.78576	0.0033
ZIMBABWE does not Granger Cause UGANDA	559	0.32935	0.7195
UGANDA does not Granger Cause ZIMBABWE		4.15289	0.0162
ALGERIA does not Granger Cause UGANDA	559	0.39747	0.6722
UGANDA does not Granger Cause ALGERIA		1.56855	0.2093
ALGERIA does not Granger Cause ZIMBABWE	559	1.89980	0.1506
ZIMBABWE does not Granger Cause ALGERIA		6.57204	0.0015