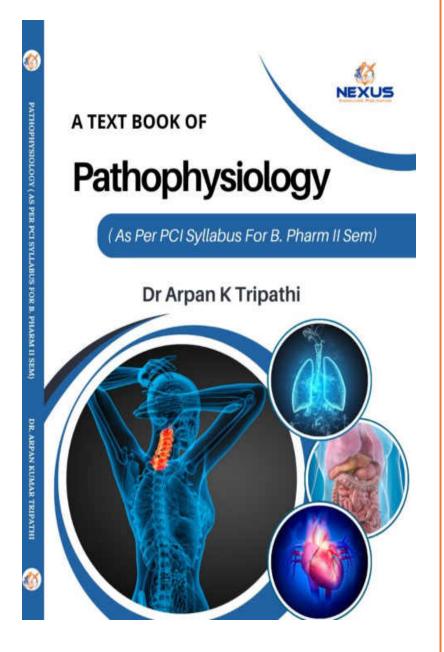
NEXUS KNOWLEDGE PUBLICATION

https://nknpub.com/index.php/1

A TEXTBOOK OF PATHOPHSIOLOGY

ISBN: 978-81-985724-1-7



Chapter- 4

Digestive, Musculoskeletal, and Cancer Diseases Overview

DR. GAURAV BHATNAGAR (PT)

Professor Musculoskeletal Physiotherapy, Maharashtra Institute of Physiotherapy, MIMSR Medical College Campus, Latur, Maharashtra, India- 413512

DR. SHRUTI TADMARE (PT)

Assistant professor Community physiotherapy, Maharashtra institute of physiotherapy, Latur, Maharashtra, India-413531

DR. JAYASANKAR NARAYANAN

Assistant Professor (Grade II), Department of Pharmacology
Faculty of Medicine and Health Sciences,
SRM Institute of Science and Technology,
SRM College of Pharmacy
Kattankulathur – 603203, Chengalpattu

District, Tamil Nadu, India. Email: narayanj@srmist.edu.in

DR. MOIDUL ISLAM JUDDER

Assistant Professor Royal School of Pharmacy, The Assam Royal Global University, Betkuchi, Opp. Tirupati Balaji Temple, NH 37, Guwahati -781035, Assam, India Email - moonzodder@gmail.com

MRS. R. SRIDEVI

Assistant Professor Department of Pharmacology, SRM College of Pharmacy SRMIST, Chennai

Email: sridevir@srmist.edu.in

Unit IV...

DIGESTIVE, MUSCULOSKELETAL, AND CANCER DISEASES OVERVIEW

DR. GAURAV BHATNAGAR (PT)

Professor Musculoskeletal Physiotherapy,
Maharashtra Institute of Physiotherapy, MIMSR Medical College Campus, Latur,
Maharashtra, India- 413512

DR. SHRUTI TADMARE (PT)

Assistant professor Community physiotherapy, Maharashtra institute of physiotherapy, Latur, Maharashtra, India-413531

DR. JAYASANKAR NARAYANAN

Assistant Professor (Grade II), Department of Pharmacology
Faculty of Medicine and Health Sciences,
SRM Institute of Science and Technology, SRM College of Pharmacy
Kattankulathur – 603203, Chengalpattu District, Tamil Nadu, India.
Email: narayanj@srmist.edu.in

DR. MOIDUL ISLAM JUDDER

Assistant Professor

Royal School of Pharmacy, The Assam Royal Global University, Betkuchi, Opp. Tirupati Balaji Temple, NH 37, Guwahati - 781035, Assam, India

Email - moonzodder@gmail.com

MRS. R. SRIDEVI

Assistant Professor

Department of Pharmacology, SRM College of Pharmacy

SRMIST, Chennai

Email: sridevir@srmist.edu.in

4.1 Inflammatory bowel disease

IBD, which stands for inflammatory bowel disease, is a collection of chronic inflammatory conditions that are characterized by their impact on the gastrointestinal tract. Crohn's disease and ulcerative colitis are the two principal types of inflammatory bowel disease (IBD). Each of these conditions has its own unique characteristics and implications for the care of patients.

Although Crohn's disease is characterized by inflammation that can affect any portion of the gastrointestinal tract, from the mouth to the anus, it most usually affects the ileum, which is the end of the small intestine, and the colon, which is the beginning of the large intestine. The inflammation that is characteristic of Crohn's disease is often patchy, which means that it might manifest itself in certain regions of the digestive system while remaining unaffected in other regions. Pain in the abdomen region, diarrhea, loss of weight, and weariness are some of the symptoms that may be caused by this ailment. There is a possibility that Crohn's disease could result in complications such as strictures, fistulas, and abscesses in certain individuals. The treatment of Crohn's disease often consists of a variety of measures, including dietary support, medication to reduce inflammation and control symptoms, and sometimes surgical operations to address problems or remove badly afflicted parts of the bowel.

In contrast, ulcerative colitis is characterized by persistent inflammation that starts in the rectum and progresses proximally across the colon. This inflammation is considered to be the hallmark of the condition. Bloody diarrhea, abdominal cramps, and an urgent need to have bowel movements are some of the symptoms that can be caused by inflammation, which normally only affects the innermost lining of the colon and rectum. It is also possible for ulcerative colitis to lead to problems, such as toxic megacolon and an increased risk of colorectal cancer. In most situations, the management of ulcerative colitis consists of taking drugs to control inflammation and symptoms, making adjustments to one's diet, and, in more severe cases, considering surgical options such as colectomy, which involves the removal of a portion or the entire colon.

It is believed that both Crohn's disease and ulcerative colitis are caused by an aberrant immune response that results in persistent inflammation. Despite the fact that the precise origin of inflammatory bowel disease (IBD) is still unknown, it is believed that it is caused by a confluence of genetic, environmental, and immunological variables. Irritable bowel disease (IBD) treatment techniques with the goals of reducing inflammation, managing symptoms, and

improving patients' quality of life are developed. It is possible that these strategies will involve the utilization of immunosuppressants, biologics, anti-inflammatory medications, and perhaps surgery in certain instances. It is necessary to provide patients with inflammatory bowel disease with regular monitoring and individualized treatment programs in order to effectively control flare-ups and consequences, as well as to address the specific needs of each patient.

❖ Crohn's Disease

When it comes to the gastrointestinal tract, Crohn's disease is a chronic inflammatory bowel illness that is characterized by continuous inflammation. This disease can affect any part of the gastrointestinal tract, from the mouth to the anus. The ileum, which is the terminal segment of the small intestine, and the colon, which is the large intestine, are the two organs that are most frequently affected by this condition. Rather of manifesting as a continuous length of inflamed tissue, the inflammation that is characteristic of Crohn's disease is frequently discontinuous and manifests itself in patches. In contrast to other types of inflammatory bowel disease, such as ulcerative colitis, this pattern of inflammation allows for healthy tissue to be interspersed between inflamed segments. This characteristic sets it apart from other variations of the disease.

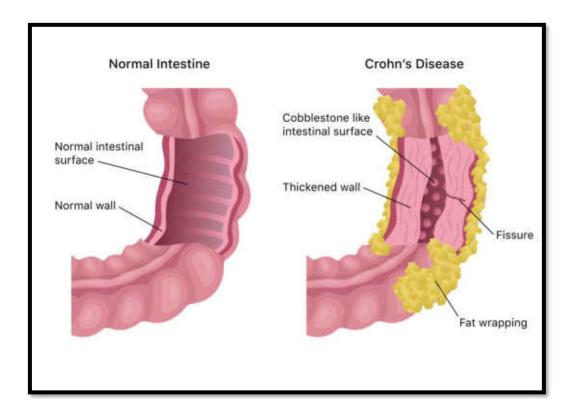


Figure 1: Crohn's Disease

It is possible for the symptoms of Crohn's disease to vary greatly depending on the location of the inflammation and the degree to which it is present. Symptoms that are frequently experienced include cramping and pain in the abdominal region, which are typically directed toward the lower right side of the abdomen. Another common symptom is diarrhea, which can sometimes be bloody. This symptom can contribute to severe weight loss and exhaustion. You may also experience diarrhea. Additionally, patients who suffer from Crohn's disease may experience a diminished appetite in addition to systemic symptoms such as fever and joint discomfort. It is possible for complications to develop as the disease progresses. These complications include bowel obstructions, which can result in severe abdominal pain and distension; fistulas, which are abnormal connections that can form between different parts of the intestine or between the intestine and other organs; and abscesses, which are localized collections of pus that can lead to additional discomfort and potential infections.

An all-encompassing method that incorporates clinical examination in addition to a variety of diagnostic techniques is commonly utilized in the process of diagnosing Crohn's disease. The presence of anemia and high indicators of inflammation, both of which are symptomatic of a continuous inflammatory process, can be determined by the use of blood tests. It is possible to rule out other potential causes of gastrointestinal problems, such as infections, with the assistance of stool testing. Intestinal imaging tests such as abdominal ultrasound, computed tomography (CT) scans, and magnetic resonance imaging (MRI) provide detailed images of the intestines, which assist in locating areas of inflammation and issues. Endoscopic procedures, such as colonoscopy and ileoscopy, make it possible to directly observe the segments of the gut that are impacted. The diagnosis of Crohn's disease can be confirmed by the use of biopsies, which are taken during these procedures and involve the examination of tissue samples for alterations that are diagnostic of the disease.

Inflammation reduction, symptom management, and the maintenance of remission periods are the primary foci of treatment for Crohn's disease. A mixture of drugs is often used for treatment. These treatments include amino salicylates, which are used to reduce inflammation; corticosteroids, which are used for more acute episodes of inflammation; immunomodulators, which are used to dampen the immune response; and biologics, which are recommended for more severe instances. Modifications to the patient's diet may be necessary in order to address malabsorption issues and control symptoms. This will ensure that patients obtain appropriate nourishment despite the difficulties they are experiencing with their gastrointestinal tract. It is possible that surgical intervention will be required in situations where medical therapy alone is

not sufficient. Resection of damaged parts of the intestine or treatments to address issues such as blockages or fistulas are examples of surgical interventions that may be performed through surgical interventions. The purpose of treatment is to enhance the quality of life, successfully manage symptoms, and either avoid or treat problems that are linked with Crohn's disease.

***** Ulcerative Colitis

The condition known as ulcerative colitis is a form of inflammatory bowel disease (IBD) that is distinguished by persistent inflammation of the colon (also known as the large intestine) and the rectum. It is possible to differentiate this disorder from Crohn's disease by observing the pattern of inflammation that it causes and the locations that it impacts. When a person has ulcerative colitis, the inflammation starts in the rectum and moves proximally through the colon in a continuous fashion. There are no healthy segments that are interspersed between the sections that are inflamed. This continuous pattern of inflammation is one of the defining characteristics of ulcerative colitis, which differentiates it from Crohn's disease, which might present with patches of inflammation that are intermittently distributed throughout the gastrointestinal system.

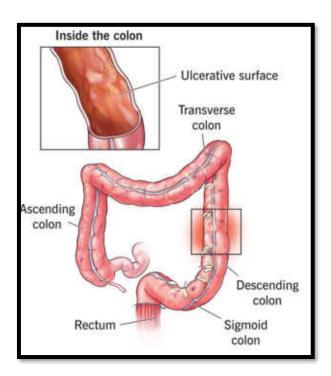


Figure 2: Ulcerative Colitis

The effects of ulcerative colitis on the colon and rectum are the primary cause of the symptoms that are associated with the condition. Symptoms that are frequently experienced include cramping, abdominal pain, and recurrent diarrhea, which may be bloody or contain mucous.

Additionally, patients may have a sense of urgency and a frequent desire to have bowel movements, both of which can result in discomfort and a disruption of their normal daily activities. There is also the possibility of experiencing fever, exhaustion, and a loss of weight. A toxic megacolon, which is a condition in which the colon gets overly dilated, colon perforation, and an increased risk of colorectal cancer are some of the problems that can arise from severe cases of ulcerative colitis. The patient's health may be negatively impacted even further as a result of these issues, which may require some extra medical procedures.

The clinical evaluation, laboratory testing, and imaging studies that are used to diagnose ulcerative colitis are all important components of the diagnostic process. It is possible for blood tests to reveal anemia as well as high levels of inflammatory triggers. It is possible to rule out illnesses and determine whether or not blood or mucus is present through the use of stool tests. Imaging examinations, such as CT scans or abdominal ultrasounds, can provide information about the severity of the condition and allow for the identification of any problems that may be present. Colonoscopy is an important diagnostic tool because it enables direct visualization of the colon and the rectum region of the body. During this treatment, biopsies can be obtained from the mucosal lining of the colon in order to verify the diagnosis and determine the level of inflammation that is present.

The management of ulcerative colitis focuses on lowering inflammation, regulating symptoms, and establishing and sustaining remission of the condition. The use of anti-inflammatory drugs, such as amino salicylates, which are intended to reduce inflammation in the colon, is frequently used into treatment regimens. In cases of more severe flare-ups, corticosteroids may be administered in order to immediately bring under control the extreme inflammation. In situations where traditional treatments are ineffective or the condition is more severe, immunomodulators and biologics are utilized as effective therapy options. It may be necessary to make adjustments to one's diet and receive nutritional support in order to effectively manage symptoms and guarantee enough nourishment. It is possible that surgery will be required in certain circumstances, particularly in the event that the patient does not react to medicinal treatment or if major problems arise. One of the surgical alternatives that may be considered is a colectomy, which is a surgical procedure that involves the removal of a portion or the entire colon. This may result in the requirement of an ostomy or an ileal pouch-anal anastomosis (IPAA) in order to restore bowel function. The purpose of treatment is to ease symptoms, enhance quality of life, and reduce the impact that ulcerative colitis has on the patient's overall health as much as possible.

Symptoms

Ulcerative colitis is characterized by a variety of symptoms that initially manifest in the gastrointestinal tract and have the potential to drastically damage the quality of life of those who are affected by it. This illness is characterized by a specific set of symptoms, one of which being bloody diarrhea. Patients frequently experience numerous bowel movements, and the stool that they pass may contain blood and mucous in addition to other substances. The bleeding that occurs as a consequence of the inflammation and ulceration of the mucosal lining of the colon is the direct source of this symptom. Blood in the stool is a key indicator that should prompt additional medical evaluation because it might be a cause for concern and should be taken seriously.

Ulcerative colitis is characterized by a large number of symptoms, including abdominal pain and cramps. The discomfort and pain that may be experienced in the abdominal region are the result of the inflammation and ulceration of the colon. The level of this pain might range from a modest cramping sensation to a severe discomfort that can be incapacitating. It is common for the extent and intensity of the inflammation within the colon to coincide with the level of pain that is experienced and the location of the pain.

Patients who suffer from ulcerative colitis may experience an urgent need to defecate, which, depending on the severity of the condition, may occur simultaneously. This sense of urgency is frequently accompanied by a sensation of incomplete evacuation, which may result in repeated trips to the bathroom, which in turn disrupts daily activities and has an effect on the quality of life experienced overall. Having to use the restroom frequently and urgently can be a source of anguish and add to the emotional and psychological stress that most people experience.

Another prominent symptom is weight loss, which frequently occurs as a consequence of the manifestation of persistent diarrhea, abdominal pain, and a diminished appetite together. It is possible for an individual to experience insufficient nutritional intake and unexpected weight loss as a result of persistent diarrhea and malabsorption of nutrients associated with inflammation. Loss of weight might be a cause for concern because it indicates that the body is unable to retain appropriate nourishment and health throughout the process.

Patients may also develop systemic symptoms such as fever and exhaustion in addition to these gastrointestinal problems while they are undergoing treatment. The occurrence of fever is frequently an indication of more severe disease activity and can be brought on by systemic

inflammation. It is normal for people to report feeling tired, and this feeling is frequently associated with the body's reaction to persistent inflammation, nutritional inadequacies, and disturbed sleep patterns as a result of frequent bowel movements and experiencing discomfort.

Profound instances of ulcerative colitis have the potential to result in severe consequences. One of these complications is toxic megacolon, which is a serious condition in which the colon gets overly dilated and has the potential to lead to severe complications such as perforation or rupture. This condition is a medical emergency and calls for immediate medical attention in order to prevent outcomes that could be potentially fatal. Moreover, patients who have been suffering from ulcerative colitis for an extended period of time have a higher likelihood of developing colon cancer. Chronic inflammation and repeated injury to the lining of the colon can raise the possibility of dysplastic alterations and cancer over time. In order to control this risk, it is necessary to conduct regular surveillance and use early detection measures during the course of treatment.

In general, the intensity of the symptoms of ulcerative colitis can vary, and they have the potential to profoundly impact a patient's day-to-day life as well as their overall health and wellbeing. When it comes to enhancing one's quality of life and lowering the likelihood of consequences, appropriate management of these symptoms is quite necessary.

Diagnosis

Evaluation of the patient's clinical condition, endoscopic procedures, and histological examination are all components of the comprehensive approach that is required for the diagnosis of ulcerative colitis. This comprehensive procedure is essential for correct diagnosis and distinguishing this condition from other illnesses that affect the gastrointestinal tract.

In order to diagnose ulcerative colitis, the first step is to examine the patient's clinical presentation. In order to arrive at a preliminary diagnosis, medical professionals have to rely on the patient's symptoms, which may include bloody diarrhea, abdominal pain, and an urgent need to defecate. In order to determine whether or not a patient has ulcerative colitis, it is helpful to have a comprehensive patient history that includes detail about the duration and pattern of symptoms, as well as any related systemic indications such as fever or weight loss. The existence of symptoms such as weight loss and abdominal discomfort, in conjunction with the pattern of diarrhea, gives vital clues that determine the next steps in the diagnostic process.

When it comes to accurately diagnosing ulcerative colitis, endoscopy is an indispensable diagnostic tool. The colonoscopy provides the physician with the opportunity to directly observe the colon and the rectum, which enables the physician to evaluate the level of inflammation and its severity. During this operation, the endoscope is advanced through the colon after being implanted through the rectum. This allows for the provision of real-time images of the mucosal lining. Inflammation that is continuous and originates at the rectum and extends proximally into the colon is one of the defining signs of ulcerative colitis, which can be identified with the help of this visual examination. The colonoscopy also makes it possible to collect biopsy samples from the areas that are affected by the condition. The histological study of these biopsies has the potential to reveal distinctive alterations that are linked with ulcerative colitis. These changes include crypt abscesses, which are clusters of neutrophils that are located within the intestinal glands, as well as other inflammatory changes.

By evaluating the patient's overall health and locating signs of inflammation, blood tests are utilized to provide additional evidence in support of the diagnosis. White blood cell and C-reactive protein (CRP) levels that are considered to be elevated may be indicative of systemic inflammation. On the other hand, anemia may be the consequence of persistent blood loss that is caused by the illness. The results of these tests are helpful in determining the severity of the inflammation and determining how it will affect the patient's overall health.

The purpose of stool studies is to eliminate the possibility of infections or other gastrointestinal disorders that may be causing symptoms that are similar to those of ulcerative colitis. It is possible to examine samples of stool to determine whether or not they contain any infections, parasites, or other abnormalities. This helps identify ulcerative colitis from other potential concerns that impact the gastrointestinal system, such as infectious causes of diarrhea and other potential medical conditions.

In conjunction with one another, these diagnostic instruments make it possible to conduct a thorough assessment of ulcerative colitis. A comprehensive evaluation of the condition is achieved by the combination of clinical symptoms, endoscopic findings, the results of a biopsy, and laboratory tests. This ensures that an accurate diagnosis is accomplished and that suitable therapy methods are implemented.

❖ Treatment

The goal of treatment for ulcerative colitis is to ease symptoms, reduce inflammation, and sustain remission over the long term. The disease is efficiently managed through the utilization

of this technique, which incorporates medicine, alterations to one's lifestyle, and, when necessary, surgical intervention.

Medication is an essential component in the treatment and management of ulcerative colitis. The major objective of pharmacological treatment is to minimize inflammation within the colon and rectum, with the end goal of easing symptoms and preventing flare-ups. Amino salicylates, such as mesalamine, are frequently the initial medication that is administered. They reduce inflammation by acting directly on the mucosal lining of the intestine, which is how they bring about their effects. In most circumstances, these drugs are useful for mild to moderate cases, and they also assist in maintaining remission conditions. The use of corticosteroids, such as prednisone, may be recommended for patients experiencing more severe inflammation. In spite of the fact that these medications are powerful anti-inflammatory agents that can rapidly alleviate symptoms during flare-ups, physicians typically only prescribe them for brief periods of time because of the potential adverse effects that may occur with prolonged usage. Immunomodulators, such as azathioprine or mercaptopurine, are frequently utilized for long-term care or in situations where patients do not respond to other treatments. These immunomodulators help decrease the immunological response that contributes to inflammation. Infliximab and adalimumab are two examples of biologics that are used to treat moderate to severe cases of inflammatory arthritis that do not respond to traditional treatments. These biologics target specific proteins that are involved in the inflammatory process. The administration of these medications, which are commonly given through injection or infusion, has the potential to provide significant relief and long-term remission for a large number of patients.

In order to effectively manage ulcerative colitis, it is necessary to make dietary adjustments and receive nutritional support. It may be necessary for patients to make adjustments to their diet in order to avoid foods that are known to aggravate symptoms, such as foods heavy in fiber, dishes that are spicy, or dairy products. Because of the disease's potential to cause malabsorption and shortages in nutrients, nutritional supplementation is of the utmost importance. Managing symptoms, ensuring proper nutrient intake, and improving general health can all be accomplished with the collaboration of a dietitian in the development of a diet plan that is both balanced and appropriate. Supplements or other specific nutritional items may be necessary for patients in certain circumstances in order to remediate inadequacies and provide support for their dietary requirements.

When medicinal care is insufficient or when the condition creates considerable difficulties, surgical intervention becomes a consideration that should be taken into account. It is possible that surgical solutions will be required in situations when the disease is resistant to treatment or when complications such as severe bleeding, perforation, or malignancy manifest themselves. The definitive treatment for ulcerative colitis is a surgical procedure known as a colectomy, which involves the removal of the colon. Ileal pouch-anal anastomosis (IPAA) is one of the surgical procedures that may be considered depending on the severity of the disease and the preferences of the patient. This procedure involves the creation of a new reservoir for stool from the ileum and its attachment to the anus, which enables the patient to have intestinal function that is nearly normal. Patients also have the option of undergoing a total colectomy with permanent ileostomy, which involves the formation of a stoma for the purpose of waste removal. This procedure involves the end of the ileum being brought through a hole in the abdominal wall. The use of an external pouch to collect stool is required for this method, although it is capable of efficiently managing the disease in situations where other therapies have been unsuccessful.

Second Considerations

Inflammatory bowel illnesses that are chronic in nature, such as Crohn's disease and ulcerative colitis, are characterized by periods of exacerbation and remission. In order to effectively manage these diseases, a multi-pronged approach is required, which includes the combination of medicine, alterations to one's lifestyle, and consistent monitoring.

In order to effectively manage Crohn's disease and ulcerative colitis, it is essential to make adjustments to one's lifestyle. These adjustments can have a substantial impact on the management of symptoms and general well-being. When it comes to the treatment of inflammatory bowel disease (IBD), stress management is recognized as an essential component. Because emotional and psychological stress can make symptoms worse and cause flare-ups, it may be good to incorporate stress-relieving strategies such as mindfulness, meditation, and counseling into one's treatment plan. In addition, it is necessary to recognize possible food triggers and steer clear of them. Keeping a food diary and working with a dietician can be helpful in identifying and avoiding the foods that are causing symptoms to become more severe. This is because many people discover that particular meals can make their symptoms worse. A few examples of this would be foods that are high in fiber, dairy goods, and spicy foods. It is also possible to improve overall health and alleviate symptoms by ensuring appropriate hydration and adhering to a balanced diet that is adapted to the specific

requirements of the individual. Exercising on a regular basis, within one's tolerance level, can help enhance overall well-being and assist in the management of certain symptoms.

Individuals who suffer from Crohn's disease and ulcerative colitis should make it a priority to maintain regular follow-up appointments with their healthcare providers. Continuous monitoring makes it possible to make prompt adjustments to treatment plans based on the development of the disease and the patient's reaction to treatment. In order to evaluate the progression of the condition and identify potential consequences at an earlier stage, this includes routine checkups, laboratory testing, and imaging scans. It is possible for medical professionals to make adjustments to drug schedules, suggest additional therapies, or investigate novel treatment alternatives depending on the circumstances. When gastroenterologists, dietitians, and other medical experts work together to coordinate their efforts, they are able to guarantee that a complete approach is taken to controlling the disease and resolving any challenges that may arise.

Both the understanding of inflammatory bowel disease and the treatment of it are continuing to improve as a result of advancements in medical research. New insights into the underlying mechanisms of Crohn's disease and ulcerative colitis are being uncovered as a result of research into the pathophysiology of these disorders. This research is leading to the development of targeted medicines and biologic drugs. With these advancements, there is hope for therapy alternatives that are both more effective and more individualized. Personalized medicine and regenerative medicine are two examples of revolutionary approaches that are currently being investigated in clinical trials and studies. These approaches hold the potential to enhance patient outcomes. It is the goal of medical research to enhance the quality of life for those who are affected by inflammatory bowel disease (IBD) by refining treatment options, reducing side effects, and eventually improving the quality of life.

4.1.1 Jaundice

According to medical professionals, jaundice is a clinical illness that is defined by the yellowing of the skin, sclerae (the white area of the eyes), and mucous membranes. This yellowing is caused by an accumulation of bilirubin in the blood.



Figure 3: Jaundice

The breakdown of red blood cells results in the production of bilirubin, which is a yellow fluorescent pigment. The liver is responsible for its processing, and the bile is typical for its elimination. The condition known as jaundice is not an illness in and of itself; rather, it is a sign of a more fundamental disorder that affects the metabolism or excretion of bilirubin.

A Causes of Jaundice

Jaundice is characterized by a yellowing of the skin and sclera (the white area of the eyes) due to excessive amounts of bilirubin in the blood. The classification of jaundice into prehepatic, hepatic, and post hepatic kinds is based on the underlying etiology and the stage at which bilirubin metabolism is interrupted. Each type of jaundice reflects various disease processes and requires specific diagnostic and treatment techniques.

Prehepatic Jaundice: This type of jaundice originates before bilirubin reaches the liver for processing. It is primarily caused by diseases that contribute to the excessive destruction of red blood cells; a process known as hemolysis. Hemolytic anemia is a major cause of prehepatic jaundice and encompasses different disorders, such as sickle cell disease, thalassemia, and autoimmune hemolytic anemia. These illnesses accelerate the breakdown of red blood cells, leading to an increased production of unconjugated (indirect) bilirubin, which exceeds the liver's capacity to conjugate and handle it. Another prominent cause is hemolytic illness of the

newborn, which comes from an incompatibility between the mother's and baby's blood types (e.g., Rh or ABO incompatibility). This disorder leads to fast destruction of fetal red blood cells and increased amounts of unconjugated bilirubin in the newborn, presenting as jaundice soon after birth.

Hepatic Jaundice: Hepatic jaundice results from abnormalities affecting the liver's capacity to process and conjugate bilirubin. Hepatitis is a main cause, where inflammation of the liver from viral infections (such as hepatitis A, B, or C), excessive alcohol use, or autoimmune illnesses inhibits the liver's capacity to process bilirubin properly. This leads to the buildup of both conjugated and unconjugated bilirubin in the blood. Cirrhosis, another cause of hepatic jaundice, involves persistent liver damage from several sources, including prolonged alcohol use, chronic viral hepatitis, or nonalcoholic fatty liver disease. The gradual scarring of the liver tissue affects normal liver function, particularly bilirubin processing. Gilbert's Syndrome is a hereditary disorder that disrupts the conjugation process of bilirubin, resulting in minor increases of unconjugated bilirubin without severe liver damage or symptoms.

This type of jaundice is known as post hepatic jaundice, and it is caused by an obstruction in the bile ducts. This obstruction prevents the normal excretion of conjugated (direct) bilirubin from the liver into the gut. The accumulation of bilirubin in the liver and bloodstream can be caused by gallstones, which are one of the most prevalent causes. Gallstones can obstruct the bile ducts and slow the passage of bile, which can lead to their accumulation. Another significant factor is cholangiocarcinoma, which is a cancer of the bile ducts that can induce jaundice by obstructing the flow of bile and causing it to become blocked. Post hepatic jaundice can also be caused by pancreatic cancer, particularly tumors that are positioned close to the bile ducts. This is because pancreatic cancer can compress or invade the bile ducts, which results in comparable obstructive health problems. Because of the existence of these blockages, conjugated bilirubin accumulates in the blood, which is then reflected in the distinctive yellowing of the skin and eyes. This condition is characterized by a yellowing of the skin and eyes.

Jaundice is a multidimensional disorder that can be classified according to the location and nature of the disturbance in bilirubin metabolism. In conclusion, jaundice is a condition that can be classified. There are three types of jaundice: prehepatic jaundice, hepatic jaundice, and post hepatic jaundice. Prehepatic jaundice is caused by an excessive breakdown of red blood cells, it is caused by liver malfunction, and it is caused by obstructions in the bile ducts. The

ability to diagnose the underlying cause of jaundice and to determine the right treatment methods for the management of jaundice is facilitated by having an understanding of these categories.

Symptoms and Diagnosis

The yellowing of the skin and eyes is the most prominent symptom of jaundice. This symptom gets more noticeable as the levels of bilirubin in the blood increase. Jaundice is quite prevalent. Bilirubin, which is a byproduct of the regular breakdown of red blood cells, has accumulated, which is the cause of this yellow tint. As bilirubin levels rise, the yellowing of the whites of the eyes becomes more noticeable. The severity of this symptom can vary. The underlying cause of jaundice can cause a variety of symptoms to appear in addition to the obvious yellowing of the skin.

In the early stages of jaundice, black urine is one of the early and unmistakable indicators observed. Urine has a dark amber color, which is commonly described as having a tea-colored appearance. This is because of the elevated amounts of bilirubin that spill over into the urine. One reason for this is that the kidneys are responsible for excreting excess bilirubin, which the liver is unable to handle. One other typical symptom is the presence of feces that are white or clay-colored. In the process of producing bile, which is responsible for the typical brown color of stools, bilirubin is an essential component. Paler stools are the result of a decrease in the amount of bilirubin that is present in the bile, which can be caused by dysfunction in either the liver or the bile ducts. Furthermore, people who have jaundice frequently experience itching, sometimes known as pruritus syndrome. An annoying itch that can be widespread and extremely uncomfortable is the result of bilirubin deposits in the skin, which triggers this condition. This symptom is frequently seen in patients with hepatic and post hepatic jaundice, which is characterized by a disruption in the processing and excretion of bilirubin.

Jaundice: A Diagnosis Procedure

In order to correctly diagnose jaundice, it is necessary to do a comprehensive assessment of the patient's medical history, examination of their symptoms, and a battery of diagnostic tests to identify the underlying cause. Laboratory testing is the most important component in the process of identifying jaundice. Examining the levels of total bilirubin and its components (conjugated and unconjugated) is often the first step in the diagnostic process. Blood tests are typically performed. The ratio of these fractions can provide important hints, including the following: When compared to elevated conjugated bilirubin levels, which are symptomatic of

hepatic or post hepatic causes, such as liver illness or bile duct obstruction, elevated unconjugated bilirubin levels are frequently indicative of prehepatic causes, such as hemolysis. In addition, it is vital to do liver function tests, particularly those that detect enzymes such as alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase. The diagnostic process can be further guided by the presence of elevated levels of these enzymes, which can indicate inflammation or injury to the liver. The complete blood count (CBC) is a diagnostic tool that can offer further insights, notably in the identification of hemolytic anemia, which is a condition that can lead to prehepatic jaundice.

When there is a suspicion of structural abnormalities, imaging examinations are an extremely important part of the diagnostic process for jaundice symptoms. Because it is non-invasive and extremely successful in seeing the liver, gallbladder, and bile ducts, ultrasound is frequently the first imaging modality that is utilized. Gallstones, obstructions in the bile ducts, and abnormalities in the liver can all be identified with its assistance. Additional information on the structure of the liver, the existence of tumors, or any other abnormalities that might be contributing to jaundice can be obtained by the use of a CT scan or an MRI in more complex instances. This allows for a more detailed look of the abdominal organs. An examination of the liver may be carried out in specific circumstances, such as when the reason for jaundice is not yet known or when there is a suspicion of liver disease. For the purpose of determining the degree of liver damage, inflammation, or disease, this process includes removing a small sample of liver tissue, which is then inspected under a microscope. The diagnosis of disorders such as hepatitis, cirrhosis, or liver cancer can be particularly helpful in guiding the treatment approach. A liver biopsy can be particularly beneficial in this regard.

***** Treatment and Management

Due to the fact that jaundice is a symptom rather than an illness, the therapy and management of jaundice generally concentrate on locating and treating the underlying cause of the condition. The treatment options that are effective differ depending on whether the jaundice is prehepatic, hepatic, or post hepatic. Each of these types of jaundice requires a different approach to be taken.

In situations with prehepatic jaundice, the treatment consists of controlling the underlying cause of excessive destruction of red blood cells, which is referred to as hemolysis. Interventions such as blood transfusions, corticosteroids, or other immunosuppressive medications may be necessary for patients suffering from hemolytic anemia, which is

characterized by increased levels of unconjugated bilirubin. This is especially true in cases where an autoimmune-related disease is present. It is possible that a splenectomy, which is the removal of the spleen, is required in some circumstances if the spleen is significantly contributing to the loss of red blood cells. Furthermore, it is essential to monitor and treat any underlying genetic diseases, such as sickle cell disease or thalassemia, in order to forestall the occurrence of additional hemolytic episodes.

In the case of hepatic jaundice, which is caused by liver malfunction, the treatment focuses on the management of the particular liver condition under consideration. In the case of viral hepatitis, antiviral drugs may be recommended in order to lessen the amount of viral load and stop any further damage to the liver. In the case of alcoholic liver disease, the most important step is to stop drinking alcohol. This, in conjunction with receiving supportive care, can assist in halting the progression of liver damage. In addition, it is vital to make changes to one's lifestyle, such as adopting a nutritious diet, engaging in regular physical activity, and avoiding substances that are damaging to the liver. In most cases, therapy is not required for inherited diseases such as Gilbert's syndrome, which is characterized by mild jaundice that occurs intermittently. However, patients are encouraged to avoid triggers such as stress or fasting, as these substances have the potential to increase symptoms. In more severe forms, such as cirrhosis, treatment may involve controlling consequences, such as fluid retention or hepatic encephalopathy. In more advanced cases, liver transplantation may be investigated as a potential therapeutic option.

It is necessary to take a different strategy when treating post hepatic jaundice because it is caused by an obstruction in the bile ducts. First and foremost, the objective is to alleviate the obstruction and bring the flow of bile back to normal. It is frequently possible to accomplish this with the use of surgical or endoscopic treatments. In the event that gallstones are obstructing the bile ducts, for instance, an endoscopic retrograde cholangiopancreatography (ERCP) operation might be carried out in order to remove the stones. When tumors, such as those caused by cholangiocarcinoma or pancreatic cancer, are the cause of the obstruction, it may be required to perform surgery in order to remove the tumor or, in certain instances, to bypass the obstruction. Stenting is another method that can be utilized to hold the bile ducts open. In addition to these operations, it is essential to manage any associated disorders, such as infections or inflammation, in order to prevent any further difficulties from occurring.

The management of symptoms and the prevention of consequences associated with jaundice frequently require supportive care in addition to the treatment of the underlying causes of the condition at hand. The importance of ensuring appropriate hydration cannot be overstated, particularly in situations when there is a possibility of dehydration as a result of vomiting or diarrhea. Because liver failure can result in malnutrition and vitamin shortages, nutritional supplementation is also quite important under these circumstances. This may require making adjustments to one's diet, taking supplements, and, in more severe cases, receiving sustenance through parenteral means. In addition, the management of itching, also known as pruritus, which is a typical and irritating symptom of jaundice, may require the use of antihistamines or other medications that assist in lowering the levels of bilirubin in the skin.

The management of jaundice requires a number of key components, including regular monitoring and follow-up with healthcare experts. As part of this process, periodic blood tests are performed to determine the levels of bilirubin, liver function tests are performed to monitor the progression or improvement of liver disease, and imaging investigations are performed to evaluate the efficacy of treatments for bile duct obstructions. Continuous monitoring assists in the early detection of potential consequences, such as liver failure or cholangitis, which enables urgent intervention to be taken.

4.1.2 Hepatitis (A, B, C, D, E, F) alcoholic liver disease

***** Hepatitis Overview

Hepatitis is a broad word that refers to the inflammation of the liver, a crucial organ responsible for various essential processes, including detoxification, protein synthesis, and the creation of biochemicals necessary for digesting. Hepatitis can occur due to several causes, including viral infections, exposure to toxins, excessive alcohol consumption, autoimmune illnesses, and certain drugs. The most prevalent and well-known cause of hepatitis is viral infection, which can result in many forms of the disease, classed principally as Hepatitis A, B, C, D, and E. Each kind of viral hepatitis is caused by a different virus and has various mechanisms of transmission, clinical symptoms, and long-term implications.

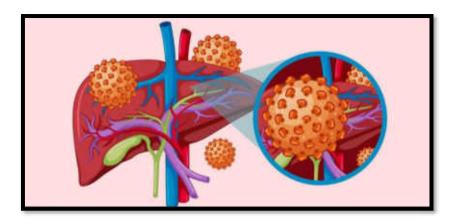


Figure 4: Hepatitis

Hepatitis A is primarily spread through ingestion of contaminated food or drink, or close contact with an infected person. It is usually an acute, short-term illness, and most persons recover totally without lasting liver damage. However, in rare situations, it can lead to severe problems, especially in older persons or individuals with previous liver diseases. Vaccination is highly successful in preventing Hepatitis A.

Hepatitis B is a more serious infection that can be transferred through contact with infected blood, semen, or other body fluids. It can be spread from mother to kid at birth, through sharing needles, or through unprotected sexual intercourse. While many persons infected with Hepatitis B recover totally, a considerable minority acquire chronic Hepatitis B, which can lead to serious liver damage over time, including cirrhosis (scarring of the liver), liver failure, or liver cancer. There is a vaccine available that is highly successful in avoiding Hepatitis B infection.

Hepatitis C is primarily transferred by blood-to-blood contact, often through sharing needles or other equipment to inject drugs. It can also be spread by non-sterile medical equipment or transfusions of unscreened blood products. Unlike Hepatitis A and B, there is no vaccine for Hepatitis C, and it commonly evolves to a chronic illness. Chronic Hepatitis C is a significant cause of liver transplantation and can progress to severe consequences such as cirrhosis and liver cancer. However, with recent improvements in antiviral medicines, many persons with Hepatitis C can now be cured.

Hepatitis D, also known as delta hepatitis, is a distinct type of viral hepatitis that exclusively occurs in individuals who are already infected with Hepatitis B. This is because the Hepatitis D virus requires the Hepatitis B virus to proliferate. Co-infection with Hepatitis D and B can

lead to more severe liver damage than infection with Hepatitis B alone. Hepatitis D is less common internationally but remains a significant public health risk in particular locations.

Hepatitis E is comparable to Hepatitis A in terms of transmission, generally transferred by contaminated water. It is especially common in locations with poor sanitation. Hepatitis E normally results in an acute infection that heals on its own, but it can be severe in pregnant women, leading to greater risks of complications and mortality.

The idea of a "Hepatitis F" has been discussed in several research, however it is not officially recognized by the World Health Organization (WHO) as a distinct viral organism. Research is ongoing to establish whether a new type of virus may be classed as Hepatitis F, but currently, no definitive evidence supports its presence as a separate form of viral hepatitis.

Hepatitis can present in either acute or chronic forms. Acute hepatitis refers to the initial phase of inflammation, which can range from moderate to severe and can last up to six months. Chronic hepatitis develops when the inflammation persists for longer than six months, generally leading to significant liver damage. Chronic hepatitis can result in catastrophic complications, including cirrhosis, liver failure, and liver cancer. The chance of having chronic hepatitis varies based on the kind of hepatitis virus involved, the individual's immune response, and other factors such as age, co-existing health problems, and lifestyle choices.

Early diagnosis and treatment are critical in treating hepatitis and preventing its progression to more severe stages. Public health activities, including immunization programs, safe blood transfusion practices, harm reduction strategies for those who inject drugs, and public education campaigns, play a critical role in preventing the development of viral hepatitis and its accompanying problems.

> Hepatitis A (HAV)

The acute viral illness known as hepatitis A (HAV) is caused by the Hepatitis A virus, which is notorious for its ability to attack the liver in particular. As a result of the fact that the fecal-oral route is the primary mode of transmission of HAV, it is more frequent in areas that have inadequate sanitation and restricted access to clean water. When food or water in these regions becomes contaminated with the excrement of an infected individual, the virus has the potential to spread rapidly all over the region. Additionally, it is known that the virus can spread through close physical contact, which can occur within households or in settings such as daycares where hygiene procedures may be compromised. Viral transmission can also occur through the intake

of shellfish that has been picked from polluted waters and is either raw or undercooked. This mode of infection is less common.

The clinical manifestation of hepatitis A can vary, but some of the most common symptoms include fatigue, nausea, vomiting, abdominal pain, lack of appetite, and jaundice, which is characterized by yellowing of the skin and eyes. Jaundice is caused by the liver's inability to metabolize bilirubin, which gives the appearance of yellowing. In other instances, particularly in young children, the infection may not present any symptoms at all. The degree of symptoms can range from mild to severe during the course of the infection. In spite of the fact that the acute phase of hepatitis A can be distressing and incapacitating, it is often self-limiting, and the majority of people recover entirely within a few weeks to months without experiencing any long-term damage to their liver. It is essential to note that once a person recovers from HAV, they have immunity to the virus that lasts for their entire life, which means they cannot become infected again.

Hepatitis A is distinguished from other types of hepatitis by the fact that it does not result in chronic liver damage. This is one of the most important distinctive characteristics of Hepatitis A. Hepatitis A is an acute infection that does not result in any long-term complications, in contrast to Hepatitis B or Hepatitis C, in which the virus can remain in the body for an extended period of time and cause chronic inflammation of the liver, cirrhosis, or even cancer of the liver. As a result of this trait, the prognosis for HAV infection is often excellent, particularly when appropriate supportive attention is provided. Fulminant hepatitis, on the other hand, is a severe form of liver failure that can be life-threatening, particularly in older persons or those who have preexisting liver disorders. Fulminant hepatitis can be caused by HAV infection in extremely rare cases because of its severity.

It is widely acknowledged that vaccination is one of the most effective public health interventions that can be implemented. Vaccination plays a significant part in the prevention of hepatitis A. Only one or two doses of the Hepatitis A vaccination are required to provide protection against the virus that is effective for an extended period of time when administered. It is routinely advised for children in a number of countries, as well as for adults who are at a higher risk of infection. This includes individuals who are traveling to regions with a high HAV incidence, people who have chronic liver illness, and those who work in conditions where they may be exposed to the virus. Improvements in sanitation and the promotion of good hygiene

habits, such as thorough handwashing, are critical methods for reducing the spread of hepatitis A infections. Vaccination is also an important component of this strategy.

In general, hepatitis A is a disease that may be prevented via the implementation of good public health measures, despite the fact that it can cause severe illness, particularly during outbreaks. In many regions of the world, the incidence of HAV has significantly decreased as a result of the combination of vaccination and improved sanitation. However, there are still obstacles to be faced in regions that have limited resources accessible. Campaigns to raise public awareness and encourage vaccination continue to be essential in lowering the global burden of hepatitis A, particularly in areas where the virus continues to be prevalent.

> Hepatitis B (HBV)

The Hepatitis B virus (HBV) is the causative agent of the severe viral illness known as hepatitis B. This virus takes aim at the liver and has the potential to cause both acute and chronic liver damage. HBV is typically transmitted through contact with infectious body fluids, such as blood, sperm, vaginal secretions, and saliva in some instances. Salivation is also a potential vector for HBV transmission. A number of common means of infection include sexual contact that is not protected, the sharing of needles or other drug paraphernalia, and the transmission of the virus from mother to child during childbirth, which is referred to as vertical transmission. As a result of this latter approach, which contributes to the high prevalence of chronic HBV infections beginning at a young age, it is particularly relevant in locations where hepatitis B is endemic.

The clinical manifestations of hepatitis B differ from one instance of the illness to another, depending on whether it is acute or chronic. There are a variety of symptoms that can be associated with acute hepatitis B. Some of these symptoms include exhaustion, jaundice, dark urine, joint pain, and abdominal pain. However, Acute Hepatitis B may also be asymptomatic, especially in youngsters. In spite of the fact that a significant number of people who have acute Hepatitis B recover entirely and develop immunity that lasts a lifetime, there is a subgroup of those who are infected who are unable to eliminate the virus from their bodies, which results in chronic infection. This is especially true for newborns and young children. Chronic hepatitis B is a disorder that lasts for a long period of time and is characterized by constant replication of the virus in the liver, which results in persistent inflammation and damage. Chronic inflammation can, over time, develop to significant liver disorders such as cirrhosis, liver

failure, and hepatocellular carcinoma, which is a type of liver cancer. Cirrhosis is a painful condition that affects the liver.

There is a considerable burden of chronic hepatitis B around the world, particularly in regions of Asia and Africa where the virus is widespread and where transmission from mother to child is common. According to research, people who have a persistent HBV infection have a significantly increased likelihood of getting cirrhosis and liver cancer in comparison to individuals who do not have the virus. Because of this heightened risk, it is more important than ever to detect and treat HBV at an early stage in order to prevent or lessen the severity of potentially devastating effects. The screening for hepatitis B virus (HBV) is extremely important, particularly for pregnant women, high-risk groups such as healthcare workers, and individuals who come from regions with a high prevalence of these viruses. The early diagnosis of liver disease enables timely intervention, which may include antiviral therapy. This treatment has the potential to suppress the virus, reduce inflammation in the liver, and reduce the likelihood of the disease progressing to a more severe form.

Vaccination is the most important component in preventing hepatitis B, and it has been demonstrated to be highly efficient in lowering the number of people who are infected with HBV all over the world. The hepatitis B vaccine, which is typically given in three doses, offers protection that is considered to be long-lasting and is included in the routine immunization schedules of a number of countries. There has been a significant reduction in the rates of chronic HBV infection, particularly in countries where the virus is endemic, as a result of universal vaccination programs, particularly those that target newborns. Screening of blood products, safe sexual practices, and harm reduction strategies for people who inject drugs, such as needle exchange programs, are all examples of preventative measures that can be taken in addition to vaccination.

There are antiviral medications available for people who have chronic Hepatitis B. These medications, which include entecavir and tenofovir, have been demonstrated to effectively reduce viral replication, lower liver enzyme levels, and reduce the risk of liver disease progression. Despite the fact that these treatments do not cure the infection, they are extremely important in the management of the disease and in preventing the development of complications such as cirrhosis and liver cancer. It is essential for individuals who have chronic HBV to undergo routine monitoring of their liver function and viral load in order to evaluate the efficacy of treatment and identify any signs of disease progression.

Hepatitis B continues to be a significant problem for the health of people all over the world, particularly because of the fact that it has the potential to cause chronic liver disease and liver cancer. There is, however, the potential for a significant reduction in the impact of HBV through the implementation of widespread vaccination, early detection, and effective treatment. The expansion of vaccination coverage, the enhancement of access to screening and treatment, and the raising of awareness regarding the transmission and prevention of hepatitis B are the primary focuses of ongoing efforts to improve public health practices.

➤ Hepatitis C (HCV)

The hepatitis C virus (HCV) is the causative agent of the viral infection known as hepatitis C, which is transmitted mostly through the exchange of blood between individuals. Because the most typical method of transmission is through the sharing of needles or other equipment used to inject drugs, the human cytomegalovirus (HCV) is especially widespread among individuals who inject drugs. Other potential modes of transmission include obtaining infected blood products or organ transplants; however, the risks associated with these modes of transmission have been greatly decreased as a result of the deployment of stringent blood screening measures. The human cytomegalovirus (HCV) can also be spread in healthcare settings through unintentional needlestick injuries, but this case is very uncommon. There is a possibility of transmission through non-sterile tattoo or piercing equipment, as well as from mother to child during birthing, although this is a less usual occurrence.

Hepatitis C is frequently referred to as a "silent" infection due to the fact that many people may not experience any symptoms for years, thereby remaining unaware that they are infected with the virus. The majority of the time, acute HCV infection is asymptomatic or manifests with minor symptoms that are not specific to the infection, such as fatigue, fever, or jaundice. On the other hand, the true cause for concern with HCV is the fact that it has a propensity to develop into a chronic infection. Chronic Hepatitis C is a condition in which the virus continues to reside in the liver and causes continuing inflammation. It is estimated that between 75 and 85 percent of people who are infected with HCV will develop chronic Hepatitis C. Over the course of time, this persistent inflammation can result in serious damage to the liver, which may include fibrosis (also known as scarring), cirrhosis, liver failure, and hepatocellular carcinoma, which is a kind of liver cancer. Because the likelihood of having these consequences rises with the length of time that the infection has been present, it is essential to recognize and treat the infection as soon as possible.

On the other hand, there is currently no vaccine available for Hepatitis C, in contrast to Hepatitis A and B. In the lack of a vaccine, the prevention of HCV transmission has become increasingly difficult, particularly in populations that are at a higher risk of contracted the virus. Harm reduction initiatives, including as needle exchange programs and safe injection practices, are at the center of public health strategies aimed at reducing the spread of the human cytomegalovirus (HCV). These strategies also emphasize screening and education in order to detect and treat infections at an earlier stage. To avoid occupational transmission of infectious diseases in healthcare settings, it is vital to adhere to infection control measures with a high level of rigor. These practices include the use of personal protective equipment and the careful handling of needles.

The landscape of therapy for hepatitis C has been completely transformed as a result of developments in antiviral medicines, despite the difficulties associated with antiviral prevention. The development of direct-acting antivirals (DAAs) has made it possible to treat the virus in the vast majority of patients, with cure rates that are higher than 90 percent in several instances. These drugs are effective because they target particular stages in the life cycle of the HCV virus. As a result, they are able to effectively prevent the virus from multiplying and allow the liver to repair. A course of oral medication that lasts between eight and twelve weeks is all that is required for treatment, which is normally well tolerated. By making these extremely effective medications available, the HCV has been turned from a disease that is chronic and has the potential to be fatal into a disease that can be cured, which has considerably improved the prognosis for persons who are afflicted with the virus.

Finding a case of hepatitis C at an early stage is absolutely necessary in order to stop the progression of liver disease. It is advised that high-risk groups undergo routine screening for HCV. These high-risk categories include individuals who inject drugs, people who have HIV, those who had blood products prior to the advent of broad screening, and people born between 1945 and 1965, a cohort that has been demonstrated to have a greater prevalence of HCV. Once the infection has been identified, timely treatment with DAAs can not only kill the infection but also lessen the likelihood of liver-related problems and enhance the patient's overall survival rate. In order to effectively manage chronic HCV and evaluate the efficacy of treatment, it is essential to do routine monitoring of liver function and viral load.

The advent of highly efficient antiviral therapies offers optimism for treating the infection in the majority of patients, despite the fact that hepatitis C poses substantial difficulties to public health due to the fact that it has the potential to cause chronic liver damage and there is no vaccine available to prevent it. Continuous efforts to improve screening, access to treatment, and harm reduction measures are important in order to reduce the worldwide burden of HCV and prevent the severe liver damage that can occur from chronic infection. These efforts are essential in order to prevent the spread of the virus.

➤ Hepatitis D (HDV)

Hepatitis D, which is often referred to as delta hepatitis, is a distinct and severe form of viral hepatitis that is brought on by the Hepatitis D virus (HDV). As opposed to other hepatitis viruses, the Hepatitis D Virus (HDV) is an incomplete virus that is incapable of replicating on its own. In order to proliferate, it is necessary for the presence of the Hepatitis B virus (HBV). Due to the fact that it is dependent on HBV, hepatitis D can only arise in people who are already infected with HBV. This can happen either simultaneously (also known as co-infection) or as a superinfection in people who already have a chronic HBV infection. When compared to HBV infection alone, the presence of both HBV and HDV together results in a more severe form of liver disease.

The transmission of human papillomavirus (HDV) is similar to that of hepatitis B virus (HBV), as it takes place through contact with infected bodily fluids such blood, sperm, and vaginal secretions. Unprotected sexual contact, the sharing of needles or other drug paraphernalia, and the transmission of the virus from mother to child during childbirth are all common ways that the virus is passed back and forth. Individuals who are already HBV-positive and who work in the healthcare industry or who undergo dialysis or blood transfusions on a regular basis are also at a higher risk of getting hypertension virus (HDV). HDV is frequently observed in the same communities that are at risk for HBV. These populations include individuals who inject drugs and those who reside in regions where HBV is endemic. This is because HDV and HBV share the same routes of transmission.

Sometimes the clinical manifestations of hepatitis D are more severe than those of hepatitis B virus infection on its own. HDV and HBV can co-infect, which can result in a quick and severe acute hepatitis. This type of hepatitis may resolve in some people, but it can also lead to fulminant hepatitis, which is a form of acute liver failure that poses a significant risk to the patient's life. When HDV superinfects an individual who already has a chronic HBV infection, the likelihood of the individual developing chronic liver disease is greatly increased during the course of the infection. Cirrhosis, liver failure, and hepatocellular carcinoma are all conditions

that are more likely to develop in patients who have chronic hepatitis D infection. This is because chronic hepatitis D infection frequently causes quicker liver damage. Due to this, Hepatitis D is considered to be one of the most severe kinds of viral hepatitis, and its prognosis is significantly worse when compared to other types of hepatitis infections.

The absence of a vaccination that is specific to HDV is one of the most significant obstacles present in the management of hepatitis D. Vaccination against Hepatitis B, on the other hand, is an efficient method of preventing infection with Hepatitis D Virus (HDV) because HDV cannot live without an HBV infection. Because of this, widespread vaccination against HBV not only lowers the number of cases of liver disease that are caused by HBV, but it also acts as a key preventative measure against the human papillomavirus (HDV). The prevalence of human papillomavirus (HBV) has decreased in regions where the coverage of HBV vaccine is high, which highlights the significance of HBV vaccination as a public health measure.

The therapy alternatives that are available for those who are already infected with HDV are limited and less effective than the treatment options that are available for other types of hepatitis. It is common practice to employ interferon-based therapies as part of the current therapeutic approach. These medicines have the potential to inhibit the replication of HDV and enhance liver function in certain patients. On the other hand, these treatments are not beneficial in every single patient, and a significant number of patients only have partial or transient responses. Efforts are currently being made to produce more efficient antiviral medicines that specifically target human papillomavirus (HDV), with the objective of enhancing the outcomes for individuals who are afflicted with this difficult infection. Monitoring liver function, treating consequences, and resolving HBV co-infection are the primary objectives of HDV infection management until more effective medicines become available. This is done with the goal of reducing the total burden of liver disease.

Individuals who are already infected with HBV are at a significant risk of developing Hepatitis D, which is a particularly severe form of viral hepatitis that carries major health hazards. Due to the fact that HBV is necessary for the replication of HDV, immunization against HBV is an essential preventative step for developing HDV. There are now just a few therapeutic options available for chronic HDV; however, recent developments in research have shown that there is the potential for additional successful medicines in the future. For the purpose of mitigating the effects of this severe liver illness, public health efforts continue to concentrate on the

immunization against HBV and the management of individuals who are co-infected with the virus.

Hepatitis E (HEV)

Hepatitis E is a viral infection that is caused by the Hepatitis E virus (HEV). Similar to Hepatitis A, the fecal-oral route is the primary mode of transmission for hepatitis E. The most common method of transmission is through the ingestion of water that has been contaminated with feces. As a result, HEV is more widespread in areas where there is a lack of access to clean water and basic sanitation. Poor sanitation infrastructure is frequently linked to outbreaks of hepatitis E, particularly in regions that have been impacted by natural disasters or in refugee camps, where the likelihood of water contamination is higher. The disease is endemic in many regions of Asia, Africa, the Middle East, and Central America, where it continues to be a substantial challenge to the prevention and treatment of public health issues.

In most cases, hepatitis E results in an acute infection that resolves on its own and does not develop to a chronic form of liver disease. Jaundice, exhaustion, nausea, vomiting, abdominal discomfort, and fever are some of the symptoms that may be associated with hepatitis E. These symptoms are similar to those that are associated with other types of viral hepatitis. The majority of people who become infected with the virus recover completely within a few weeks and do not experience any long-term harm to their liver. On the other hand, the condition frequently manifests itself in a more severe form in some demographics, particularly among pregnant women. Hepatitis E can produce fulminant hepatitis in pregnant women, particularly those who are in their third trimester of pregnancy. Fulminant hepatitis is a form of liver failure that is both severe and quick, and it is associated with a significant risk of death. As a result of the fact that the death rate for pregnant women who have HEV can reach as high as 25 percent, this illness that occurs during pregnancy is particularly dangerous. There is a lack of complete understanding regarding the precise causes behind this greater severity in pregnant women; nonetheless, it is believed that it is connected to hormonal and immunological changes that occur during pregnancy.

In addition to pregnant women, other populations that are at risk include those who already have liver illness and people who have immune systems that are compromised. These individuals may also face more severe results if they become infected with head and neck transmission (HEV). Nevertheless, hepatitis E is typically a mild condition that goes away on its own for the majority of people in the general population. As there is no specific antiviral

medication available for hepatitis E, the treatment that is typically provided is supportive and focuses on ensuring that the patient stays hydrated and managing their symptoms.

Vaccines against hepatitis E have been developed and are already available in certain countries; however, they are not yet available for widespread usage across the world. China is responsible for the development of the first HEV vaccine, which is also referred to as Hecolin or HEV 239. This vaccine has been demonstrated to be successful in preventing the virus, particularly in groups that are at a high risk. On the other hand, the vaccine is not normally included in routine vaccination programs in the majority of nations, and its availability is restricted. As a consequence of this, the prevention of hepatitis E is primarily dependent on public health interventions that are targeted at enhancing sanitation and ensuring access to safe drinking water. In areas where the virus is endemic, it is essential to make an effort to educate the general public about safe water practices, appropriate hand hygiene, and the dangers of consuming contaminated food or water in order to reduce the number of people who contract the sickness.

Taking action to address the underlying issues that contribute to inadequate sanitation and water contamination is another component of preventing the spread of hepatitis E. When it comes to preventing the spread of HEV in areas where it is endemic, it is absolutely necessary to make investments in infrastructure that will offer clean water, good sewage disposal, and efficient waste management. In the event of an emergency situation, such as a natural catastrophe or a humanitarian crisis, it is essential to ensure that individuals have access to appropriate sanitation facilities and safe drinking water. This is a crucial component of disease prevention efforts.

In a nutshell, the presence of hepatitis E is a major cause for concern about public health in areas that have inadequate sanitation and restricted access to clean water. Although the infection is often self-limiting and moderate for the majority of people, it puts pregnant women and other susceptible populations at a significant risk of experiencing serious complications. The development of a vaccine against HEV provides a glimmer of hope for lessening the burden of the disease; nevertheless, until the vaccine is widely available, public health efforts must concentrate on enhancing sanitation, ensuring that water supplies are safe, and teaching communities about preventative measures. The measures that are being made are absolutely necessary in order to contain epidemics and safeguard people that are at risk of experiencing serious repercussions from hepatitis E.

4.2 Disease of bones and joints

Illnesses that affect the musculoskeletal system and have an effect on the structure, function, and overall health of bones and joints are referred to as diseases of bones and joints. These diseases span a wide spectrum of illnesses. Genetic factors, aging, trauma, infections, and autoimmune disorders are some of the potential causes of these diseases. Other potential causes include infectious diseases.



Figure 5: Disease of Bones and Joints

Conditions that affect the bones and joints can have substantial repercussions, including the inability to move freely, the presence of discomfort, and a decline in the overall quality of life. To effectively manage and prevent bone and joint disorders, it is vital to have a thorough understanding of the various types of bone and joint diseases, as well as their characteristics, symptoms, and treatment choices.

Osteoporosis is one of the most prevalent bone illnesses. It is a condition that is characterized by the loss of bone density and mass, which causes bones to become more fragile and prone to fractures. Osteoporosis is frequently referred to as a "silent disease" due to the fact that it does not manifest any signs until a fracture takes place. Due to the decline in estrogen levels that assist maintain bone density, this disorder is most prevalent in older persons, particularly postmenopausal women. This is because estrogen levels help maintain bone density. Ageing, having a family history of osteoporosis, having a low body weight, not getting enough calcium and vitamin D, and leading a sedentary lifestyle are all factors that increase the likelihood of

developing osteoporosis. Maintenance of a balanced diet that is abundant in calcium and vitamin D, participation in weight-bearing activity on a consistent basis, and, in certain instances, the use of drugs to strengthen bones are all necessary components in the prevention of osteoporosis.

The most prevalent types of arthritis are osteoarthritis and rheumatoid arthritis. Arthritis is another important category of joint illnesses that encompasses a variety of diseases that affect the joints. The slow wear and tear of cartilage, the tissue that cushions the ends of bones in the joints, is the cause of osteoarthritis, a degenerative joint disease. This condition is found in those who have osteoarthritis. The deterioration of cartilage can result in the bones rubbing against one another, which can lead to discomfort, stiffness, and edema. Joints that bear weight, such as the knees, hips, and spine, are frequently affected by osteoarthritis, which is a condition that is more prevalent in people who are older. The treatment for osteoarthritis focuses on the control of pain, the preservation of joint function, and the enhancement of quality of life. This is accomplished through a mix of medication, physical therapy, and, in more severe situations, joint replacement surgery.

On the other hand, rheumatoid arthritis is an autoimmune illness in which the immune system assaults the synovium, which is the lining of the joints, in an incorrect manner. Because of this, inflammation, swelling, and eventually injury to the joints are caused. Rheumatoid arthritis, in contrast to osteoarthritis, can affect numerous joints at the same time and is frequently symmetrical, which means that it affects the same joints on both sides of the body. Systemic symptoms, such as weariness and fever, can also be caused by the disease, and it can also affect other organs over its course. When it comes to controlling rheumatoid arthritis, early diagnosis and therapy are absolutely necessary in order to minimize joint deterioration and prevent the loss of function. medications known as disease-modifying antirheumatic medications (DMARDs) and biologic medicines, which are able to target particular components of the immune system, are generally utilized in the treatment modalities.

Despite the fact that they are less common, infections of the bones and joints can still result in catastrophic problems. A bone infection known as osteomyelitis is typically brought on by bacteria and can manifest itself following a surgical procedure, an injury, or the transmission of the infection from one part of the body to another through the bloodstream. Osteomyelitis is characterized by a number of symptoms, including intense pain in the treated area, fever, and edema. Additionally, if the infection is not treated in a timely manner, it may result in the

deterioration of bone and may necessitate surgical intervention in order to remove diseased tissue. Septic arthritis, which is an infection of the joint, also carries major hazards, as it can result in the destruction of the joint and extreme pain if it is not treated immediately with antibiotics and drainage of the fluid that is flowing through the infected joint.

Other metabolic bone illnesses, such as Paget's disease and osteoma Acia, also play a vital role in bone and joint health. These conditions are in addition to the ones mentioned above. Paget's disease is a chronic condition that causes improper bone remodeling, which results in abnormally enlarged and weaker bones. This condition is caused by a disruption in the normal process of bone remodeling. The condition known as osteoma Acia, which is defined by the weakening of bones as a result of a lack of vitamin D or issues with the body's capacity to metabolize this mineral, can result in bone pain, fractures, and weakness in the muscles. In order to effectively manage symptoms and prevent complications, individualised treatment strategies are required for both disorders. These strategies may include the use of nutritional supplements and pharmaceuticals.

A person's mobility, freedom, and overall well-being can be significantly impacted by bone and joint illnesses, which can have a profound impact on an individual's life cycle. The fact that chronic pain and disability are common results highlights the significance of early diagnosis, treatment that is successful, and preventative actions. When it comes to maintaining healthy bones and joints, it is crucial to engage in regular physical exercise, consume a diet that is well-balanced and abundant in critical nutrients, and steer clear of risk factors such as smoking and drinking an excessive amount of alcohol. The advancements that have been made in medical research continue to lead to a greater knowledge of these disorders, which in turn leads to the development of novel medicines that provide hope for better management and an improved quality of life for individuals who are struggling with them.

4.2.1 Rheumatoid arthritis

Rheumatoid arthritis, often known as RA, is a persistent inflammatory condition that mostly impacts the joints. It is characterized by inflammation, pain, and eventually destruction to the joints. On the other hand, rheumatoid arthritis is the result of an aberrant immune response in which the body's immune system mistakenly targets the synovium, which is the lining of the membranes that surround the joints. This is in contrast to osteoarthritis, which is caused by the wear and tear of cartilage. The synovium becomes thicker as a result of this autoimmune

onslaught, which in turn can cause cartilage and bone to be destroyed within the joint. This inflammation can become chronic, which can lead to increased pain and discomfort.

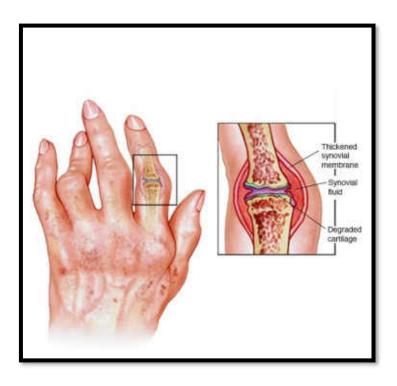


Figure 6: Rheumatoid Arthritis

There is a lack of complete understanding of the precise causation of rheumatoid arthritis; nonetheless, it is believed that a mix of genetic, environmental, and hormonal variables are involved in its development. A higher likelihood of getting rheumatoid arthritis has been associated with the presence of particular genes that are associated with the immune system, such as the HLA-DRB1 gene. There is a possibility that those who are genetically predisposed to the disease could be triggered to develop the condition by environmental factors such as smoking and exposure to specific viruses. Alterations in hormone levels, particularly those associated with estrogen, could possibly play a factor in the development of rheumatoid arthritis (RA), which is more prevalent in females, particularly those between the ages of 30 and 50.

One of the most distinguishing features of rheumatoid arthritis is that it has a tendency to impact joints in a symmetrical manner. This means that if one joint on one side of the body is affected, the joint on the opposite side of the body is likely to be affected as well. The joints in the hands, wrists, knees, and feet are the ones that are affected the most frequently by this condition. One of the most common early symptoms of rheumatoid arthritis (RA) is joint stiffness, which is especially noticeable in the morning or after periods of inactivity. Other early symptoms

include joint discomfort, swelling, and soreness. There is a possibility that joint deformities will develop as the condition advances, which will greatly hinder the capacity to carry out activities of daily living.

Rheumatoid arthritis is a systemic disease, which means that it can affect other regions of the body in addition to the joints. This means that it might cause issues in the joints. Lungs, the heart, blood vessels, and the eyes are just some of the organs and tissues that may experience inflammation as a result of this condition. Some people who have rheumatoid arthritis, for instance, may develop rheumatoid nodules, which are solid lumps of tissue that are located under the skin near joints that are afflicted by the condition. As a result of the immunosuppressive medicines that are frequently utilized for the management of rheumatoid arthritis (RA), some individuals may develop consequences such as lung illness, cardiovascular concerns, or an increased risk of infections.

Rheumatoid arthritis treatment has seen substantial development over the years, with the key objectives being the reduction of inflammation, the alleviation of symptoms, the prevention of damage to joints and organs, and the enhancement of overall quality of life to the patient. In order to properly manage rheumatoid arthritis (RA), early diagnosis and treatments are essential. In most cases, the treatment consists of a mix of drugs, physical therapy, changes in lifestyle, and occasionally surgical procedures. The most important component of the treatment for rheumatoid arthritis (RA) is the use of disease-modifying antirheumatic medications (DMARDs), which include methotrexate. These treatments reduce the progression of the disease and protect joints from being damaged. Biologic drugs, which are able to target particular components of the immune system, have also emerged as a significant alternative for patients who do not react to conventional DMARDs.

The therapy of rheumatoid arthritis (RA) also includes the management of pain. It is usual practice to alleviate pain and inflammation with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids; nevertheless, it is typically recommended to avoid using these medications for an extended period of time due to the potential adverse effects they may cause. In order to assist patients in maintaining joint function and mobility, as well as adapting to any limits that may be induced by the condition, physical therapy and occupational therapy play an extremely important contribution. Managing stress, maintaining a balanced diet, and engaging in regular exercise are all essential components of managing the overall health and well-being of those who have rheumatoid arthritis (RA).

Living with rheumatoid arthritis can be difficult owing to the fact that it is a chronic condition that can have substantial effects on both the body and the mind. The unpredictability of flare-ups, the chance of joint abnormalities, and the danger of comorbidities can all contribute to a decrease in the quality of life for a great number of people. Many people who have rheumatoid arthritis (RA) are now able to lead lives that are both active and fulfilling as a result of advancements in treatment and an all-encompassing management approach. Ongoing research is helping to further our understanding of rheumatoid arthritis (RA), with the ultimate goal of generating treatments that are even more successful and, ultimately, discovering a cure for the condition.

4.2.2 Osteoporosis and gout

Osteoporosis is a systemic bone disease that is defined by decreasing bone density and degeneration of bone tissue, which ultimately leads to an increased risk of fractures. This ailment is usually described to as a "silent disease" due to the fact that it does not manifest any symptoms until a fracture takes place, which is typically the initial sign that the disease is present. An imbalance between bone resorption and bone creation is the root cause of osteoporosis. As people get older, bone resorption frequently outpaces bone formation, which leads in weakening bones. The aging process, the postmenopausal state of women as a result of decreasing estrogen levels, a family history of osteoporosis, and lifestyle variables such as insufficient calcium and vitamin D intake, a lack of physical activity, smoking, and excessive alcohol use are all important risk factors. Osteoporosis is a condition that primarily affects people who are in their later years, mainly women. However, it can also affect younger people and men, particularly those who are afflicted with certain medical illnesses or who are on long-term steroid therapy.

In order to effectively manage osteoporosis, the basic method comprises making adjustments to one's lifestyle as well as receiving medicinal treatments that are targeted at increasing bone density and decreasing the likelihood of fractures. The adoption of a diet that is abundant in calcium and vitamin D, the participation in weight-bearing and muscle-strengthening exercises, and the avoidance of habits that contribute to bone loss, such as smoking and excessive alcohol use, are all examples of lifestyle adjustments that individuals can make. Bisphosphonates, which inhibit bone resorption, selective estrogen receptor modulators (SERMs) and hormone replacement therapy (HRT), which aim to maintain bone density by mimicking the effects of estrogen, and newer agents such as denosumab and teriparatide, which target different aspects

of bone metabolism, are all examples of these types of pharmacological treatments for osteoporosis. It is recommended to have routine bone density examinations, which are typically carried out with the assistance of dual-energy X-ray absorptiometry (DEXA), in order to evaluate bone health and make any necessary adjustments to treatment.

Gout is a form of inflammatory arthritis that is brought on by the accumulation of uric acid crystals in the joints. This condition is characterized by excruciating pain, redness, and swelling that comes on suddenly and is severe. The ailment is frequently characterized by severe discomfort in a single joint, most frequently the big toe. However, other joints, such as the ankles, knees, and wrists, can also be affected by the condition under certain circumstances. Gout is a condition that develops when the body either synthesizes an excessive amount of uric acid or fails to excrete an adequate amount of it. This results in hyperuricemia, which is the elevated level of uric acid that is present in the blood. When the levels of uric acid in the body reach an abnormally high level, it has the potential to crystallize and deposit in the joints, resulting in inflammation and pain. A diet that is heavy in purines, which can be found in red meat, shellfish, and alcohol, as well as obesity, certain medical problems (such as kidney disease and hypertension), and a genetic predisposition are all variables that can increase the likelihood of developing gout.

Strategies that are both acute and chronic are utilized in the therapy of gout management. Nonsteroidal anti-inflammatory medications (NSAIDs), colchicine, and corticosteroids are frequently used for the treatment of acute attacks in order to alleviate pain and reduce inflammation. A primary aim of long-term care is the reduction of uric acid levels in order to forestall the occurrence of future attacks and consequences, such as injury to the joints and kidney stones. Uric acid synthesis can be decreased using medications like allopurinol and febuxostat, while uricosuric drugs like probenecid can increase the amount of uric acid that is excreted from the body. Modifications to one's lifestyle are also essential in the management of gout. These modifications include dietary adjustments to reduce the consumption of purinerich foods, the maintenance of a healthy weight, constant hydration, and the reduction of alcohol consumption. As persistent gout can lead to joint injury and the creation of tophi, which are huge deposits of uric acid crystals that can cause deformities and functional impairments, it is vital to perform regular monitoring and therapy in order to control symptoms and avoid the progression of the condition

The causes, symptoms, and treatment options for osteoporosis and gout are very different from one another, despite the fact that both conditions have a significant impact on bone and joint health. Gout care focuses on regulating uric acid levels and addressing acute inflammatory episodes, in contrast to osteoporosis management, which focuses on maintaining bone density and preventing fractures. The ability to comprehend and handle these disorders by means of proper therapy and adjustments to one's way of life can contribute to the enhancement of one's quality of life and the reduction of the likelihood of difficulties.

4.3 Principles of cancer

Disorders that are characterized by uncontrolled cell growth and proliferation, which can lead to the creation of malignant tumors, are collectively referred to as cancer. Cancer is a complex and multifaceted collection of disorders. Exploring the underlying mechanisms, behaviors, and effects that cancer has on the body is necessary in order to have an understanding of the fundamentals of cancer. The creation of viable medicines and the advancement of cancer research are both dependent on the successful application of these ideas. Among the fundamental principles are the characteristics that are characteristic of cancer, the elements that are hereditary and environmental, the microenvironment of the tumor, and the processes of metastasis and resistance.

1. Hallmarks of Cancer: The notion of "hallmarks of cancer," established by researchers Douglas Hanahan and Robert Weinberg, highlights the essential traits that are shared by all types of cancer. Among these distinguishing characteristics are:

By either creating their own growth signals or by hijacking normal signaling pathways in order to promote continuous cell division, cancer cells frequently exhibit uncontrolled growth. Supporting Proliferative Signaling Cancer cells frequently exhibit uncontrolled growth.

It is possible for cancer cells to circumvent or disable mechanisms that normally regulate cell growth and prevent uncontrolled proliferation. These mechanisms include tumor suppressor genes such as p53 and Rb. Cancer cells are able to navigate around these mechanisms.

Resisting Cell Death Cancer cells frequently acquire mutations that enable them to avoid apoptosis, also known as programmed cell death. This enables damaged cells to survive and continue to proliferate.

By avoiding the natural processes of cellular aging, tumor cells are able to keep their capacity to divide eternally, which enables them to preserve their ability to replicate forever. The activation of telomerase, an enzyme that extends the protective caps at the ends of chromosomes, is a common method for accomplishing this goal.

Inducing Angiogenesis: Tumors have the ability to induce angiogenesis, which is the production of new blood vessels, in order to supply the expanding tumor with more nutrients and oxygen, which in turn supports the tumor's growth.

Cancer cells have the ability to penetrate the tissues that are surrounding them and spread to organs that are further away, a process that is referred to as metastasis. Actively activating invasion and metastasis. The ability to survive in the bloodstream or lymphatic system, as well as alterations in cell adhesion and enhanced motility, are all important components of this process.

2. Factors Related to Genetics and the Environment The development of cancer is caused by a confluence of genetic alterations and environmental exposures.

Cancer is frequently caused by mutations in particular genes that affect cell growth, repair, and division. These genes are responsible for regulating these processes. There are genes known as oncogenes that, when altered, are responsible for the progression of cancer. On the other hand, tumor suppressor genes generally prevent the creation of cancer but can become inactive in cancer. In addition, mutations in genes that repair DNA can result in genomic instability, which in turn might raise the chance of developing cancer.

Exposure to certain environmental variables, such as tobacco smoke, radiation, and chemicals that are known to cause cancer, can lead to the induction of genetic mutations that play a role in the development of cancer. A person's diet, the amount of alcohol they consume, and the amount of physical activity they get all play a part in influencing their risk of developing cancer.

Some people inherit genetic mutations that put them at risk for developing cancer. This is referred to as inherited genetic risk. Some examples of these types of mutations are the BRCA1 and BRCA2 genes, which are linked to breast and ovarian cancer, as well as Lynch syndrome, which raises the risk of colon cancer as well as other types of cancer.

3. Tumor Microenvironment: The tumor microenvironment (TME) is made up of the cells, blood vessels, immune cells, and extracellular matrix that are in close proximity to cancer cells

and interact with them. TME exerts an influence on the formation and progression of tumors by means of:

Interactions Between Cells Cancer cells form interactions with the stromal cells that surround them, which include fibroblasts and immune cells. These interactions can either encourage or discourage the growth of the tumor. For instance, tumor-associated macrophages have the potential to contribute to inflammation and tissue remodeling, both of which are beneficial to the growth of tumors.

Extracellular Matrix (ECM): The ECM is responsible for providing structural support to tissues and has the ability to alter the behavior of cancer cells. In order to facilitate invasion and metastasis, tumor cells have the ability to change the extracellular matrix (ECM).

Tumors have the ability to circumvent immune monitoring by establishing an immunosuppressive microenvironment through the process of immunological modulation. In addition, they may create substances that decrease the function of immune cells or attract regulatory T cells, which suppress the reactions of the immune system against tumors.

4. Metastasis: The process by which cancer cells move from their original site to distant organs and tissues is referred to as metastasis. This intricate process is comprised of multiple steps, including:

As a result of eroding the extracellular matrix (ECM) and breaking through tissue barriers, cancer cells are able to infect the tissues that are nearby.

Once tumor cells have entered the bloodstream or lymphatic system, they are able to circulate and be delivered to distant locations. This process is referred to as intravasation.

Extravasation is the process by which cancer cells travel to distant regions and infiltrate new tissues after leaving the circulation or lymphatic system.

Once cancer cells have entered a new tissue, they must make adjustments to the new environment, establish a blood supply, and continue to proliferate in order to form secondary tumors. This process is referred to as colonization.

Oncology faces a significant obstacle in the form of resistance to therapy, which is prevalent in the field of oncology. Several different processes can lead to the development of resistance in cancer cells

Genetic Mutations: Treatments may be rendered ineffective if they contain mutations in genes that are the focus of the therapy. Alterations in the EGFR gene, for instance, have the potential to result in resistance to EGFR inhibitors in lung cancer patients.

Responses that are Adaptive Cancer cells have the ability to activate alternative pathways or boost drug efflux mechanisms in order to negate the effects of treatment.

Microenvironmental Factors: The TME has the potential to affect the efficacy of drugs by influencing the availability of therapeutic substances or by resulting in the creation of physical barriers.

The comprehension of these concepts offers a broad perspective on the biology of cancer and contributes to the development of strategies for the diagnosis, treatment, and prevention of the disease. Research that is now being conducted continues to shed light on the complexity of cancer and produce medicines that are more effective in order to enhance patient outcomes and survival rates.

4.3.1 Classification

In the field of oncology, cancer categorization is a fundamental notion that assists in the diagnosis, treatment, and study of various types of cancer. The process entails classifying malignancies according to a variety of factors, such as their origin, histological characteristics, genetic alterations, and clinical behavior. This classification is essential for the development of focused treatments, the comprehension of disease prognosis, and the facilitation of communication among healthcare providers. Among the fundamental principles that underpin the classification of cancer are the categorization of the disease according to its genesis, histological and molecular characteristics, genetic and genomic profiles, and clinical characteristics.

1. Classification based on origin:

The identification of the tissue or organ from which the disease originated is frequently the first step in the classification of cancer. This preliminary classification is essential due to the fact that various forms of cancer originate from various tissues and exhibit varied clinical behaviors and treatment methods.

These cancers start from epithelial cells, which are the cells that line the surfaces and cavities of the body. Carcinomas are the cells that cause these cancers. There are numerous subtypes of

carcinomas, which are further divided according to the kind of epithelial cell and tissue that are involved. Carcinomas are the most prevalent type of cancer. As an illustration, glandular epithelial cells are the source of adenocarcinomas, whereas squamous cell carcinomas develop from squamous epithelial cells. Breast cancer, also known as adenocarcinoma, and skin cancer, sometimes known as squamous cell carcinoma, are two instances of common cancers.

There are a variety of mesenchymal tissues that can give rise to sarcomas. These tissues include bone, muscle, fat, and connective tissues. The frequency of these malignancies is lower than that of carcinomas, and they are classified according to the particular type of mesenchymal tissue that is affected. On the other hand, osteosarcoma (bone) and liposarcoma (fat) are two examples.

Leukemias are diseases that affect the bone marrow and blood, and they are defined by the uncontrolled development of abnormal white blood cells. Leukemias can be quite dangerous. The classification of these conditions is determined by the kind of white blood cell that is afflicted (for example, lymphoid or myeloid) as well as the rate at which the disease progresses (acute or chronic). Certain types of leukemia, such as acute lymphoblastic leukemia (ALL) and chronic myeloid leukemia (CML), are examples.

Lymphomas are cancers that start in lymphatic tissues and impact lymphocytes, which are a cell type that belongs to the white blood cell category. Hodgkin lymphoma, which is distinguished by the presence of Reed-Sternberg cells, and non-Hodgkin lymphoma, which encompasses a wide variety of lymphoid malignancies, are the two types of lymphomas that are distinguished through their classification.

Melanomas: Melanomas are cancers that originate from melanocytes, which are cells in the skin that produce pigment. Although melanomas are most commonly connected with skin cancer, they can also develop in other parts of the body, like the eye and the mucous membranes for example.

Histological characteristics are used to classify the tissue.

The examination of cancer tissues under a microscope for the purpose of determining the type of cancer cells and the degree to which they have differentiated is what is known as histological categorization. It is possible to forecast the behavior of the tumor and how it will react to therapy with the help of this classification.

In the process of grading tumors, the degree to which cancer cells resemble normal cells is taken into consideration. Grades can range from low to high. When compared to high-grade tumors, low-grade tumors are more similar to normal tissue and likely to be less aggressive. On the other hand, high-grade tumors are more aberrant and have a tendency to develop and spread more quickly.

Tumor staging is a term that reflects the degree to which cancer has spread throughout the body. The TNM system is frequently utilized, wherein the letter 'T' denotes the magnitude of the main tumor, the letter 'N' shows the involvement of lymph nodes in the region, and the letter 'M' denotes the presence of distant metastases. Stage 0 refers to the in situ stage, whereas Stage IV refers to the advanced metastatic stage of the malignancy. A prognosis can be determined and treatment can be planned with the assistance of staging.

Section 3: Classification Based on Molecular and Genetic Characteristics:

Molecular biology has made significant strides in recent years, which has resulted in the classification of malignancies according to their genetic and molecular characteristics. This classification has the potential to offer insights into the mechanisms that underlie cancer and to direct targeted therapy.

Specific mutations in oncogenes, which are genes that fuel the progression of cancer, and tumor suppressor genes, which are genes that ordinarily prevent cancer, are particularly important for understanding cancer. Mutations in the BRCA1 and BRCA2 genes, for instance, have been linked to an increased risk of breast and ovarian cancer. On the other hand, mutations in the EGFR gene have been shown to influence the extent to which lung cancer patients respond to targeted therapy.

Molecular Subtypes: The process of molecular profiling of cancers can reveal unique subtypes based on patterns of gene expression, protein markers, and other biomarkers. An example of this would be breast cancer, which may be subdivided into subtypes such as HER2-positive, hormone receptor-positive, and triple-negative, each of which has a unique treatment strategy and result.

In addition, the classification of malignancies requires an understanding of the roles that particular genes play in the development of tumors. These genes include oncogenes and tumor suppressor genes. On the other hand, tumor suppressor genes generally prevent cancer from

occurring, whereas oncogenes encourage the growth and survival of cancer cells. There is the potential for abnormalities in these genes to direct diagnostic and therapeutic treatments.

Classification according to Clinical Characteristics:

The process of clinical categorization entails analyzing the symptoms, responses to treatment, and outcomes for patients that are associated with various categories of cancer. The management of the condition and the planning of treatment are both enhanced by this method, which provides more context.

signs and Presentation: The earliest signs of cancer can vary greatly depending on the type of tumor and the location of the tumor. It is helpful in early detection and diagnosis to have a thorough understanding of the clinical presentation.

Response to Treatment: The efficacy of various therapies, including as surgery, chemotherapy, radiation therapy, and immunotherapy, might vary depending on the kind of cancer and the subtypes of cancer. A clinical classification allows for the customization of treatment plans and the modification of techniques based on the reactions of patients.

An additional component of clinical categorization is the evaluation of factors that have an effect on the outcomes of patients, such as the patient's age, overall health, and the presence of comorbid conditions. The treatment decisions that are made are guided by prognostic criteria, which also assist in predicting the chances of treatment success and survival.

4.3.2 Etiology and pathogenesis of cancer

The etiology and pathogenesis of cancer are the study of the factors that lead to the development and progression of cancer, as well as the mechanisms that are responsible for these processes. The development of preventative tactics, diagnostic tools, and tailored medicines rely heavily on having a solid understanding of these elements. Comparatively, pathogenesis focuses on the biological processes and molecular alterations that drive cancer growth and progression, whereas etiology is concerned with determining the many variables that contribute to the formation of cancer.

1. The Causes of Cancer: Genetics

Multiple factors, both internal and external, can play a role in the development of cancer, making it a multifactorial disease. There are several key etiological causes, including:

The development of cancer is mostly influenced by genetic alterations, which are important to the disease. Genes that typically control cell proliferation and repair DNA damage can be affected by these mutations. Oncogenes, which are responsible for promoting cell growth and survival, can also be affected. A number of malignancies, including breast and ovarian cancers, have been related to mutations in the BRCA1 and BRCA2 genes. On the other hand, mutations in the TP53 gene are common in a variety of cancers.

Environmental Carcinogens: Certain environmental chemicals can cause genetic mutations or disturb normal cellular processes, both of which can lead to the development of cancer if that person is exposed to them. Chemicals (such as tobacco smoke and asbestos), physical agents (such as radiation and ultraviolet light), and biological agents (such as viruses and bacteria) are all examples of elements that can cause cancer. Among the many factors that contribute to the development of lung cancer, the carcinogenic effects of tobacco smoke are well-documented.

There are a number of infectious agents that can have a role in the development of cancer. These agents include viruses, bacteria, and parasites that can cause persistent infections or initiate inflammation. Examples of viruses that are linked to cancer include the human papillomavirus (HPV), which is linked to cervical cancer as well as other malignancies, and the hepatitis B and C viruses, which are linked to liver cancer. An infection caused by Helicobacter pylori is linked to the development of stomach cancer because it causes persistent inflammation and affects the mucosal tissue.

A person's lifestyle choices, which include their food, level of physical activity, and amount of alcohol use, can have an effect on their likelihood of developing cancer. An increased risk of numerous malignancies, including colon cancer, has been linked to drinking an excessive amount of alcohol and eating a diet that is heavy in processed foods and low in fruits and vegetables, for example.

Cancer susceptibility can be increased by inherited genetic mutations, which are referred to as genetic predisposition. Lynch syndrome and familial adenomatous polyposis are two examples of familial cancer syndromes that are linked to an increased likelihood of acquiring more than one type of cancer. An individual's genetic predisposition can interact with environmental circumstances to further increase the likelihood of developing cancer.

2. Cancer's pathogenesis, which includes:

A set of biological changes and processes that have the effect of transforming normal cells into cancerous ones are referred to as the pathogenesis of cancer. These alterations can be roughly classified into a number of main mechanisms, including the following:

Cellular Transformation: The process by which normal cells are transformed into malignant cells by the application of genetic and epigenetic modifications is the first step in the development of cancer. A number of mutations that interfere with normal cell development and regulatory mechanisms are accumulated during this metamorphosis. There are a number of important processes that contribute to excessive cell proliferation, including the activation of oncogenes and the inactivation of genes that limit tumor growth.

Once the cancer has begun to spread, it will go through a process known as promotion and progression, which is characterized by the acquisition of further mutations and the continuation of the cell's growth. Progression is the acquisition of further genetic changes that increase the aggressiveness and heterogeneity of the tumor, whereas promotion of the tumor entails the proliferation of cells that have beneficial mutations.

As tumors continue to expand, they demand a greater supply of oxygen and nutrients, which is referred to as angiogenesis. Through the production of pro-angiogenic substances like vascular endothelial growth factor (VEGF), cancer cells, in order to fulfill these requirements, induce the development of new blood vessels, which is referred to as angiogenesis. This mechanism contributes to the formation of tumors and makes it easier for cancer cells to communicate with one another.

Metastasis and Invasion: One of the most important aspects of cancer pathogenesis is the capacity of cancer cells to infiltrate the tissues that are nearby and to spread to other locations. Degradation of extracellular matrix (ECM) components, enhanced cell motility, and entrance into the circulation or lymphatic system are some of the phases involved in this process. All of these steps are necessary. Metastatic cancer cells are required to adjust to new settings and create secondary tumors in organs that are located at a greater distance.

The expression of immune checkpoint proteins, which inhibit immune responses, the secretion of immunosuppressive factors, and the recruitment of regulatory immune cells, which suppress anti-tumor activity are all examples of mechanisms that cancer cells can use to evade immune surveillance. Cancer cells can also evade immune surveillance through a variety of other

mechanisms. In spite of the presence of an immune response, cancer cells are able to continue to divide and develop thanks to this immune evasion.

Cancer cells frequently display genomic instability, which is characterized by elevated rates of mutations, chromosomal abnormalities, and modifications in DNA repair systems. Genomic instability is a characteristic of cancer cells. The generation of a varied pool of genetic variations, which can drive tumor expansion and resistance to therapy, is one of the ways in which this instability influences the progression of cancer.

3. The interaction between pathogenesis and etiological factors:

The complicated connection that occurs between etiological variables and the pathophysiology of cancer is a source of great concern. Cancer cells' biological processes can, in turn, affect how they respond to external variables. Environmental and genetic factors can both have an impact on the molecular mechanisms that are responsible for the development of cancer. On the other hand, the presence of particular mutations may modify the way in which cancer cells interact with their microenvironment. For instance, individuals who have genetic predispositions may be more sensitive to the carcinogenic effects of environmental agents.

To summarize, the etiology and pathogenesis of cancer comprise a wide variety of variables and processes that contribute to the formation and progression of the disease. These factors and processes are referred to as its "pathogenesis." The advancement of cancer research, the improvement of cancer prevention and early diagnosis, and the development of more effective treatments relies heavily on an understanding of these fundamental concepts.

References

- 1. Adapa, S., Aeddula, N. R., Konala, V. M., Chenna, A., Naramala, S., Madhira, B. R., ... & Bose, S. (2020). COVID-19 and renal failure: challenges in the delivery of renal replacement therapy. *Journal of clinical medicine research*, *12*(5), 276.
- 2. Adiamah, A., Skorepa, P., Weimann, A., & Lobo, D. N. (2019). The impact of preoperative immune modulating nutrition on outcomes in patients undergoing surgery for gastrointestinal cancer: a systematic review and meta-analysis. *Annals of Surgery*, 270(2), 247-256.
- 3. Ahmed, M., & Ahmed, S. (2019). Functional, diagnostic and therapeutic aspects of gastrointestinal hormones. *Gastroenterology research*, 12(5), 233.
- 4. Alam, A., Thelin, E. P., Tajsic, T., Khan, D. Z., Khellaf, A., Patani, R., & Helmy, A. (2020). Cellular infiltration in traumatic brain injury. Journal of neuroinflammation, 17, 1-17.
- 5. Alizadeh, A., Dyck, S. M., & Karimi-Abdolrezaee, S. (2019). Traumatic spinal cord injury: an overview of pathophysiology, models and acute injury mechanisms. *Frontiers in neurology*, 10, 282.
- 6. Ansari, J., & Gavins, F. N. (2019). Ischemia-reperfusion injury in sickle cell disease: from basics to therapeutics. The American Journal of Pathology, 189(4), 706-718.
- 7. Arnett, D. K., Blumenthal, R. S., Albert, M. A., Buroker, A. B., Goldberger, Z. D., Hahn, E. J., ... & Ziaeian, B. (2019). 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, 74(10), 1376-1414.
- 8. Arnett, D. K., Blumenthal, R. S., Albert, M. A., Buroker, A. B., Goldberger, Z. D., Hahn, E. J., ... & Ziaeian, B. (2019). 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*, 140(11), e596-e646.
- 9. Ashley, C., & Dunleavy, A. (2018). *The renal drug handbook: the ultimate prescribing guide for renal practitioners*. CRC press.
- 10. Authors/Task Force Members:, McDonagh, T. A., Metra, M., Adamo, M., Gardner, R. S., Baumbach, A., ... & Waltenberger, J. (2022). 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC).

- With the special contribution of the Heart Failure Association (HFA) of the ESC. European journal of heart failure, 24(1), 4-131.
- 11. Bagwe-Parab, S., Yadav, P., Kaur, G., Tuli, H. S., & Buttar, H. S. (2020). Therapeutic applications of human and bovine colostrum in the treatment of gastrointestinal diseases and distinctive cancer types: The current evidence. *Frontiers in Pharmacology*, 11, 01100.
- 12. Barros, L. L., Farias, A. Q., & Rezaie, A. (2019). Gastrointestinal motility and absorptive disorders in patients with inflammatory bowel diseases: Prevalence, diagnosis and treatment. *World journal of gastroenterology*, 25(31), 4414.
- 13. Bektas, A., Schurman, S. H., Sen, R., & Ferrucci, L. (2018). Aging, inflammation and the environment. Experimental gerontology, 105, 10-18.
- 14. Benfaremo, D., Manfredi, L., Luchetti, M. M., & Gabrielli, A. (2018). Musculoskeletal and rheumatic diseases induced by immune checkpoint inhibitors: a review of the literature. *Current drug safety*, *13*(3), 150-164.
- 15. Bennett, C. F., Latorre-Muro, P., & Puigserver, P. (2022). Mechanisms of mitochondrial respiratory adaptation. *Nature Reviews Molecular Cell Biology*, *23*(12), 817-835.
- 16. Berk, M., Köhler-Forsberg, O., Turner, M., Penninx, B. W., Wrobel, A., Firth, J., ... & Marx, W. (2023). Comorbidity between major depressive disorder and physical diseases: a comprehensive review of epidemiology, mechanisms and management. *World Psychiatry*, 22(3), 366-387.
- 17. Biver, E., Berenbaum, F., Valdes, A. M., de Carvalho, I. A., Bindels, L. B., Brandi, M. L., ... & Rizzoli, R. (2019). Gut microbiota and osteoarthritis management: An expert consensus of the European society for clinical and economic aspects of osteoporosis, osteoarthritis and musculoskeletal diseases (ESCEO). *Ageing research reviews*, 55, 100946.
- 18. Black, L. M., Lever, J. M., & Agarwal, A. (2019). Renal inflammation and fibrosis: a double-edged sword. *Journal of Histochemistry & Cytochemistry*, 67(9), 663-681.
- 19. Bojar, R. M. (2020). *Manual of perioperative care in adult cardiac surgery*. John Wiley & Sons.
- 20. Bonanni, R., Cariati, I., Tancredi, V., Iundusi, R., Gasbarra, E., & Tarantino, U. (2022). Chronic pain in musculoskeletal diseases: Do you know your enemy?. *Journal of clinical medicine*, *11*(9), 2609.
- 21. Boothby, I. C., Cohen, J. N., & Rosenblum, M. D. (2020). Regulatory T cells in skin injury: At the crossroads of tolerance and tissue repair. *Science immunology*, 5(47), eaaz9631.

- 22. Calabrese, L. H., Calabrese, C., & Cappelli, L. C. (2018). Rheumatic immune-related adverse events from cancer immunotherapy. *Nature Reviews Rheumatology*, *14*(10), 569-579.
- 23. Carter, P., Lagan, J., Fortune, C., Bhatt, D. L., Vestbo, J., Niven, R., ... & Miller, C. A. (2019). Association of cardiovascular disease with respiratory disease. *Journal of the American College of Cardiology*, 73(17), 2166-2177.
- 24. Castiglione, V., Aimo, A., Vergaro, G., Saccaro, L., Passino, C., & Emdin, M. (2022). Biomarkers for the diagnosis and management of heart failure. *Heart failure reviews*, 1-19.
- 25. Chavakis, T., Mitroulis, I., & Hajishengallis, G. (2019). Hematopoietic progenitor cells as integrative hubs for adaptation to and fine-tuning of inflammation. Nature immunology, 20(7), 802-811.
- 26. Chen, L., Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J., ... & Zhao, L. (2018). Inflammatory responses and inflammation-associated diseases in organs. Oncotarget, 9(6), 7204.
- 27. Chen, Y., Huang, T., Yu, Z., Yu, Q., Wang, Y., Hu, J. A., ... & Yang, G. (2022). The functions and roles of sestrins in regulating human diseases. *Cellular & Molecular Biology Letters*, 27, 1-24.
- 28. Cheville, A., Smith, S., Barksdale, T., & Asher, A. (2021). Cancer rehabilitation. *Braddom's Physical Medicine and Rehabilitation*, 568-593.
- 29. Craig, E., & Cappelli, L. C. (2018). Gastrointestinal and hepatic disease in rheumatoid arthritis. *Rheumatic Disease Clinics*, 44(1), 89-111.
- 30. Cristina, N. M., & Lucia, D. A. (2021). Nutrition and healthy aging: Prevention and treatment of gastrointestinal diseases. *Nutrients*, *13*(12), 4337.
- 31. Cruz, C. S. D., & Kang, M. J. (2018). Mitochondrial dysfunction and damage associated molecular patterns (DAMPs) in chronic inflammatory diseases. Mitochondrion, 41, 37-44.
- 32. Dainton, M. (2024). Acute kidney injury. *Renal nursing: care and management of people with kidney disease*, 115-131.
- 33. Dalili, D., Isaac, A., Bazzocchi, A., Åström, G., Bergh, J., Lalam, R., ... & Mansour, R. (2020, December). Interventional techniques for bone and musculoskeletal soft tissue tumors: current practices and future directions-part I. ablation. In *Seminars in Musculoskeletal Radiology* (Vol. 24, No. 06, pp. 692-709). Thieme Medical Publishers, Inc..
- 34. Damluji, A. A., Forman, D. E., Van Diepen, S., Alexander, K. P., Page, R. L., Hummel,
- S. L., ... & American Heart Association Council on Clinical Cardiology and Council on

- Cardiovascular and Stroke Nursing. (2020). Older adults in the cardiac intensive care unit: factoring geriatric syndromes in the management, prognosis, and process of care: a scientific statement from the American Heart Association. *Circulation*, 141(2), e6-e32.
- 35. De Ligt, K. M., Heins, M., Verloop, J., Smorenburg, C. H., Korevaar, J. C., & Siesling, S. (2019). Patient-reported health problems and healthcare use after treatment for early-stage breast cancer. *The Breast*, *46*, 4-11.
- 36. Domínguez-Andrés, J., Dos Santos, J. C., Bekkering, S., Mulder, W. J., van der Meer, J. W., Riksen, N. P., ... & Netea, M. G. (2023). Trained immunity: adaptation within innate immune mechanisms. Physiological reviews, 103(1), 313-346.
- 37. Drewes, A. M., Olesen, A. E., Farmer, A. D., Szigethy, E., Rebours, V., & Olesen, S. S. (2020). Gastrointestinal pain. *Nature reviews Disease primers*, *6*(1), 1.
- 38. Dumitru, C., Kabat, A. M., & Maloy, K. J. (2018). Metabolic adaptations of CD4+ T cells in inflammatory disease. Frontiers in Immunology, 9, 540.
- 39. Ekinci, C., Karabork, M., Siriopol, D., Dincer, N., Covic, A., & Kanbay, M. (2018). Effects of volume overload and current techniques for the assessment of fluid status in patients with renal disease. *Blood Purification*, 46(1), 34-47.
- 40. Elad, S., Zadik, Y., Caton, J. G., & Epstein, J. B. (2019). Oral mucosal changes associated with primary diseases in other body systems. *Periodontology* 2000, 80(1), 28-48.
- 41. ElHawary, H., Baradaran, A., Abi-Rafeh, J., Vorstenbosch, J., Xu, L., & Efanov, J. I. (2021, August). Bone healing and inflammation: principles of fracture and repair. In Seminars in plastic surgery (Vol. 35, No. 03, pp. 198-203). Thieme Medical Publishers, Inc..
- 42. Elkon, K. B. (2018). Cell death, nucleic acids, and immunity: inflammation beyond the grave. *Arthritis & Rheumatology*, 70(6), 805-816.
- 43. El-Tallawy, S. N., Nalamasu, R., Salem, G. I., LeQuang, J. A. K., Pergolizzi, J. V., & Christo, P. J. (2021). Management of musculoskeletal pain: an update with emphasis on chronic musculoskeletal pain. *Pain and therapy*, *10*, 181-209.
- 44. Enck, P., & Mazurak, N. (2018). The "Biology-First" Hypothesis: Functional disorders may begin and end with biology—A scoping review. *Neurogastroenterology & Motility*, 30(10), e13394.
- 45. ESC guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 2—care pathways, treatment, and follow-up." *Cardiovascular Research* 118, no. 7 (2022): 1618-1666.

- 46. Felgueiras, H. P., Antunes, J. C., Martins, M. C. L., & Barbosa, M. A. (2018). Fundamentals of protein and cell interactions in biomaterials. In *Peptides and Proteins as Biomaterials for Tissue Regeneration and Repair* (pp. 1-27). Woodhead Publishing.
- 47. Fisher, L., Fisher, A., & Smith, P. N. (2020). Helicobacter pylori related diseases and osteoporotic fractures (Narrative Review). *Journal of clinical medicine*, 9(10), 3253.
- 48. Gadiparthi, C., Hans, A., Potts, K., & Ismail, M. K. (2018). Gastrointestinal and hepatic disease in the inflammatory myopathies. *Rheumatic Disease Clinics*, 44(1), 113-129.
- 49. Gerstein, H. C., Sattar, N., Rosenstock, J., Ramasundarahettige, C., Pratley, R., Lopes, R. D., ... & Branch, K. (2021). Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. *New England journal of medicine*, 385(10), 896-907.
- 50. Gragnano, A., Negrini, A., Miglioretti, M., & Corbière, M. (2018). Common psychosocial factors predicting return to work after common mental disorders, cardiovascular diseases, and cancers: a review of reviews supporting a cross-disease approach. *Journal of occupational rehabilitation*, 28, 215-231.
- 51. Gusev, E., & Zhuravleva, Y. (2022). Inflammation: A new look at an old problem. International Journal of Molecular Sciences, 23(9), 4596.
- 52. Haanen, J., Ernstoff, M. S., Wang, Y., Menzies, A. M., Puzanov, I., Grivas, P., ... & Obeid, M. (2020). Autoimmune diseases and immune-checkpoint inhibitors for cancer therapy: review of the literature and personalized risk-based prevention strategy. *Annals of oncology*, 31(6), 724-744.
- 53. Healy, L. M., Yaqubi, M., Ludwin, S., & Antel, J. P. (2020). Species differences in immune-mediated CNS tissue injury and repair: A (neuro) inflammatory topic. Glia, 68(4), 811-829.
- 54. Heerspink, H. J., Sjöström, C. D., Jongs, N., Chertow, G. M., Kosiborod, M., Hou, F. F., ... & Wheeler, D. C. (2021). Effects of dapagliflozin on mortality in patients with chronic kidney disease: a pre-specified analysis from the DAPA-CKD randomized controlled trial. *European heart journal*, 42(13), 1216-1227.
- 55. Hines, R. L., & Jones, S. B. (Eds.). (2021). Stoelting's Anesthesia and Co-Existing Disease E-Book: Stoelting's Anesthesia and Co-Existing Disease E-Book. Elsevier Health Sciences.
- 56. Hollenberg, S. M., Warner Stevenson, L., Ahmad, T., Amin, V. J., Bozkurt, B., Butler, J., ... & Storrow, A. B. (2019). 2019 ACC expert consensus decision pathway on risk assessment, management, and clinical trajectory of patients hospitalized with heart failure: a

- report of the American College of Cardiology Solution Set Oversight Committee. *Journal of the American College of Cardiology*, 74(15), 1966-2011.
- 57. Hong, Y., Wu, C., & Wu, B. (2020). Effects of resistance exercise on symptoms, physical function, and quality of life in gastrointestinal cancer patients undergoing chemotherapy. *Integrative Cancer Therapies*, 19, 1534735420954912.
- 58. Huang, K., Cai, H. L., Bao, J. P., & Wu, L. D. (2020). Dehydroepiandrosterone and agerelated musculoskeletal diseases: Connections and therapeutic implications. *Ageing Research Reviews*, 62, 101132.
- 59. Humphrey, J. D., & Schwartz, M. A. (2021). Vascular mechanobiology: homeostasis, adaptation, and disease. Annual review of biomedical engineering, 23(1), 1-27.
- 60. Inglis, J. E., Lin, P. J., Kerns, S. L., Kleckner, I. R., Kleckner, A. S., Castillo, D. A., ... & Peppone, L. J. (2019). Nutritional interventions for treating cancer-related fatigue: a qualitative review. *Nutrition and cancer*, 71(1), 21-40.
- 61. Irani, S. (2020). New insights into oral cancer—Risk factors and prevention: A review of literature. *International Journal of Preventive Medicine*, 11.
- 62. James, M. T., Levey, A. S., Tonelli, M., Tan, Z., Barry, R., Pannu, N., ... & Hemmelgarn, B. R. (2019). Incidence and prognosis of acute kidney diseases and disorders using an integrated approach to laboratory measurements in a universal health care system. *JAMA Network Open*, 2(4), e191795-e191795.
- 63. Jansen, F. M., Vavricka, S. R., den Broeder, A. A., de Jong, E. M., Hoentjen, F., & van Dop, W. A. (2020). Clinical management of the most common extra-intestinal manifestations in patients with inflammatory bowel disease focused on the joints, skin and eyes. *United European gastroenterology journal*, 8(9), 1031-1044.
- 64. Jentzer, J. C., Bihorac, A., Brusca, S. B., Del Rio-Pertuz, G., Kashani, K., Kazory, A., ... & Critical Care Cardiology Working Group of the Heart Failure and Transplant Section Leadership Council. (2020). Contemporary management of severe acute kidney injury and refractory cardiorenal syndrome: JACC council perspectives. *Journal of the American College of Cardiology*, 76(9), 1084-1101.
- 65. Kalantar-Zadeh, K., Jafar, T. H., Nitsch, D., Neuen, B. L., & Perkovic, V. (2021). Chronic kidney disease. *The lancet*, 398(10302), 786-802.
- 66. Kalantar-Zadeh, K., Lockwood, M. B., Rhee, C. M., Tantisattamo, E., Andreoli, S., Balducci, A., ... & Li, P. K. T. (2022). Patient-centred approaches for the management of unpleasant symptoms in kidney disease. *Nature Reviews Nephrology*, *18*(3), 185-198.

- 67. Katabathina, V. S., Menias, C. O., Khanna, L., Murphy, L., Dasyam, A. K., Lubner, M. G., & Prasad, S. R. (2019). Hereditary gastrointestinal cancer syndromes: role of imaging in screening, diagnosis, and management. *Radiographics*, *39*(5), 1280-1301.
- 68. Kostine, M., Rouxel, L., Barnetche, T., Veillon, R., Martin, F., Dutriaux, C., ... & Schaeverbeke, T. (2018). Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer—clinical aspects and relationship with tumour response: a single-centre prospective cohort study. *Annals of the rheumatic diseases*, 77(3), 393-398.
- 69. Krueger, K. M., Ison, M. G., & Ghossein, C. (2020). Practical guide to vaccination in all stages of CKD, including patients treated by dialysis or kidney transplantation. *American Journal of Kidney Diseases*, 75(3), 417-425.
- 70. Lahousse, A., Roose, E., Leysen, L., Yilmaz, S. T., Mostaqim, K., Reis, F., ... & Nijs, J. (2021). Lifestyle and pain following cancer: state-of-the-art and future directions. *Journal of clinical medicine*, *11*(1), 195.
- 71. Lam, G. A., Albarrak, H., McColl, C. J., Pizarro, A., Sanaka, H., Gomez-Nguyen, A., ... & Paes Batista da Silva, A. (2023). The oral-gut axis: periodontal diseases and gastrointestinal disorders. *Inflammatory bowel diseases*, 29(7), 1153-1164.
- 72. Lameire, N. H., Levin, A., Kellum, J. A., Cheung, M., Jadoul, M., Winkelmayer, W. C., ... & Srisawat, N. (2021). Harmonizing acute and chronic kidney disease definition and classification: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. *Kidney international*, 100(3), 516-526.
- 73. Larsson, S. C., & Burgess, S. (2021). Causal role of high body mass index in multiple chronic diseases: a systematic review and meta-analysis of Mendelian randomization studies. *BMC medicine*, 19, 1-10.
- 74. Larsson, S. C., & Burgess, S. (2022). Appraising the causal role of smoking in multiple diseases: A systematic review and meta-analysis of Mendelian randomization studies. *EBioMedicine*, 82.
- 75. Lee, P., Chandel, N. S., & Simon, M. C. (2020). Cellular adaptation to hypoxia through hypoxia inducible factors and beyond. Nature reviews Molecular cell biology, 21(5), 268-283.
- 76. Lewis, R., Gómez Álvarez, C. B., Rayman, M., Lanham-New, S., Woolf, A., & Mobasheri, A. (2019). Strategies for optimising musculoskeletal health in the 21 st century. *BMC musculoskeletal disorders*, 20, 1-15.

- 77. Liem, R. I., Lanzkron, S., D. Coates, T., DeCastro, L., Desai, A. A., Ataga, K. I., ... & Mustafa, R. A. (2019). American Society of Hematology 2019 guidelines for sickle cell disease: cardiopulmonary and kidney disease. *Blood advances*, *3*(23), 3867-3897.
- 78. Luan, X., Tian, X., Zhang, H., Huang, R., Li, N., Chen, P., & Wang, R. (2019). Exercise as a prescription for patients with various diseases. *Journal of sport and health science*, 8(5), 422-441.
- 79. Luttrell, T. (2024). Trauma and Inflammation of Soft Tissue: Rehabilitation and Wound Healing and Remodeling of Collagen. In Foundations of Orthopedic Physical Therapy (pp. 2-37). Routledge.
- 80. Mandras, S. A., Mehta, H. S., & Vaidya, A. (2020, September). Pulmonary hypertension: a brief guide for clinicians. In *Mayo Clinic Proceedings* (Vol. 95, No. 9, pp. 1978-1988). Elsevier.
- 81. Mannes, M., Schmidt, C. Q., Nilsson, B., Ekdahl, K. N., & Huber-Lang, M. (2021, December). Complement as driver of systemic inflammation and organ failure in trauma, burn, and sepsis. In Seminars in immunopathology (pp. 1-16). Springer Berlin Heidelberg.
- 82. Marotto, D., Atzeni, F., Ardizzone, S., Monteleone, G., Giorgi, V., & Sarzi-Puttini, P. (2020). Extra-intestinal manifestations of inflammatory bowel diseases. *Pharmacological Research*, *161*, 105206.
- 83. Mata, R., Yao, Y., Cao, W., Ding, J., Zhou, T., Zhai, Z., & Gao, C. (2021). The dynamic inflammatory tissue microenvironment: Signality and disease therapy by biomaterials. Research.
- 84. Meduri, G. U., & Chrousos, G. P. (2020). General adaptation in critical illness: glucocorticoid receptor-alpha master regulator of homeostatic corrections. Frontiers in endocrinology, 11, 161.
- 85. Meizlish, M. L., Franklin, R. A., Zhou, X., & Medzhitov, R. (2021). Tissue homeostasis and inflammation. Annual review of immunology, 39(1), 557-581.
- 86. Modi, Z. J., Lu, Y., Ji, N., Kapke, A., Selewski, D. T., Dietrich, X., ... & Gipson, D. S. (2019). Risk of cardiovascular disease and mortality in young adults with end-stage renal disease: an analysis of the US renal data system. *JAMA cardiology*, *4*(4), 353-362.
- 87. Mullens, W., Damman, K., Testani, J. M., Martens, P., Mueller, C., Lassus, J., ... & Coats, A. (2020). Evaluation of kidney function throughout the heart failure trajectory—a position statement from the Heart Failure Association of the European Society of Cardiology. *European journal of heart failure*, 22(4), 584-603.

- 88. Murphey, M. D., & Kransdorf, M. J. (2021). Staging and classification of primary musculoskeletal bone and soft-tissue tumors according to the 2020 WHO update, from the AJR special series on cancer staging. *American Journal of Roentgenology*, 217(5), 1038-1052.
- 89. Nadim, M. K., Forni, L. G., Bihorac, A., Hobson, C., Koyner, J. L., Shaw, A., ... & Kellum, J. A. (2018). Cardiac and vascular surgery–associated acute kidney injury: the 20th international consensus conference of the ADQI (acute disease quality initiative) group. *Journal of the American Heart Association*, 7(11), e008834.
- 90. Naik, S., & Fuchs, E. (2022). Inflammatory memory and tissue adaptation in sickness and in health. Nature, 607(7918), 249-255.
- 91. Nanchal, R., Subramanian, R., Karvellas, C. J., Hollenberg, S. M., Peppard, W. J., Singbartl, K., ... & Alhazzani, W. (2020). Guidelines for the management of adult acute and acute-on-chronic liver failure in the ICU: cardiovascular, endocrine, hematologic, pulmonary, and renal considerations. Critical care medicine, 48(3), e173-e191.
- 92. Natoli, G., & Ostuni, R. (2019). Adaptation and memory in immune responses. Nature immunology, 20(7), 783-792.
- 93. Ndumele, C. E., Rangaswami, J., Chow, S. L., Neeland, I. J., Tuttle, K. R., Khan, S. S., ... & American Heart Association. (2023). Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. *Circulation*, *148*(20), 1606-1635.
- 94. Neag, M. A., Mocan, A., Echeverría, J., Pop, R. M., Bocsan, C. I., Crişan, G., & Buzoianu, A. D. (2018). Berberine: Botanical occurrence, traditional uses, extraction methods, and relevance in cardiovascular, metabolic, hepatic, and renal disorders. *Frontiers in pharmacology*, *9*, 557.
- 95. Neagu, M., Constantin, C., Popescu, I. D., Zipeto, D., Tzanakakis, G., Nikitovic, D., ... & Tsatsakis, A. M. (2019). Inflammation and metabolism in cancer cell—mitochondria key player. Frontiers in Oncology, 9, 348.
- 96. Niec, R. E., Rudensky, A. Y., & Fuchs, E. (2021). Inflammatory adaptation in barrier tissues. Cell, 184(13), 3361-3375.
- 97. Ogbechi, J., Clanchy, F. I., Huang, Y. S., Topping, L. M., Stone, T. W., & Williams, R. O. (2020). IDO activation, inflammation and musculoskeletal disease. *Experimental Gerontology*, *131*, 110820.

- 98. Oldroyd, A. G., Allard, A. B., Callen, J. P., Chinoy, H., Chung, L., Fiorentino, D., ... & Aggarwal, R. (2021). A systematic review and meta-analysis to inform cancer screening guidelines in idiopathic inflammatory myopathies. *Rheumatology*, 60(6), 2615-2628.
- 99. Oliveira, C. B., Maher, C. G., Franco, M. R., Kamper, S. J., Williams, C. M., Silva, F. G., & Pinto, R. Z. (2020). Co-occurrence of chronic musculoskeletal pain and cardiovascular diseases: a systematic review with meta-analysis. *Pain Medicine*, *21*(6), 1106-1121.
- 100. Ostermann, M., Bellomo, R., Burdmann, E. A., Doi, K., Endre, Z. H., Goldstein, S. L., ... & Zarbock, A. (2020). Controversies in acute kidney injury: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. *Kidney international*, 98(2), 294-309.
- 101. Palmer, W., Bancroft, L., Bonar, F., Choi, J. A., Cotten, A., Griffith, J. F., ... & Pfirrmann, C. W. (2020). Glossary of terms for musculoskeletal radiology. *Skeletal radiology*, 49, 1-33.
- 102. Paolino, S., Pacini, G., Patanè, M., Alessandri, E., Cattelan, F., Goegan, F., ... & Cutolo, M. (2019). Interactions between microbiota, diet/nutrients and immune/inflammatory response in rheumatic diseases: focus on rheumatoid arthritis. *Reumatologia/Rheumatology*, 57(3), 151-157.
- 103. Pawa, S., Banerjee, P., Kothari, S., D'Souza, S. L., Martindale, S. L., Gaidos, J. K., ... & Burke, C. A. (2021). Are all endoscopy-related musculoskeletal injuries created equal? Results of a national gender-based survey. *Official journal of the American College of Gastroenterology* (ACG, 116(3), 530-538.
- 104. Pearson, G. J., Thanassoulis, G., Anderson, T. J., Barry, A. R., Couture, P., Dayan, N., ... & Wray, W. (2021). 2021 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults. *Canadian journal of cardiology*, 37(8), 1129-1150.
- 105. Peiseler, M., Schwabe, R., Hampe, J., Kubes, P., Heikenwälder, M., & Tacke, F. (2022). Immune mechanisms linking metabolic injury to inflammation and fibrosis in fatty liver disease—novel insights into cellular communication circuits. Journal of hepatology, 77(4), 1136-1160.
- 106. Platz, E., Jhund, P. S., Girerd, N., Pivetta, E., McMurray, J. J., Peacock, W. F., ... & Study Group on Acute Heart Failure of the Acute Cardiovascular Care Association and the Heart Failure Association of the European Society of Cardiology. (2019). Expert consensus document: reporting checklist for quantification of pulmonary congestion by lung ultrasound in heart failure. *European journal of heart failure*, 21(7), 844-851.

- 107. Qu, F., Guilak, F., & Mauck, R. L. (2019). Cell migration: implications for repair and regeneration in joint disease. *Nature Reviews Rheumatology*, *15*(3), 167-179.
- 108. Rajendran, P., Chen, Y. F., Chen, Y. F., Chung, L. C., Tamilselvi, S., Shen, C. Y., ... & Huang, C. Y. (2018). The multifaceted link between inflammation and human diseases. Journal of cellular physiology, 233(9), 6458-6471.
- 109. Ranasinghe, R., Mathai, M., & Zulli, A. (2022). A synopsis of modern-day colorectal cancer: Where we stand. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*, 1877(2), 188699.
- 110. Rangaswami, J., Bhalla, V., Blair, J. E., Chang, T. I., Costa, S., Lentine, K. L., ... & American Heart Association Council on the Kidney in Cardiovascular Disease and Council on Clinical Cardiology. (2019). Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation*, 139(16), e840-e878.
- 111. Renzi, C., Kaushal, A., Emery, J., Hamilton, W., Neal, R. D., Rachet, B., ... & Lyratzopoulos, G. (2019). Comorbid chronic diseases and cancer diagnosis: disease-specific effects and underlying mechanisms. *Nature reviews clinical oncology*, *16*(12), 746-761.
- 112. Reyes-Hinojosa, D., Lozada-Pérez, C. A., Cuevas, Y. Z., López-Reyes, A., Martínez-Nava, G., Fernández-Torres, J., ... & Martínez-Flores, K. (2019). Toxicity of cadmium in musculoskeletal diseases. *Environmental Toxicology and Pharmacology*, 72, 103219.
- 113. Ribaldone, D. G., Pellicano, R., & Actis, G. C. (2019). The gut and the Inflammatory Bowel Diseases inside-out: The extra-intestinal manifestations. *Minerva gastroenterologica e dietologica*, 309-318.
- 114. Rivera-Izquierdo, M., Cabeza, L., Láinez-Ramos-Bossini, A., Quesada, R., Perazzoli, G., Alvarez, P., ... & Melguizo, C. (2019). An updated review of adipose derived-mesenchymal stem cells and their applications in musculoskeletal disorders. *Expert Opinion on Biological Therapy*, 19(3), 233-248.
- 115. Rosenstock, J., Perkovic, V., Johansen, O. E., Cooper, M. E., Kahn, S. E., Marx, N., ... & Carmelina Investigators. (2019). Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *Jama*, 321(1), 69-79.
- 116. Rossi, F., Tortora, C., Paoletta, M., Marrapodi, M. M., Argenziano, M., Di Paola, A., ... & Iolascon, G. (2022). Osteoporosis in childhood cancer survivors: physiopathology, prevention, therapy and future perspectives. *Cancers*, *14*(18), 4349.

- 117. Ryan, A. M., & Sullivan, E. S. (2021). Impact of musculoskeletal degradation on cancer outcomes and strategies for management in clinical practice. Proceedings of the Nutrition Society, 80(1), 73-91.
- 118. Sange, A. H., Srinivas, N., Sarnaik, M. K., Modi, S., Pisipati, Y., Vaidya, S., ... & Sange, I. (2021). Extra-intestinal manifestations of inflammatory bowel disease. *Cureus*, *13*(8).
- 119. Sardu, C., Gambardella, J., Morelli, M. B., Wang, X., Marfella, R., & Santulli, G. (2020). Hypertension, thrombosis, kidney failure, and diabetes: is COVID-19 an endothelial disease? A comprehensive evaluation of clinical and basic evidence. *Journal of clinical medicine*, *9*(5), 1417.
- 120. Sarnak, M. J., Amann, K., Bangalore, S., Cavalcante, J. L., Charytan, D. M., Craig, J. C., ... & Conference Participants. (2019). Chronic kidney disease and coronary artery disease: JACC state-of-the-art review. *Journal of the American College of Cardiology*, 74(14), 1823-1838.
- 121. Savira, F., Magaye, R., Liew, D., Reid, C., Kelly, D. J., Kompa, A. R., ... & Wang, B. H. (2020). Cardiorenal syndrome: Multi-organ dysfunction involving the heart, kidney and vasculature. *British journal of pharmacology*, *177*(13), 2906-2922.
- 122. Schieda, N., Blaichman, J. I., Costa, A. F., Glikstein, R., Hurrell, C., James, M., ... & Hiremath, S. (2018). Gadolinium-based contrast agents in kidney disease: a comprehensive review and clinical practice guideline issued by the Canadian Association of Radiologists. *Canadian journal of kidney health and disease*, 5, 2054358118778573.
- 123. Serhan, C. N., Gupta, S. K., Perretti, M., Godson, C., Brennan, E., Li, Y., ... & Wolkenhauer, O. (2020). The atlas of inflammation resolution (AIR). Molecular aspects of medicine, 74, 100894.
- 124. Sharma, A., Zhao, X., Hammill, B. G., Hernandez, A. F., Fonarow, G. C., Felker, G. M., ... & DeVore, A. D. (2018). Trends in noncardiovascular comorbidities among patients hospitalized for heart failure: insights from the get with the guidelines—heart failure registry. *Circulation: Heart Failure*, 11(6), e004646.
- 125. Silveira, E. A., da Silva Filho, R. R., Spexoto, M. C. B., Haghighatdoost, F., Sarrafzadegan, N., & de Oliveira, C. (2021). The role of sarcopenic obesity in cancer and cardiovascular disease: a synthesis of the evidence on pathophysiological aspects and clinical implications. *International journal of molecular sciences*, 22(9), 4339.
- 126. Song, Y., Wu, Z., & Zhao, P. (2022). The function of metformin in aging-related musculoskeletal disorders. *Frontiers in Pharmacology*, *13*, 865524.

- 127. Stout, K. K., Daniels, C. J., Aboulhosn, J. A., Bozkurt, B., Broberg, C. S., Colman, J. M., ... & Van Hare, G. F. (2019). 2018 AHA/ACC guideline for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, 73(12), 1494-1563.
- 128. Stout, K. K., Daniels, C. J., Aboulhosn, J. A., Bozkurt, B., Broberg, C. S., Colman, J. M., ... & Van Hare, G. F. (2019). 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, 73(12), e81-e192.
- 129. Sturgeon, K. M., Mathis, K. M., Rogers, C. J., Schmitz, K. H., & Waning, D. L. (2019). Cancer-and chemotherapy-induced musculoskeletal degradation. *JBMR plus*, *3*(3), e10187.
- 130. Suzuki, K. (2019). Chronic inflammation as an immunological abnormality and effectiveness of exercise. *Biomolecules*, 9(6), 223.
- 131. Tsutsui, H., Isobe, M., Ito, H., Okumura, K., Ono, M., Kitakaze, M., ... & Yamashina, A. (2019). JCS 2017/JHFS 2017 guideline on diagnosis and treatment of acute and chronic heart failure—digest version—. *Circulation Journal*, 83(10), 2084-2184.
- 132. Tucker-Bartley, A., Lemme, J., Gomez-Morad, A., Shah, N., Veliu, M., Birklein, F., ... & Upadhyay, J. (2021). Pain phenotypes in rare musculoskeletal and neuromuscular diseases. *Neuroscience & Biobehavioral Reviews*, *124*, 267-290.
- 133. Turakhia, M. P., Blankestijn, P. J., Carrero, J. J., Clase, C. M., Deo, R., Herzog, C. A., ... & Wanner, C. (2018). Chronic kidney disease and arrhythmias: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. *European heart journal*, 39(24), 2314-2325.
- 134. Vaduganathan, M., Mensah, G. A., Turco, J. V., Fuster, V., & Roth, G. A. (2022). The global burden of cardiovascular diseases and risk: a compass for future health. *Journal of the American College of Cardiology*, 80(25), 2361-2371.
- 135. VanWagner, L. B., Harinstein, M. E., Runo, J. R., Darling, C., Serper, M., Hall, S., ... & Hammel, L. L. (2018). Multidisciplinary approach to cardiac and pulmonary vascular disease risk assessment in liver transplantation: an evaluation of the evidence and consensus recommendations. *American Journal of Transplantation*, 18(1), 30-42.
- 136. Varela, M. L., Mogildea, M., Moreno, I., & Lopes, A. (2018). Acute inflammation and metabolism. Inflammation, 41, 1115-1127.

- 137. Vasconcelos, D. P., Águas, A. P., Barbosa, M. A., Pelegrín, P., & Barbosa, J. N. (2019). The inflammasome in host response to biomaterials: Bridging inflammation and tissue regeneration. Acta biomaterialia, 83, 1-12.
- 138. Villeneuve, D. L., Landesmann, B., Allavena, P., Ashley, N., Bal-Price, A., Corsini, E., ... & Tschudi-Monnet, F. (2018). Representing the process of inflammation as key events in adverse outcome pathways. Toxicological sciences, 163(2), 346-352.
- 139. Weiskirchen, R., Weiskirchen, S., & Tacke, F. (2019). Organ and tissue fibrosis: Molecular signals, cellular mechanisms and translational implications. Molecular aspects of medicine, 65, 2-15.
- 140. Whelton, P. K., Carey, R. M., Aronow, W. S., Casey, D. E., Collins, K. J., Dennison Himmelfarb, C., ... & Wright, J. T. (2018). 2017
- ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, 71(19), e127-e248.
- 141. Wiles, K., Chappell, L., Clark, K., Elman, L., Hall, M., Lightstone, L., ... & Bramham, K. (2019). Clinical practice guideline on
- 142. Wong, S. K., Chin, K. Y., & Ima-Nirwana, S. (2020). Berberine and musculoskeletal disorders: the therapeutic potential and underlying molecular mechanisms. *Phytomedicine*, 73, 152892.
- 143. Yang, Y. J., & Kim, D. J. (2021). An overview of the molecular mechanisms contributing to musculoskeletal disorders in chronic liver disease: osteoporosis, sarcopenia, and osteoporotic sarcopenia. *International journal of molecular sciences*, 22(5), 2604.
- 144. Zanelli, M., Pizzi, M., Sanguedolce, F., Zizzo, M., Palicelli, A., Soriano, A., ... & Ascani, S. (2021). Gastrointestinal manifestations in systemic mastocytosis: the need of a multidisciplinary approach. *Cancers*, *13*(13), 3316.
- 145. Zhang, Q., & Cao, X. (2021). Epigenetic remodeling in innate immunity and inflammation. Annual review of immunology, 39(1), 279-311.
- 146. Zhang, S., Miller, D. D., & Li, W. (2021). Non-musculoskeletal benefits of vitamin D beyond the musculoskeletal system. *International journal of molecular sciences*, 22(4), 2128.
- 147. Zhang, S., Xing, M., & Li, B. (2019). Recent advances in musculoskeletal local drug delivery. *Acta biomaterialia*, *93*, 135-151.
- 148. Zhao, H. M., Xie, Y. X., Wang, C., Chinese Association of Rehabilitation Medicine, Respiratory Rehabilitation Committee of Chinese Association of Rehabilitation Medicine, &

Cardiopulmonary Rehabilitation Group of Chinese Society of Physical Medicine and Rehabilitation. (2020). Recommendations for respiratory rehabilitation in adults with coronavirus disease 2019. *Chinese medical journal*, 133(13), 1595-1602.

149. Ziade, N., El Khoury, B., Zoghbi, M., Merheb, G., Abi Karam, G., Mroue', K., & Messaykeh, J. (2020). Prevalence and pattern of comorbidities in chronic rheumatic and musculoskeletal diseases: the COMORD study. *Scientific reports*, *10*(1), 7683.

150. Zügel, M., Maganaris, C. N., Wilke, J., Jurkat-Rott, K., Klingler, W., Wearing, S. C., ... & Hodges, P. W. (2018). Fascial tissue research in sports medicine: from molecules to tissue adaptation, injury and diagnostics: consensus statement. British journal of sports medicine, 52(23), 1497-1497.