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THE ASSOCIATION OF MATRIX METALLOPROTEINASE-7, 10 WITH *HEPATITIS C* VIRUS INFECTIONS IN CHRONIC KIDNEY DISEASES

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QABAS FADHIL ALWAN ALANBARY

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By Qabas Fadhil Alwan ALANBARY

December 2023

We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science

Advisor **:** Asst. Prof. Dr. Zehra CAN KARAHAN
Co-Advisor **:** Asst. Prof. Dr. May Khaleel ISMAEL

Examining Committee Members:

Chairman **:** Asst. Prof. Dr. Zehra CAN KARAHAN
BIOLOGY
Çankırı Karatekin University

Member **:** Asst. Prof. Esin KIRAY
BIOLOGY
Ahi Evran University

Member **:** Asst. Prof. Filiz SARIKAYA PEKACAR
BIOLOGY
Çankırı Karatekin University

Approved for the Graduate School of Natural and Applied Sciences

Prof. Dr. Hamit ALYAR
Director of Graduate School

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Qabas Fadhil Alwan ALANBARY

ABSTRACT

THE ASSOCIATION OF MATRIX METALLOPROTEINASE-7, 10 WITH *HEPATITIS C* VIRUS INFECTIONS IN CHRONIC KIDNEY DISEASES

Qabas Fadhil Alwan ALANBARY

Master of Science in Biology

Advisor: Asst. Prof. Dr. Zehra CAN KARAHAN

Co-Advisor: Asst. Prof. Dr. May Khaleel ISMAEL

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The kidney is the most important excretory organ in humans, as it processes approximately 2,000 liters of blood daily, and when the kidneys are unable to remove wastes and are unable to maintaining the internal balance of mineral salts and water is kidney failure. Therefore, this study aimed to find non-invasive biomarkers to predict the diagnosis and monitor the progression of chronic kidney disease (CKD): including the level of matrix metallo proteinase MMP7 and MMP10**.** Patients with CKD infected with hepatitis (HCV) were the focus of this study. 90 blood samples were collected, including 22 samples from individuals in good health (the control group): 22 samples from patients suffering from chronic kidney disease and hepatitis C infection, and 46 samples from the patients suffering from chronic kidney disease (samples were taken for Iraqi patients at Medical City Hospital after obtaining their verbal consent).The Sandwich ELISA technique was used in this study for blood samples taken to extract serum. It has been shown that the prevalence of chronic kidney disease (CKD) increases with age, especially from the age of 40 years and above. The results showed that the majority of patients suffering from chronic kidney disease (CKD) are male. This may be due to the activity of sex hormones or physical stress. The prevalence of chronic kidney disease (CKD) was found to be higher in rural areas compared to urban areas. It was noted that the majority of participants in the study had the ability to read and write. The research revealed that the majority of patients suffered from chronic kidney disease for two to three years. The significant number of patients with chronic kidney disease suffer from diabetes, as it is

one of the main causes of kidney disorders. It was noted that MMP10 and MMP7 levels are higher in patients with CKD compared to patients with chronic kidney disease and hepatitis C virus. It was found that they have a positive relationship with degrees of renal fibrosis and a negative relationship with kidney function. In conclusion, elevated levels of MMP10 and MMP7 may be a marker for predicting tissue damage and worsening renal status in patients with CKD.

2023, 62 pages

Keywords: MMP-7, MMP-10, Chronic kidney diseases, Hepatitis C virus infection, ELISA

ÖZET

KRONİK BÖBREK HASTALIKLARINDA *HEPATİT C* VİRÜS ENFEKSİYONLARI İLE MATRİKS METALLOPROTEİNAZ-7, 10 İLİŞKİSİ

Qabas Fadhil Alwan ALANBARY
Biyoloji, Yüksek Lisans
Tez Danışmanı: Dr. Öğr. Üyesi Zehra CAN KARAHAN
Eş Danışman: Dr. Öğr. Üyesi May Khaleel ISMAEL
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Böbrek, günde yaklaşık 2.000 litre kanı işlediğinden insanlarda en önemli boşaltım organıdır ve böbreklerin atıkları uzaklaştıramaması ve mineral tuzlar ile suyun iç dengesini koruyamaması böbrek yetmezliğine neden olur. Bu nedenle, bu çalışma, kronik böbrek hastalığının (KBH) tanısını tahmin etmek ve ilerlemesini izlemek için matriks metalo proteinaz (MMP7 ve MMP10) seviyesi dahil, invazif olmayan biyobelirteçler bulmayı amaçladı. Hepatit (HCV) ile enfekte KBH'li hastalar bu çalışmanın odak noktasıydı. Sağlık durumu iyi olan kişilerden (kontrol grubu) 22 örnek, kronik böbrek hastalığı ve hepatit C enfeksiyonu olan hastalardan 22 örnek ve kronik böbrek hastalığı olan hastalardan 46 örnek dahil olmak üzere 90 kan örneği toplandı (örnekler Irak'tan Medical City Hastanesi'ndeki hastaların sözlü onamları alındıktan toplandı). Bu çalışmada serum ekstraksiyonu için alınan kan örneklerinde sandviç ELISA tekniği kullanıldı. KBH prevalansının yaşla birlikte, özellikle de 40 yaş ve üzerinden itibaren arttığı gösterildi. Sonuçlar, KBH'dan muzdarip hastaların çoğunluğunun erkek olduğunu gösterdi. Bunun nedeni seks hormonlarının aktivitesi veya fiziksel stres olabilir. KBH prevalansının kırsal kesimde kentsel kesime göre daha yüksek olduğu belirlendi. Araştırmaya katılanların çoğunluğunun okuma-yazma becerisine sahip olduğu kaydedildi. Araştırma, hastaların çoğunluğunun iki ila üç yıldır kronik böbrek hastalığına sahip olduğunu ortaya çıkardı. Kronik böbrek hastalığı olan hastaların önemli bir kısmı, böbrek rahatsızlıklarının ana nedenlerinden biri olan diyabetten muzdaripti. KBH hastalarında MMP10 ve MMP7 düzeylerinin kronik böbrek hastalığı ve hepatit C virüsü

hastalarına göre daha yüksek olduğu kaydedildi. Böbrek fibrozisinin dereceleri ile pozitif, böbrek fonksiyonu ile ise negatif bir ilişkiye sahip oldukları bulundu. Sonuç olarak MMP10 ve MMP7'nin yüksek seviyelerinin KBH'li hastalarda doku hasarını ve böbrek durumunun kötüleşmesini öngörmeye yönelik bir işaret olduğu düşünülebilir.

2023, 62 Sayfa

Anahtar Kelimeler: MMP-7, MM0-10, Kronik böbrek hastalıkları, Hepatit C virüsü enfeksiyonu, ELISA

PREFACE AND ACKNOWLEDGEMENTS

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Qabas Fadhil Alwan ALANBARY

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CONTENTS

LIST OF ABBREVLATION

CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
DKD	Diabetes kidney disease
DM	Diabetes melitus
ECM	Extracellular matrix
ELISA	Enzyme linked immunosorbent assay
ESRD	End stage renal disease
GFR	Glomerular filtration rate
GN	Glomerulonephritis
GT	Gamma glutamyl transpeptidase
HCV	Hepatitis c virus
HD	Human dialysis
HF	Heart failure
HRV	Heart rate variability
MMP10	Matrix metalloproteinase-10
MMP7	Matrix metalloproteinase-7
MMPs	Matrix metalloproteinase

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1. INTRODUCTION

Defects lasting longer than three months in kidney anatomy or function are associated with a glomerular filtration rate (GFR) of less than 60 mL per minute per 1.73 m^2. This condition is known as chronic kidney disease (CKD). Albuminuria, aberrant urine sediment, abnormal renal imaging findings, abnormal serum electrolyte or acid-base derangements, and proteinuria are all signs of chronic kidney disease (Levin *et al*. 2013). Early identification is essential for starting prompt therapeutic measures, reducing nephrotoxin exposure, stopping future declines in GFR, and getting ready for renal replacement therapy since Increased danger is associated with chronic kidney disease (CKD) of developing kidney failure, and death (Pereira *et al*. 2000). The yearly screening for CKD of people with diabetes or hypertension is advised by several guidelines. Patients should also be tested if they have additional risk factors, cardiovascular disease, old age, low birth weight, obesity, and a family history of chronic kidney disease (Correa *et al*. 2020). Few extensive epidemiologic studies including Despite the fact that it is predicted that CKD patients high rates of *Hepatitis C* virus infection, predialysis patients with CKD has been carried out in various geographical locations. 7.6% HCV infection was found by Lee *et al.* (2014). *Hepatitis C* is one of the main causes of liver cirrhosis worldwide. In addition to its effects in the liver, chronic *hepatitis C* virus infection shows extra-hepatic activity in various organs and tissues including kidneys1. Recent evidence suggests a link between hepatitis C virus infection and chronic kidney disease, Chronic HCV and CKD are major public health issues all over the world, globally, an estimated 71 million people have chronic hepatitis C infection and the rate of CKD in the adult general population of industrialized countries is around 10-15% (Glasssock *et al*. 2017). HCV-infected individuals is connected with insulin resistance, type 2 diabetes, and hyperlipidemia. This suggests that insulin resistance and the vascular issues it causes either directly or indirectly encourage renal decline. A direct cytopathic impact is brought on by chronic HCV infection as well as an immunological response. Indicating that, contrary to popular belief, HCV has a higher impact on renal decline brought on by glomerulonephritis (GN). As a result, individuals with HCV infection should routinely be monitored for the early diagnosis of (GN) (Kim and Song 2018).

Aim of the study

1- The socio-demographic data of all study participants will be documented (age, gender, habitation, educational levels, and occupational status).
2- The clinical characteristics of the patient group should be evaluated, including family history of CKD, history of diabetes mellitus, and disease duration.
3- Estimate the matrix metalloproteinase-10 serum level among study groups.
4- Estimate the matrix metalloproteinase-7 serum level among study groups.
5- Investigation of the roles of matrix metalloproteinase-10 and 7 as biomarkers for predicting the severity and tissue damage to the kidney in patients with CKD.

2. LITERATURE REVIEW

2.1 Defining Chronic Kidney Disease (CKD)

Each human kidney has roughly 1 million glomeruli at birth, according to a commonly used statistic (Boriani *et al*. 2015). This is based on RA Moore's 1931 study, in which glomeruli in a cross-section of kidneys were counted during autopsy. A man in his forties has between 800,000 and each kidney has an average of 1,000,000 glomeruli, and postnatal nephrogenesis does not occur, senile glomeruli loss occurs in humans, similar to that in rats, and there is a glomeruli loss in each kidney between the ages of 40 and 50. an individual's two kidneys have roughly the same number of glomeruli. Loss of kidney function develops slowly over a period of months or years in people with chronic kidney disease (CKD) (Botirovna *et al*. 2020). In most cases, no symptoms manifest at first, but later on, you may notice things like leg swelling, fatigue, vomiting, lack of appetite, and disorientation, High blood pressure, bone disease, and anemia are all conditions that may arise as a result of hormonal malfunction in the kidneys (Liao *et al*. 2012). Heart problems are another major cause of mortality and hospitalization for those with chronic kidney disease. Diseases including diabetes, hypertension, glomerulonephritis, and polycystic kidney disease all contribute to the development of chronic kidney disease) (Botirovna *et al*. 2020). Having a close relative with renal failure is a risk factor blood tests measuring estimated glomerular filtration rate (eGFR) and urine albumin levels are used for diagnosis (Vasiri 2006). In order to identify the root reason, a doctor may utilize ultrasound or a kidney biopsy, there are other severity-based staging systems in use today (Botirovna *et al*. 2020). It is advised to screen those who are at risk. Medication to reduce blood pressure, blood sugar, and cholesterol is a possible first line of therapy (Wilson *et al.* 2017). Edema may be managed, and blood pressure can be further reduced if necessary, with the use of loop diuretics (Libby *et al*. 2007). As stated in the previous paragraph, a low-salt diet and enough protein intake are also suggested, along with regular physical activity. Anemia and bone disease treatments may also be necessary (Jan *et al*. 2017).

It takes a long time for noticeable symptoms to appear when chronic kidney disease (CKD) first starts (Figure 2.1). The primary function of the kidneys, which most people are aware of, is the elimination of metabolic waste products. And this is the function that is used to assess if a person has CKD (Guyton 2006). Inulin clearance has been universally acknowledged as the gold standard of kidney function (Lieberthal *et al*. 1986). This is due to its excellent filtration marker properties, features such as not being generated, absorbed, or metabolized by the renal tubule, not being poisonous, and being physiologically inactive. It is also commonly acknowledged that due to its time-consuming and complex implementation, it is not practicable for widespread clinical application (Stevens *et al*. 2006).

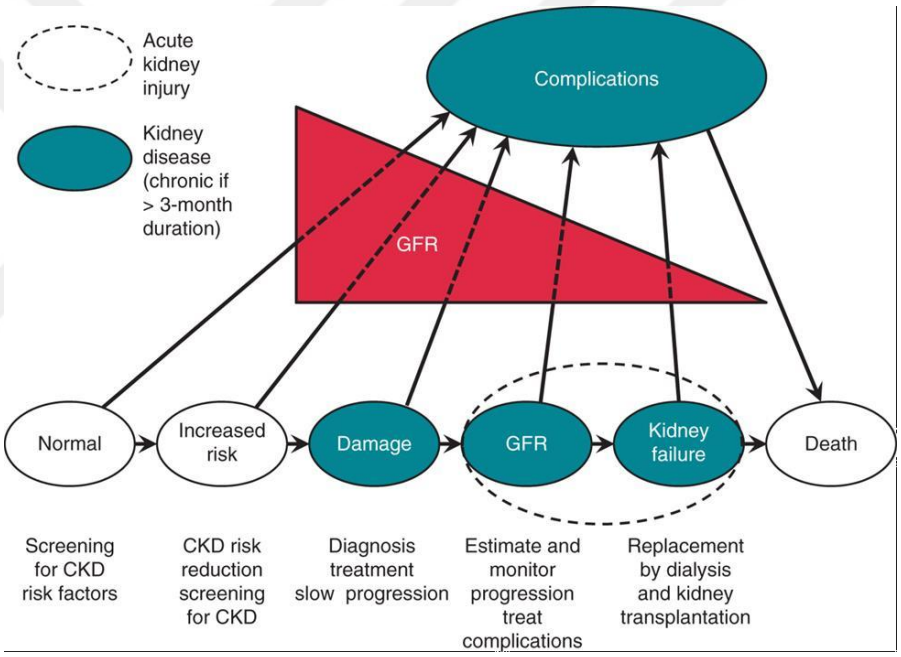

Figure 2.1 Chronic kidney disease (CKD) and how it progresses through its many forms, along with its associated consequences and potential treatment options. With the author's express consent (Boriani *et al.* 2015)

Numerous conditions for a suitable filtration marker are satisfied by serum creatinine a non-protein-bound, easily filtered, tubule-unmetabolized, physiologically inert endogenous marker. The proximal tubules, however, are where it's estimated that the kidneys are responsible for up to 60% of the body's serum creatinine production. Goes as renal function falls, and drugs like cimetidine and trimethoprim can stop this process

(Delanaye *et al.* 2010). Food, drugs, and illness all affect how much of this pool is present since creatinine is produced from muscle creatine (Nguyen and Wang 2019).

2.2 CKD in the 21st Century

The earliest description of eGFR as we presently understand patients with chronic renal illness from the MDRD trial were included in a report that described a novel equation for predicting glomerular filtration rate. The 6-variable MDRD was an equation that took into account Variables included: age, sex, body mass index, ethnicity, serum creatinine, serum urea, serum albumin, and serum uric acid levels. They showed that the equation had a strong correlation (R2 = 0.903) with the observed GFR as determined by excretion of 125I-iothalamate. 91% of the time, they could accurately estimate within 30% of predicted GFRs for GFR Both originated in the same population and perform their functions without serum albumin and urea, respectively, with just a little loss of accuracy. The R2 values for the more complex five-variable and four-variable equations were 0.899 and 0.892, respectively (Levey *et al.* 2000). Although it is noted in the recommendation, the basis for the CKD definition that is currently accepted does not explicitly include proteinuria. In Clase *et al.* (2004) there was no generally acknowledged definition of CKD prior to the release of this text. Up to 23 distinct terminologies are used to characterize chronic kidney disease (CKD): according to a report by Hsu *et al.* (2000) titled "Chronic Renal Confusion: Insufficiency, Failure, Dysfunction or Disease" (Hsu and Chertow 2000). They also discovered that the severity of these words ranged from those requiring dialysis to those with creatinine clearances as high as 75 mL/min.

2.3 Epidemiology of Chronic Kidney Disease

An international scholarly investigation revealed that the frequency of CKD, a health issue that affects people all over the world, rises with age, with a median frequency of 7.2% in people over 30 and between 23.4% and 35.8% in those over 64. According to Sircar *et al.* (2015) the mortality risk is significantly higher in this cohort, Statistics show that individuals 60 and older receiving dialysis in the West have an average 5-year survival rate was roughly 45%. This ongoing warning is necessary since, according to a

WHO assessment, chronic non-communicable degenerative illnesses currently account for 35 of the 58 million deaths globally in 2005, at least in developed nations (WHO 2005). The biggest cause of death worldwide is CKD of mortality globally and ranks in the top five killers with cancer, chronic lung disease, cardiovascular disease and type 2 diabetes, is an increasingly pressing issue. In the US, it is estimated that 13% (26 million) of non-institutionalized individuals have CKD (Matsukuma *et al.* 2017). A concerning higher percentage (15 million) of patients have CKD at an earlier stage and could go undiagnosed and untreated if they do not receive timely treatment. About 1.0 million of these patients suffer and just half a million people worldwide are keeping themselves alive thanks to dialysis or a kidney transplant. Similar prevalence rates are found in Asia, including Hong Kong, Australia, and Europe. Following 28,000 patients with CKD stages II, III, and IV, Keith *et al.* (2004) concluded that 19.9% eventually developed ESRD and had death rates of 19.5%, 24.3%, and 45.7%, correspondingly. Following 1076 patients for five and a half years, a retrospective cohort study results showed that 4% of them had ESRD and 69% of them died (Matsukuma *et al.* 2017). At every stage of CKD, declining kidney function raises the possibility of developing heart problems (Nguyen and Wang 2019).

2.4 Etiology of Chronic Kidney Disease

The many causes of CKD may be divided into categories including hereditary, glomerular, vascular, tubulointerstitial, and urinary tract obstruction (Langsford *et al.* 2017). The most frequent causes are linked to hypertension and diabetes. Due to the regulatory, endocrine, excretory, and metabolic activities of the kidney, progressive renal failure is linked to a variety of problems. These side effects include metabolic abnormalities (such as pruritus, renal osteodystrophy, insulin resistance, and dyslipidaemia): endocrine anomalies, and nephrogenic systemic fibrosis (For instance, erectile dysfunction brought on by low testosterone levels and impaired development in youngsters yielding to changes in the action of growth hormone): cardiovascular disease, calciphylaxis, neurological system dysfunction, and muscular dysfunction. Depending on the individual, the cause of the CKD, and comorbidities, these consequences and the

ensuing symptoms may differ. However, the majority of problems are made worse by ESRD and deteriorating renal function (Jalal *et al.* 2017).

2.5 Dialysis

The process of dialysis was first used in the middle of the 20th century, when Kolff-the man credited with creating the artificial kidney or dialyzer-invented it in 1943. Kolff and Scribner eventually made contributions to the development of contemporary dialysis (Davita 2017). By definition, dialysis is a therapeutic method that removes waste materials and corrects the electrolyte, water, and acid-base imbalances required when the kidneys stop working. Additionally, when the kidneys stop functioning properly, their fundamental job must be performed artificially. Dialysis is a therapy that involves the passage of blood and dialysate via a semipermeable membrane (Ding and Lo 2016). Haemodialysis and peritoneal dialysis are the two different forms of dialysis. Both of these processes filter the blood to eliminate water, creatinine, urea, and other wastes while leaving behind the red blood cells and other vital components (Davita 2017). Peritoneal dialysis employs the peritoneum, a filter located in the abdomen, during the dialysis process. The peritoneal cavity is reached by Procedure involving the implantation of a catheter via the lower abdomen wall. Once inside, the dialysis fluid is injected and later emptied from the peritoneal cavity. Because peritoneal dialysis does not require hospitalization and may be performed at home, more activities can be pursued (Wong *et al.* 2018). Hepatitis C is brought on by the viral illness hepatitis. Once the host's adaptive immune systems are suppressed by the virus, Sixty percent to eighty those who get acute hepatitis C are at a risk of acquiring chronic hepatitis C (Bang *et al.* 2016). HCV has 67 subtypes and 7 verified genotypes. Exist, and these genotypes affect both the choice of antiviral medication and the prognosis of the disease (Blach *et al.* 2017). Despite estimates from the (WHO) that more than 70 million people worldwide have infected with HCV, there is still a low level of public awareness of the disease. Due to the fact that they regularly go for extended periods of time without feeling any symptoms and have not had an HCV test done, many individuals (Modi and Liang 2008). This data was collected as part of NHES, or the National Health and Nutrition Examination Survey, 393 out of 30,140 people those who participated in it in the USA between 2001 and 2008 had

HCV infection at the time. Only 49.7% of the 170 patients who were able to be later followed up knew they had HCV infection at the time. Only 10% to 40% of people with HCV infection are thought to be aware of their virus status, according to estimates in Europe (Blachier *et al.* 2013). There are differences in HCV testing between nations, notably in low-income areas nations (Ishizaki *et al.* 2017).

A. The effect of age on the function of the renal glomeruli:

After the age of thirty, when a person begins to biologically age toward old age, the kidneys often suffer a gradual deterioration in their function and structure. The rates of filtration and blood flow in the renal glomeruli begin to decline gradually, such that the rate in people aged eighty may reach one-third compared to that in young people. Also, the kidney mass begins to decrease as the rate of glomerular disease increases with age. Therefore, at advanced ages, the kidneys are vulnerable to kidney failure, as the number of nephrons begins to decrease due to acquired kidney disease. There is some evidence indicating that not consuming foods high in dietary protein may delay the development of age-related glomerular sclerosis, and that reducing it may delay end-stage kidney disease in patients with progressive renal failure (Schoolwerth *et al.* 1975).

B. The effect of diabetes on hyperfiltration in the kidneys:

Renal hyperfiltration has been shown in patients with type 1 and type 2 diabetes, as well as in patients who suffer from a pre-diabetic condition. An example of this is metabolic syndrome. The association of pressure within the glomeruli with increased renal filtration leads to the development of kidney disease in diabetic patients. (DM). It is also possible that tubular and vascular factors contribute to the hyperfiltration condition. To this day, we note that studies focus primarily on taking medications that block the renin-angiotensin system in order to reduce constriction in the blood vessels, which leads to improving the state of hyperfiltration (Anderson *et al.* 1993).

C. Chronic kidney disease (CKD) and heart disease

Given the prevalence of heart disease in patients with chronic kidney disease (CKD) and those undergoing dialysis (HD), we must point out this. Patients on dialysis (HD) suffer from the risk of clotting and bleeding. Many patients with chronic kidney disease who require dialysis suffer from many diseases related to the heart and blood vessels, such as (atrial fibrillation, coronary artery disease, and venous clots). It has been noted that very few trials have dealt with antiplatelet or anticoagulant treatment in dialysis and some treatment indications with anticoagulants (Levey and Coresh 2012).

It has been shown that the incidence and prevalence of heart disease for patients who suffer from chronic kidney disease (CKD) is high compared to their peers who do not suffer from kidney disease, so it is necessary to find anticoagulant and antiplatelet drugs (Levey *et al.* 2011). It was also noted that the number of patients suffering from atherosclerosis and irregular heartbeats was found. Cardiovascular disease, as well as atrial fibrillation, and at the same time the increased risk of bleeding makes taking anticoagulant treatments very difficult for this group (Anderson *et al.* 1993). As for patients who suffer from coronary artery syndrome, they can continue to use old medications such as aspirin, which is the only treatment that works as an antiplatelet and has been approved for use within the guidelines for heart disease patients with chronic kidney disease (CKD), as well as the anticoagulant (heparin), which is one of the approved treatments (Levey *et al.* 2011).

Many people with CKD suffer from heart failure (HF), which is one of the main causes of their health deterioration and possibly death. As the number of CKD increases, we notice an increase in those suffering from heart failure. However, the diagnosis of HF is one of the challenges of chronic kidney disease (CKD) due to the lack of reliable biomarkers for this group in particular, because the pathophysiology between the heart and kidneys is bidirectional and extremely difficult (Avalia *et al.* 2013). CKD patients have greater risk factors for heart failure (HF), in addition to risk factors related to the kidneys, such as acid-base changes, mineral changes in the bones, malnutrition, weak heart muscle, and anemia. These factors also contribute to a noticeable decline in kidney

function for HF patients. Clinical and clinical. There are treatments that can slightly improve the health status of patients with heart failure and chronic kidney disease, so there is a necessary need to develop new HF treatments for CKD patients (Schoolwerth *et al.* 1975).

Another study dealt with the relationship of low heart rate (HRV) to CKD, as low heart rate (HRV) is usually associated with cardiovascular diseases, so its relationship with low heart rate (HRV) and (CKD) raised controversy. It was found that low heart rate is directly proportional. With the high incidence of CKD, which suggests that the decrease in heart rate may be one of the complications of chronic kidney disease and not the causative factor, but rather it may be the cause of a defect that occurred in the autonomic nervous system as a result of a decrease in the functions of the parasympathetic system compared to the parasympathetic system in theory. Which leads to an involuntary imbalance, which in turn leads to kidney damage due to changes in renal blood dynamics. Thus, it is possible to predict the risk of developing a weak heart rate and the possibility of finding new treatment methods if it is determined that the autonomic imbalance is a mechanism for kidney damage (Levey *et al.* 2011).

2.6 Hepatitis C Virus Genotype Prevalence: Global, Middle East

The WHO and Polaris Observatory's most current estimates show that In 2015, there were a total of 2 million newly diagnosed cases of HCV. a WHO Middle East and Eastern Mediterranean region, had the greatest incidence of chronic infections (2.3%): and Africa (2%), South-east Asia (1.5%) had the lowest frequency (Blach *et al.* 2017).

The capacity of different viral proteins, necessary for infection is the ability of invading proteins, both structural and non-structural, to interact with host proteins by all genotypes. The capacity to respond to medication depends on genotype, and genotype diversity makes it difficult to create effective HCV vaccinations that could be used by everyone.

2.7 Modes of transmission

HCV spreads primarily through blood contact, unsafe injection techniques in medical facilities and recreational drug injection usage are major contributors to HCV transmission globally. Healthcare-associated transmission of HCV was more common before the United States started Diagnosis HCV (Smith *et al.* 2012). However, from 2008 to 2015, 32 healthcare outbreaks with more 240 cases connected to the epidemic received reports from the public and were sent to the (Centers for Disease Control and Prevention 2016). In babies born to HCV-infected moms, vertical transmission can happen in around 6% of cases, and it may happen twice as frequently in babies born co-infected mothers or HCV infected women with high levels (Benova *et al.* 2014). Although most incidences of sexually infection have been documented among males who engage in sexual activity with other HIV-positive guys, sexual transmission is often ineffective (Hagan *et al.* 2015). Finally, non-injection drug use and unlicensed tattooing are further contexts in which HCV transmission has been documented (Hellard *et al.* 2004).

2.7.1 Testing and diagnosis

Currently, laboratories utilize immunoassays (anti-HCV) using immunoglobulin (Ig) G antibodies and nucleic acid tests (NAT) to diagnosis chronic HCV infection (Getchell *et al.* 2013). An anti-HCV antibody test should be the first step in HCV testing. No additional testing for HCV infection is necessary for people who don't have any risk factors and have a non-reactive anti-HCV antibody. For some groups with significantly weakened immune systems or those who are currently at risk of exposure to HCV due to injecting drugs or receiving hemodialysis, further testing may be necessary, To identify the presence of RNA, status of an active HCV infection, a reactive anti-HCV antibody must be confirmed with an HCV NAT (Getchell *et al.* 2013). People who have an HCV infection and a reactive anti-HCV antibody should receive the necessary HCV medical care and therapy. Reactive anti-HCV in a person without HCV infection who has a negative HCV might mean one of three things: 1) a prior infection that resolved spontaneously, 2) a prolonged virologic response from HCV therapy, erroneous anti-HCV Abs results, etc (although in populations with the ability for HCV infection) (Moyer

2013). Having the Liver cancer is more likely to occur in those who have had hepatitis C virus (HCV). Over 180 million individuals, or 2.8%people all throughout the globe, have HCV, therefore awareness of the condition is growing (Thrift *et al.* 2017). It is well recognized that HCV infection can cause liver cancer. But in addition to hepatic symptoms, HCV infection also causes autoimmunerenal, cardiovascular, nervous system, and lymphoproliferative issues in 40% to 70% of patients (Cacoub *et al.* 2019). One frequent extra hepatic symptom of renal dysfunction is a common complication of hepatitis C virus infection. Chronic hepatitis C virus (HCV) infection is associated with a number of serious health problems, including end-stage renal disease speeds up the degradation of the kidneys (Park *et al.* 2017). Among addition, rates of morbidity and death are greater in HCV-infected patients on dialysis (Scott *et al.* 2010). In individuals with chronic renal impairment, the virologic response rate and tolerance of traditional interferon Treatment for HCV infection with is especially ineffective (CKD).

2.8 HCV in Patients with CKD

Despite the fact that Immune compromised CKD patients are likely to experience Despite the widespread spread of HCV infection, there have been little systematic investigations of the disease's prevalence including pre-dialysis patients with CKD have been conducted in different geographic regions. Research conducted in Taiwan found that 8.6% of 4,185 CKD patients prior to dialysis were infected with HCV (2014). OverallMoreover, the 5-year cumulative incidence of ESRD was 52.6% higher in those with CKD and HCV infection, and the prevalence of HCV increased with increasing CKD stage than in those without HCV infection, who had a cumulative incidence of ESRD of 38.4%. However, a second Taiwanese research discovered that those with HCV infection had a higher prevalence of CKD than those without the virus (Chen *et al.* 2014).

Evidence like this suggests that HCV infection and and renal function, suggesting that it can cause CKD and speed up the development of CKD to ESRD. Renal degeneration can be caused by a variety of indications of liver-wide infection with hepatitis C virus and/or the body at large. 10% to 60% of HCV-infected individuals have insulin resistance, which has been linked to the hepatic dysfunction that HCV causes (Villar *et al.* 2017). Recently,

however, it has been shown insulin signaling is disrupted by the HCV core protein, which upregulates induction of Suppressor of Cytokine Signaling 3while lowering the expression of insulin receptor substrate 1, tumor necrosis factor-alpha, and p70 ribosomal protein S6 kinase 1. It also inhibits the expression of glucose transporter 2,4 by upregulating glucose-6-phosphatase and phosphoenolpyru (Bose *et al.* 2012). Greater triglyceride, fasting glucose values were found in HCV-infected people, as well as a strong correlation between the two parameters, according to Sciacqua *et al.* (2016). (eGFR). In those with HCV infection, Type 2 Diabetes, High Blood Lipid Levels, and Insulin Resistance as well as to cardiovascular events. This suggests that renal degeneration is either directly or indirectly facilitated by insulin resistance and accompanying vascular consequences. A direct cytopathic impact is brought on by chronic HCV infection as well as an immunological response. Hepatocytes and B-lymphocytes are two cells where HCV may enter and multiply. B-lymphocytes' CD81 transmembrane 4 family glycoprotein can bind to the HCV envelope 2 protein, which causes the cells to activate (Schamberg and Lake-Bakaar 2007). These are connected to the development of glomerulonephritis (GN) in people with HCV infection. Cryoglobulins and rheumatoid factor-IgM are produced by immunoglobulin G (IgG)-HCV complexes that are formed by persistently activated B-lymphocytes (Ferri *et al.* 2017).

The most common form of nephritis caused by Although the most common form of kidney disease caused by High-Caliber Viral Nephritis (HCV) Is Membranoproliferative Glomerulonephritis or without cryoglobulin, other manifestations have been reported. These include IgA nephropathy, focal segmental glomerulosclerosis, fibrillary glomerulonephritis, thrombotic microangiopathy, and tubulointerstitial nephritis. nephritis (Ferri *et al.* 2017). 87% of individuals with cryoglobulinemia in a multicenter study conducted in Italy had HCV infection. Additionally, according to El-Serag *et al.* (2002) 82% of patients displayed the MPGN pattern on their kidney biopsies. Based on data from the Veterans Administration, found that patients with HCV had a greater frequency of MPGN (0.36% vs. 0.05%) However, HCV infection only manifests as microalbuminuria in more than 10% of HCV-infected individuals (Liangpunsakul and Chalasani 2005). Indicating that HCV has a bigger impact than previously thought on

renal degeneration through GN. As a result, individuals with HCV infection should be regularly monitored as a means of early GN diagnosis.

2.9 HCV in Patients on Dialysis

In 2004 research found that 13.5% of HD patients had hepatitis C virus infection. (HCV). Variations across regions in this global survey ranged from 2.6% to 22.9%. As reported by Fissell *et al.* (2004). Dialysis patients in 11 Asian and Pacific countries were studied by Johnson *et al.* (2009): who looked at the prevalence of HCV. They discovered that it was 8% in patients receiving HD and 2.0% in those receiving peritoneal dialysis. Additionally, the type of dialysis used was related to the frequency of HCV infection. Since the Centers for Disease Control issued their guidelines for reducing virus transmission among chronic hemodialysis patients in 2001, the rate of viral transmission associated with HD has decreased (Wasley *et al.* 2007). Typically, HD patients get HCV through direct patient contact, transfusion of tainted blood, use of infected equipment, and other lapses in infection control (Karkar 2018). According to the study, risk factors for HCV infection include black ethnicity, hepatitis B co-infection, and drug and alcohol abuse, and that the incidence of HCV rises with HD duration (58% in > 20 years): These findings highlight the value of ongoing HCV surveillance and point to a lack of understanding of infection management in diagnostic facilities. According to Goodkin et al. (2017): Compared to HD patients without HCV, those with HD individuals had greater rates of morbidity and death due to HCV infection.

2.10 Metalloproteinase (MMPs)

The biggest family of catalytic enzymes is the metalloprotease, which is distinguished because proteolytic activity requires a divalent metal ion (López-Otn and Overall 2002). These enzymes may be divided into 27 families, with 19 ADAMs with thrombospondin motifs making up the metzincin superfamily and 23 matrix metalloproteinases (MMPs) (Blobel 2005). They can selectively release cytokines, growth hormones, or receptors linked to cell surfaces, or they can degrade significant quantities of extra matrix proteins, which affects the recruitment of immune cells (Rilla *et al.* 2019). It's crucial to keep in

mind that various metalloproteinases have been demonstrated to possess proteolytic characteristics and take role in pathogenic processes. MMP-2 and MMP-9, two local invasion-related MMPs, are found in EVs from cancer tissues.

2.10.1 Structure of MMPs

Belong to the family of endopeptidases that rely on zinc. That were initially identified over 50 years ago. The proteolytic characteristics of these enzymes give them a pivotal role tissue remodeling among its many roles in physiological and pathological processes.

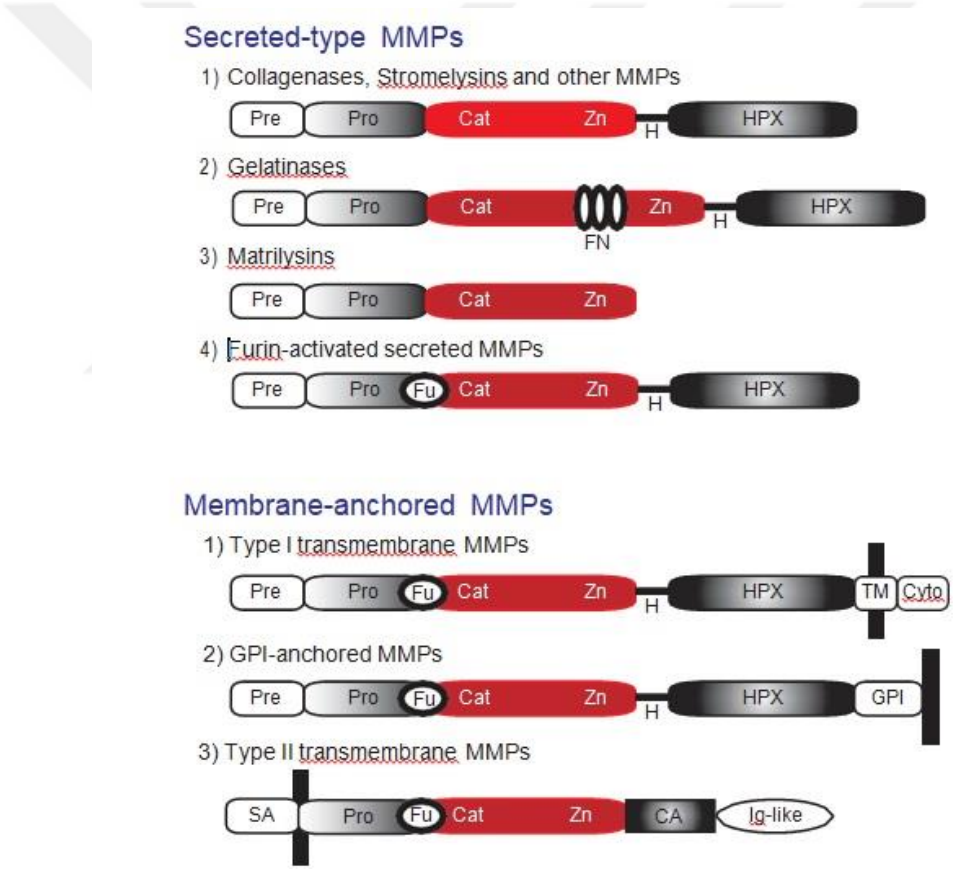

Figure 2.2 Structures of MMPs (Shimoda 2019)

Organ development, control over the growth of cancer and inflammatory processes. MMPs have a propeptide domain, a catalytic domain containing a zinc ion-binding motif, and a hemopexin-like domain at the C-terminus, all of which are connected by a flexible

hinge region. Several researchers came to this conclusion (Figure 2.2) (Kessenbrock *et al.* 2010). The 23 different MMPs seen in humans may be roughly categorized into two groups: those that are membrane-anchored and those that are secreted. Based on their selectivity for extracellular matrix (ECM) components, secreted MMPs are further categorized as collagenases, gelatinases, stromelysins, matrilysins, and other groups. MMPs that are tethered to membranes include the type I transmembrane MMPs. Glycosylphosphatidylinositol-linked Type II transmembrane metalloproteinases (MMPs) comprise MT1-MMP, MT2-MMP, MT3-MMP, and MT5-MMP, as well as MMP4 and MMP6 (MMP-23).

Tumor formation depends on gelatinases, which serve several tumorigenic purposes. These include facilitating tumor cell proliferation, migration, invasion, and metastasis. MMP-2 and MMP-9 are activated, and the fibronectin type II in their catalytic domain is digested, during this procedure. Hemopexin-like domains, a pro-domain, and a cysteine-switch motif are absent in MMP-23 but are present in other matrix metalloproteinases. These enzymes include MMP-7, MMP-26, and MMP-23, to name a few examples. Despite a rising rate of Inflammation of the Kidneys (CKD) worldwide, the rate is falling in the United States (Fried and Palevsky 2016, Zhang *et al.* 2016). One typical outcome is renal fibrosis of many types of chronic kidney disease that worsen with time, is the final outcome of a protracted process characterized by increasing extracellular matrix and fibroblast proliferation (ECM) development. This complex process is also the root cause resulting from fibrosis of the renal tubules, sclerosis of the glomeruli, narrowing of the renal arteries, and continuous infiltration of inflammatory cells (Liu 2011). Hypoxia, oxidative stress, and prolonged cell division into the mesenchymal state are all thought to contribute to ECM buildup, which in turn leads to renal fibrosis. End-stage renal illness caused by renal fibrosis is irreversible and leads to dialysis or kidney transplant since there is currently no cure (Boor *et al.* 2010).

Inflammation of the lung parenchyma and peripheral airways is at the root of chronic obstructive pulmonary disease (COPD): a condition that causes chronic, progressive, and sometimes permanent airflow restriction. By degrading extracellular matrix (ECM)

components, MMPs such MMP-1, MMP-2, MMP-7, and MMP-12 contribute to the pathophysiology of COPD (Churg *et al.* 2012).

Recent research found that EVs produced from macrophages had proteolytic characteristics due to elevated expression of MT1-MMP, mediating smoking-induced damage to the extracellular matrix. Moreover, EVs produced from lung epithelial cells have been shown to be high in cysteine-rich protein 61, which has been shown to stimulate the synthesis of MMP-1 and IL-8 in the lungs of COPD patients (Moon *et al.* 2014).

2.10.2 Metalloproteinase-7 (MMP-7)

Extensive studies have shown that many MMPs are implicated in regulating kidney development and the pathogenesis of kidney diseases. Dysregulation of MMPs has been described in a wide variety of kidney disorders, including acute kidney injury: chronic kidney disease (CKD): diabetic kidney disease (DKD): glomerulonephritis, and inherited kidney diseases. Over the last two decades, due to the availability of MMP knockout models and specific pharmacological inhibitors, the role of MMPs, particularly MMP-2 and MMP-9, in regulating the development and progression of kidney diseases have been extensively investigated. (Tan *et al.* 2012, Catania *et al.* 2007). Fibrosis of the kidney is caused by matrix metalloproteinase-7 (Tan *et al.* 2014). Recent evidence indicates that matrix metalloproteinase-7 (MMP-7) is both a biomarker and a critical pathogenic mediator in the initiation and progression of kidney fibrotic lesions. As reported by many researchers (Zhou *et al.* 2017). Collagen 1 and fibronectin production and deposition in the renal parenchyma are greatly reduced in MMP-7-ablated rats subjected to unilateral ureteral obstruction. Their myofibroblast activation is reduced, and they are resistant to renal fibrotic lesions (Zhou *et al.* 2017).

In addition, MMP-7 triggers E-cadherin proteolysis, extracellular matrix (ECM) accumulation, and transforming growth factor -signaling, all of which contribute to renal fibrosis (Xiao *et al.* 2016). Effectively reducing kidney damage and fibrosis is pharmacological inhibition of MMP-7 expression. To help with the creation of efficient

treatments for CKD, thus intend to synthesize recent data about Involvement of matrix metalloproteinase-7 in the etiology and development of renal fibrosis is discussed here. Another name for MMP-7, the smallest MMP in the family, is matrilysin. Other names for it contain pump- punctated metalloproteinase and matrilysin-1 (Abramson *et al.* 1995). The absence of a hemopexin domain gives MMP-7 a distinct structure compared to other MMPs at its C terminus. The research was conducted by Gaire and colleagues (1994). In humans, MMP-7 expression is only seen in a very small number of tissues and at extremely low levels. Idiopathic pulmonary fibrosis and cancer are two diseases circumstances where it is, nonetheless, elevated (Ramankulov *et al.* 2008). According to growing evidence, MMP-7 may actively contribute to renal illness. To promote tubulointerstitial fibrosis and harm renal tubules, MMP-7 activates. Renal tubular epithelium does not express matrix metalloproteinase-7 in healthy humans (Surendran *et al.* 2004). Renal biopsy samples from individuals with hydronephrosis, X-linked Alport syndrome in dogs, and inherited polycystic kidney disease. Additionally, MMP-7 correlation with the growth and progression of renal cancer (Sarkissian *et al.* 2008). Histological abnormalities, diseases such tubular degeneration, and glomerulosclerosis, are more common in very aged kidneys, where MMP-7 and its family members are also significantly up-regulated (Melk *et al.* 2005). Numerous studies have looked at How MMP-7 cause's kidney fibrosis at the molecular and cellular levels.

A. Relationship of MMP7 with cancer

MMP7 is a protein enzyme that has been proven to be present at high levels in the presence of a malignant tumor. It has countless functions that contribute to the development of several types of cancers. At the same time, it is considered a new warning and diagnostic sign for several diseases that affect humans, including cancers. Also, reducing the level of MMP7 can reduce the proliferation of And the spread of cancer cells or perhaps preventing it and reducing resistance to treatments, so it may be a new hope for treating cancer (Sripa and Pairojkul 2008).

Many studies have addressed the relationship of MMPS with some types of cancer. MMP7 was considered an important indicator of cancer through its analysis of the lymph

nodes and intestines at one of the stages of the tumor of that organ. The results showed an increase in the level of MMP7 in the serum of patients with cancer in the third stage as well as the fourth stage. Its percentage also increases in cancerous tissues in the first and second stages of the disease. Accordingly, it has been shown that MMP7 increases when there is a tissue defect resulting from infection with one of the types of cancer, especially tissues affected by the tumor and lymph nodes (Gallogly and Lazarus 2016).

In another study, the percentage of MMP7 was raised in samples taken from bile duct cancer patients, where it was found to be higher in serum compared to patients with benign bile duct type.

Therefore, the serum level of MMP7 is considered a marker of the presence of a tumor in order to distinguish between bile duct cancer and obstruction in the bile duct (Sripa and Pairojkul 2008).

Elevated levels of MMP7 were also found in breast cancer cases compared to other non-tumor tissues (Gallogly and Lazarus 2016). It has also been observed in gastrointestinal cancer such as stomach, esophagus, and pancreatic cancer (Ferlay *et al.* 2018).

It was also noted that the level of MMP7 was increased in lung tissue affected by cancer compared to healthy lung tissue, which enhances cell proliferation resulting from cancer (Gallogly and Lazarus 2016).

It was also found that an increase in the level of MMP7 in the blood serum of patients with acute myeloid leukemia is related to the degree of the disease and the clinical stage, so its importance also lies in diagnosing the stages of the disease (Sripa and Pairojkul 2008). MMP7 also plays an important role in the development of cancer stages, such as bladder, breast, and ovarian cancer, tumors of the esophagus, pancreas, and gallbladder, and skin and prostate cancers. It participates in several cellular processes such as cell migration, proliferation, and death through complex mechanisms (Ferlay *et al.* 2018).

It should be noted that MMP7 has significant proteolytic activity against a group of ECM substrates such as fernectin, collagen, and elastin. It is also considered a regulator of protein degradation on the cell surface.

2.10.3 MMP10

Matrix metalloproteinase-10, also known as an endopeptidase, is an enzyme involved in tissue repair. That requires zinc for its activity that goes by the names stromelysin-2 and tansin-2. Like MMP-3 and MMP-11, it is a member of the MMP stromelysin subfamily. This has been shown to be the case (Wozniak *et al.* 2021). Proteolytic enzyme MMP-10 is secreted as a zymogen and activated by other proteinases in the extracellular environment (Saunders *et al.* 2005). The surprising discovery that active MMP-10 may be mostly nuclear but also nuclear-localized and cytoplasm suggests that this proteinase may have other biological functions (Garcia-Irigoyen *et al.* 2014). Proteolysis is controlled by a balancing act between matrix metalloproteinases (MMPs) and their particular tissue inhibitors (tissue inhibitor of metalloproteinases,.(extracellular matrix in the vascular system plays a critical role in the development of atherosclerosis and the instability of plaques (Rodriguez *et al.* 2008). Circulating MMP levels have been linked to subclinical atherosclerosis and increased cardio- vascular risk (Back *et al.* 2010). And the proteinase activities of MMPs have been linked to some of the biological processes associated with atherosclerosis and its ischemic clinical manifestations, such as myocardial infarction and stroke. At now, understanding of the functions of MMPs and in the development of atherosclerosis in CKD is limited. Particular focus has been placed on MMP-8 and MMP-10 (Yilmaz *et al.* 2006).

Which in turn is linked to worse cardiovascular outcomes. 14 Our lab's most recent research shows that human atherosclerosis is associated with increased MMP-10 production and release by endothelial cells in response to inflammatory and prothrombotic stimuli (Montenro *et al.* 2006). In growing or healthy adult tissues, such as the kidney, MMP-10 expression is rarely noticeable. However, following tissue damage, it is dramatically elevated (Zuo *et al.* 2021). Such pathological-induced elevation of MMP-10 suggests that this proteinase may be essential for the host's defense against

environmental stressors. MMP-10 dysregulation is considered to have an impact on the etiology of a number of illnesses, such as cancer, atherosclerosis, and cardiovascular disorders.

Matrix metalloproteinase-10 (MMP-10) is an enzyme that breaks down cellular matrix largely engaged in tissue remodeling via the breakdown of numerous extra elements of proteins and polysaccharides found in the ECM, including collagens (types III, IV, and V): elastin, and proteoglycans, proteins like fibronectin and gelatin, and proteoglycans (Bäck *et al.* 2010). But new research has concluded that MMP-10 has a regulates a number of metabolic mechansims by cleaving a number of bioactive molecules at the level of numerous cells' exteriors (Zuo *et al.* 2021). Depending on the situation, Potentially, MMP-10 has both positive and negative effects on renal pathophysiology. Mediated damage healing and, but it also plays a role in the pathophysiology of chronic renal disorders (CKD). Patients with CKD have the released protein MMP-10 in their blood, and renal function and its levels are negatively correlated.

2.10.4 MMP-10 Expression in the Kidney

MMP-10 is seldom expressed in kidneys, which contrasts with the fact that it weakly stained typical tubular cells of the human kidney (Miyata *et al.* 2007). It is significantly induced in pathological situations (Zuo *et al.* 2021, Toni *et al.* 2013). These results suggest that under physiologically normal settings, MMP-10 is not necessary for the construction and function of the murine kidney. However, transgenic mice exposed to excessive MMP-10 are vulnerable to more severe podocytopathy after injury (Zuo *et al.* 2021). Several cells, including the juxtaglomerular apparatus, glomerular podocytes, and the renal tubular epithelium, can produce MMP-10 in response to various stresses (Mora-Gutiérrez *et al.* 2020).

A. The relationship of MMP10 to cancer

The degradation of the extracellular matrix by MMPS is an important point for the development and spread of tumors. It is also considered a feature of malignant human tumors, as MMPS is secreted by cells such as fibroblasts, keratinocytes, and endothelial cells. Its presence has been found to be linked to several types of cancer, and the degradation of the extracellular matrix (ECM) is one of the steps. Early stages are critical for many cancers, as MMPS matrix proteins can adhere to ECM components. MMPS is also linked to the process of cell proliferation and angiogenesis in several types of cancer. MMP10 is an important member of the MMPS family, known as stromelain 2, and it analyzes several components of the ECM and stromal connective tissue, such as fibronectin, proteoglycans, collagen, and laminin (Avalia *et al.* 2013).

By examining the relationship between MMP10, clinical and pathological phenomena, and the size of the tumor, it was found that it is present in the cytoplasm of cancer cells when suffering from kidney cancer. Thus, it can be considered as a target for a potential treatment to stop the development of the tumor. At the same time, MMP10 can protect in the case of renal failure by increasing signals to EGFR, which leads to enhancing the presence of MMP10. Tubular cells as well as their proliferation after the period of injury, so it is considered in the case of renal failure to protect the kidney from injury by inhibiting the process of cell death of tubular cells and works to enhance cell proliferation through EGFR (Avalia *et al.* 2013). It was proven in a study that dealt with the role of MMP10 in the development of cancerous tumors and liver cancer that its percentage gradually increases in the case of liver cancer, and as the stages of tumor development progress, the percentage increases (Avalia *et al.* 2013).

The presence of MMP10 is positively linked to the presence of a cancerous tumor. It has been found in many malignant tumors, such as esophageal, lung, and prostate cancer. Its percentage was found to be high in the case of malignant tumors that affect the lymph nodes after examining oral mucosal tissues. It was also high in tumor tissues compared to other tissues. Adjacent normal when examining samples taken from lung cancer patients (Avalia *et al.* 2013).

It was also found, after examining samples from ovarian cancer patients, that the level of both MMP7 and MMP10 increased in ovarian cancer cells hours after treatment and remained at a high level until 12 hours after which it began to decrease after 24 hours Therefore, we can say that MMPs participate in the proliferation and strengthening of cancer cells. For the ovary, which reinforces the theory that the metalloproteinases (MMPS) participate in the balance of the extracellular matrix (ESM), which helps in the spread and invasion of cancer cells, so it plays a major role in the deterioration of the matrix. The levels of MMPS proteins can be used in detecting the recurrence of cancerous tumors, and it has also been proven that (MMP10 It changes the position and safety of blood vessels and thus regulates the process of formation of blood vessels (Ferlay *et al.* 2018).

From the above, we find that MMPS has a role in the formation of cancer cells. For this reason, there are efforts to manufacture compounds that inhibit MMPS to target this type of protein in cancer cells... Several types of industrial inhibitors of MMPS have been developed, including LLOMASTAT, BATIMASTAT, and MARIMASTAT, and it was striking when used. LLOMASTAT inhibitor was observed to inhibit the effects of stimulating cell migration in ovarian cancer. This fully applies to the role of MMPS for cancer cell migration and angiogenesis. It also supports the role of MMP10 in the invasion and spread of ovarian cancer. Therefore, any inhibition targeting MMP10 is a potential therapeutic target for ovarian cancer in the future (Avalia *et al.* 2013).

3. MATERIALS AND INSTRUMENTS

Tables 3.1 and 3.2 detail the materials and methods used in this investigation.

Table 3.1 The materials used in this study

Kits	Company	Origin
Human metalloprotiens 7 (MMP7) by ELISA	Sunlong	China
Human metalloprotiens 10 (MMP10) by ELISA	Sunlong	China

Table 3.2 The instruments used in this study

Instruments	Company	Origin
Elisa system	Mindray	China
Incubator	JRAD	Syria
Macro centrifuge	Electric	Korea
Micropipettes different size	Dragon	China
Refrigerator	Media	Turkey

3.1 Study Design

This case-control study included 90 participants divided into three groups: the first group included 22 healthy individuals, the second group included 22 patients suffering from chronic kidney disease associated with hepatitis C infection, and the third group included 46 patients suffering from chronic kidney disease. All patients during this study were admitted to the Medina Altib Hospital in Baghdad. Where verbal consent was obtained from the research participants through interview.

3.2 Inclusion Criteria

Patients who had clinical signs of CKD only or CKD and HCV were included, and these illnesses were identified by biochemical tests and professional medical care.

3.3 Exclusion Criteria

A. Exclusion criteria for CKD diseases

Subjects with illnesses that might induce alterations in renal metabolism were not included in the present investigation.

The participants were not using any medicines or hormones known to have an effect on the kidneys. This includes sex hormones, glucocorticoids, warfarin, vitamin K, raloxifene, thyroxin, and bisphosphonates.

3.4 Samples Collection

Using a macrocentrifuge, a sample of 5 ml of blood was obtained, allowed to stand for 20 to 30 minutes to encourage the development of clots, and then centrifuged for 5 to spin at 3000 rpm for 15 minutes. Then, the non-hemolysis serum was collected and placed in a cold storage freezer (- 20 Co). Two tubes of obtained serum were separated to conduct enzymatic assays, which comprise.

3.5 Determination of Human MMP7

A. Principle

This kit employs sandwich-ELISA technology. This package has pre-coated Microelisa stripplates, with an MMP-7-specific antibody.The relevant Microelisa stripplate wells are filled with standards or samples, which are then mixed with the selected antibody. Then,

each Microelisa stripplate well is loaded with an MMP-7-specific antibody that has been HRP-conjugated and incubated. Free pieces are removed from the wash. Into each well, the TMB substrate solution is injected. Only the wells containing MMP-7 and HRP-conjugated MMP-7 antibody will first show blue when the stop solution is applied. The optical density (OD) is determined2 spectrophotometrically at a wavelength of 450 nm. OD value and MMP-7 concentration correlation, can calculate the concentration of MMP-7 in the samples by comparing the OD of the samples to the standard curve.

Figure 3.1 Determination of Human MMP7

B. Dilution of Standards

Ten of the wells on a Microelisa stripplate are reserved as controls. Wells 1 and 2 need to have 50 ml of Standard Dilution buffer and 100 ml of Standard solution added to them and well mixed. Each well receives 100 ml of the combined solution from wells 1 and 2.

There is now a total of 50 ml of the Standard Dilution buffer that has been added and well mixed. Wells 3 and 4 are combined to yield Approximately 50 ml of the answer.

Wells 3 and 4's solution is divided evenly among the other wells, adding 50 ml to each one. Standard Dilution buffer, totaling 50 ml, has been added and is well mixed. Together, Wells 7 and 8 provide 50 ml of their respective solutions to Well 8. After that, 50 mL of Standard Dilution buffer is added, and everything is well blended. The solutions from Wells 7 and 8 are mixed with those from Wells 9 and 10 at a volume ratio of 50 ml per well.

Then solution standard dilution, a buffer solution, is added and thoroughly incorporated

We use the unfilled well on the Microelisa stripplate as a blank control. Forty milliliters of sample dilution buffer and ten milliliters of sample are added to each sample well (dilution factor is 5). The samples should be put on the well's bottom, far from the well's sides. Gently agitate for optimal mixing results.

1. Incubation step 2: after using a Closure membrane to seal the plate, incubate it for 30 minutes at 37°C.
2. Cleaning solutions should be diluted with sterile water to reduce concentration.
3. Remove the membrane from the closure plate and aspirate to clean the debris, and replacing it with the cleaning solution. Washing up liquid should be thrown away after 30 seconds. Repeat this (washing) step five times. To all wells, Put 50 ml of the HRP-Conjugate reagent into every well except the blank control well.
4. Incubation.
5. Washing.
6. Coloring: Incubate at 37 °C for 15 minutes after to each well, add 50 ml of Chromogen Solution B and 50 ml of Chromogen Solution A, and then shake gently to combine. then color in complete darkness.
7. Stop the reaction by pouring 50 ml of a stop solution into each well. The well's color scheme must change from blue to yellow.
8. Utilize a 450nm absorbance O.D. Microtiter Plate Reader to read the absorbance value. Zero is used for the OD well-placed controls in the blank. After adding the stop solution, the assay must be completed no later than 15 minutes.

3.6 Determination of Human MMP10

A. Principle

This kit use the sandwich-ELISA method of analysis. One pre-coated Microelisa stripplate is included in this package with an MMP-10-specific antibody.

The relevant Microelisa stripplate wells are filled with standards or samples, which are then mixed with the selected antibody. Then, each Microelisa stripplate well is loaded with an MMP-10-specific antibody that has been HRP-conjugated and incubated. Free pieces are removed from the wash. Into each well.

Only the wells containing MMP-10 and HRP-conjugated MMP-10 antibody will first show blue when the stop solution is applied. The optical density (OD) is determined spectrophotometrically at a wavelength of 450 nm. OD value and MMP-10 concentration correlation. can calculate the concentration of MMP-10 in the samples by comparing the OD of the samples to the standard curve.

The Other Procedure steps are the same way in (3.6.Determination of Human MMP7).

3.7 Statistical Analysis

The statistical analysis of this prospective research was conducted using the statistical package for social sciences (SPSS) version 20.0. The data is characterized by its mean and standard deviation, and an independent sample t-test is used to compare between two groups. The categorical data were characterized using the count and percentage. The chi-square test or Fisher exact test is used to assess the correlation between variables. The threshold for accepting a statistically significant difference is 0.05 or below.

4. RESULTS AND DISCUSSION

4.1 Socio-demographic of Patients and Control

4.1.1 Age distribution

Table 4.1 and Figure 4.1 show the age distribution of study groups. The high number of patients (21 (30.88%) and control (7 (31.82%) was associated with age groups (50–59 years): followed by 19 (27.94%) and 15 (22.06%) within age groups (40–49 years) and >60 years, respectively, according to patients, while 5 (22.73%) was associated with the same age groups according to control. Furthermore, the patient count was 8 (11.76%) and the control count was 3 (13.64%) within the age group (30–39 years). In contrast, the lower count of patients and controls was 5 (7.35%) and 2 (9.09%) within the age group (18–20 years): respectively. The age mean of patients was 43±12 year, while age mean of control was 39.98±11.2 year, and no significance difference was found among both groups (p value=0.744) according to age.

Table 4.1 Age distribution of study groups

Age group (year)	Patients		Control		P value
	Frequency	Percentage	Frequency	Percentage	
18-20	5	7.35%	2	9.09%	0.990^{NS}
30-39	8	11.76%	3	13.64%	
40-49	19	27.94%	5	22.73%	
50-59	21	30.88%	7	31.82%	
>60	15	22.06%	5	22.73%	
mean+-SD (Minimum-maximum)	43±12 (19-70)		39.98±11.2 (20-70)		0.744^{NS}

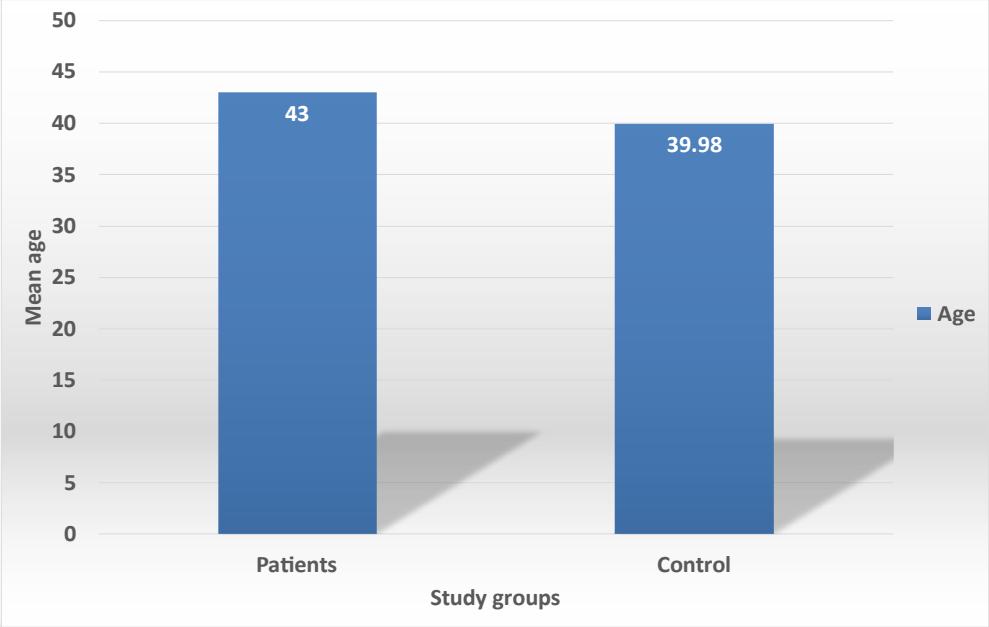

Figure 4.1 Age distribution of study groups

The findings of the current investigation suggest that the majority of the patients included in the study are elderly. This confirms that the prevalence of chronic renal disease rises in correlation with advancing age and vice versa. Concurring with our findings. A research conducted in Iraq revealed a greater prevalence of chronic kidney disease (CKD) among those aged 40 years and above (Alkhaqani 2021). According to a research done by REF, those aged 50 and above are the most prevalent age group affected by CKD (Hosny *et al.* 2017). Furthermore, Al-Nassar and AL-Bayati (2017) conducted a study on individuals suffering from end-stage renal illness who were having hemodialysis. Their findings revealed that the majority of these patients were above the age of 50 (Al-Nassar and AL-Bayati 2017). Moreover, a recent research revealed a significant prevalence of CKD in those aged 60 and above, in comparison to other age cohorts (Hirst *et al.* 2020). The incidence of CKD significantly rises with advancing age. This is because elderly people may have systemic and chronic illnesses, stress, and an accelerated rate of catabolism. Additionally, geriatric people have a decline in the glomerular filtration rate (GFR) as a result of age-related conditions, including atherosclerosis and hypertension. Furthermore, the aged experience an elevation in catabolism rates and a decline in metabolism rates, rendering them susceptible to several chronic illnesses and health issues (Fradelos 2020, Bayoumi and Wakeel 2015).

4.1.2 Gender distribution

According to gender distribution, Table 4.2 and Figure 4.2 demonstrated that the male frequency was higher among patient and control groups 41 (60.29) and 13 (59.09%): respectively, in comparison with female frequency 27 (39.71%) and 9 (40.91%): respectively. Additionally, no significance difference (p value=0.920) was found among study groups according to gender.

Table 4.2 Gender distribution among study groups

Gender	Patients		Control	
	Frequency	Percentage	Frequency	Percentage
Male	41	60.29%	13	59.09%
Female	27	39.71%	9	40.91%
P value	0.920^{NS}			

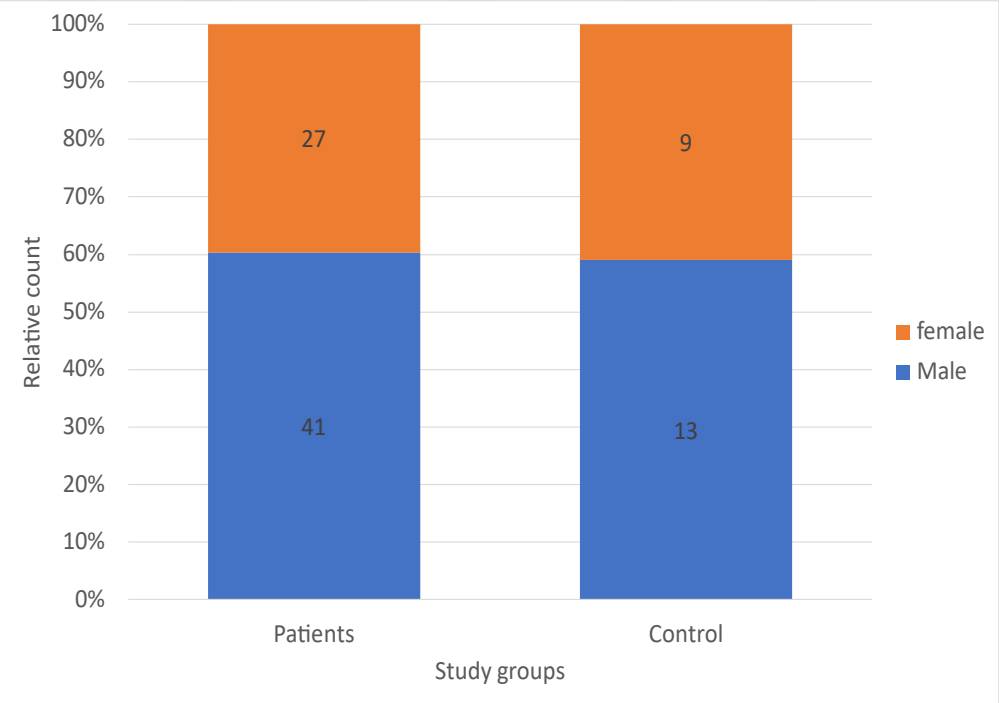

Figure 4.2 Gender distribution among study groups

The current research also examines gender, and the results reveal that males are the prevailing gender. Consistent with the current research, a prior investigation conducted in Iraq similarly observed a greater prevalence of CKD in males compared to girls (Alkhaqani 2021). Several studies consistently shown that the majority of patients with CKD are male (Al-Abedi *et al.* 2020). Furthermore, the research of gender disparities in many aspects of health and illness has been extensively studied and is presently getting increased focus in the field of nursing. Sex hormone activity, occupational stress characteristics, stress manifestation, and distribution of chronic diseases are all variables that contribute to the increased vulnerability of men to CKD in comparison to females. Furthermore, variations in lifestyle choices, such as tobacco use and alcohol use, might potentially elucidate this disparity across genders (Baqer *et al.* 2018).

4.1.3 Habitation distribution

The more study participants during the current study were from rural areas 46 (67.65%) of patients and 16 (72.73%) of control than those who come from urban areas, 22 (32.35%) of patients, and 6 (27.27%) of control. In addition, there was no significant difference among study groups (p value = 0.656) according to habitation distribution, as explained in Table 4.3 and Figure 4.3.

Table 4.3 Habitation distribution of study groups

District	Patients		Control	
	Frequency	Percentage	Frequency	Percentage
Urban	22	32.35%	6	27.27%
Rural	46	67.65%	16	72.73%
P value	0.656^{NS}			

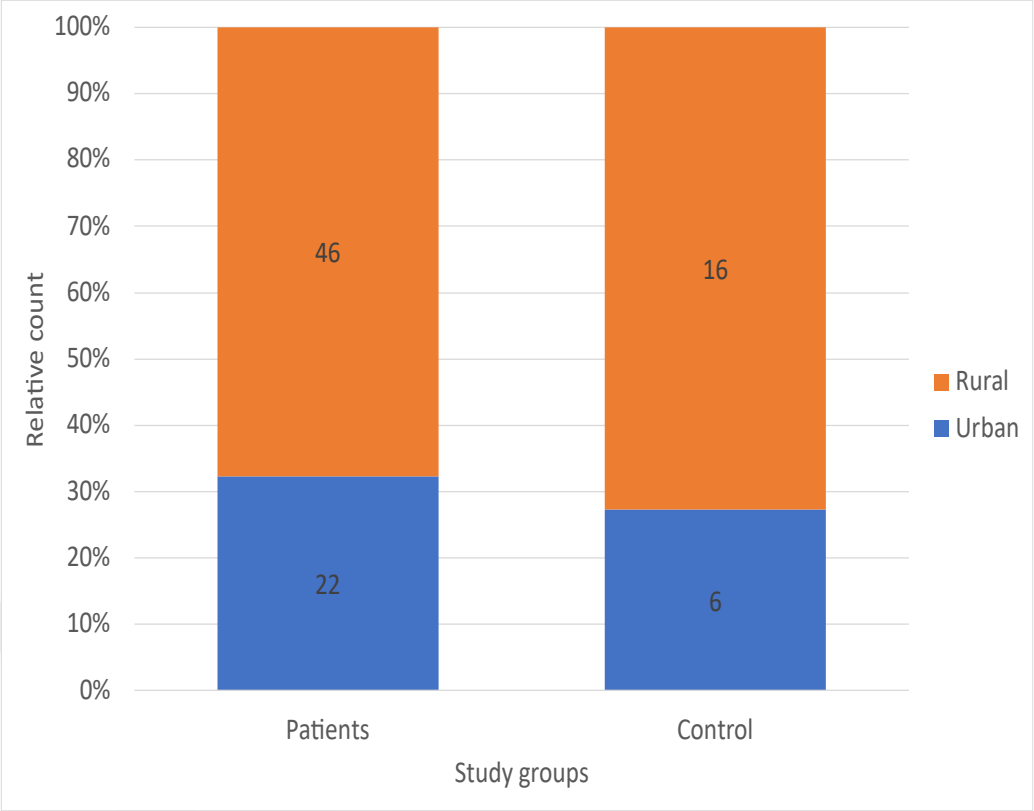

Figure 4.3 Habitation distribution of study groups

The current study found that the majority of patients were from rural areas rather than urban areas. In agreement with the current study, another Iraqi study found a high prevalence of CKD in rural areas comparable to urban areas (Kamil *et al.* 2021). Additionally, a previous study conducted in Iraq also aligned with the current study and showed that more patients suffering from CKD were from rural areas than urban areas (Alkhaqani 2021). These reasons can be attributed to the lack of health culture in the countryside, the misuse of medications that are given without prescriptions, and drinking unsterilized water in the correct way, in addition to the unhealthy lifestyle in rural areas.

4.1.4 Education level

Table 4.4 Education levels of study groups

Education level	Patients		Control	
	Frequency	Percentage	Frequency	Percentage
Doesn't read and write	13	19.12%	2	9.09%
Read and write	18	26.47%	5	22.73%
Primary school graduate	15	22.06%	8	36.36%
Intermittent school graduate	9	13.24%	4	18.18%
Secondary school graduate	7	10.29%	3	13.64%
High education	6	8.82%	0	0.00%
P value	0.439^{NS}			

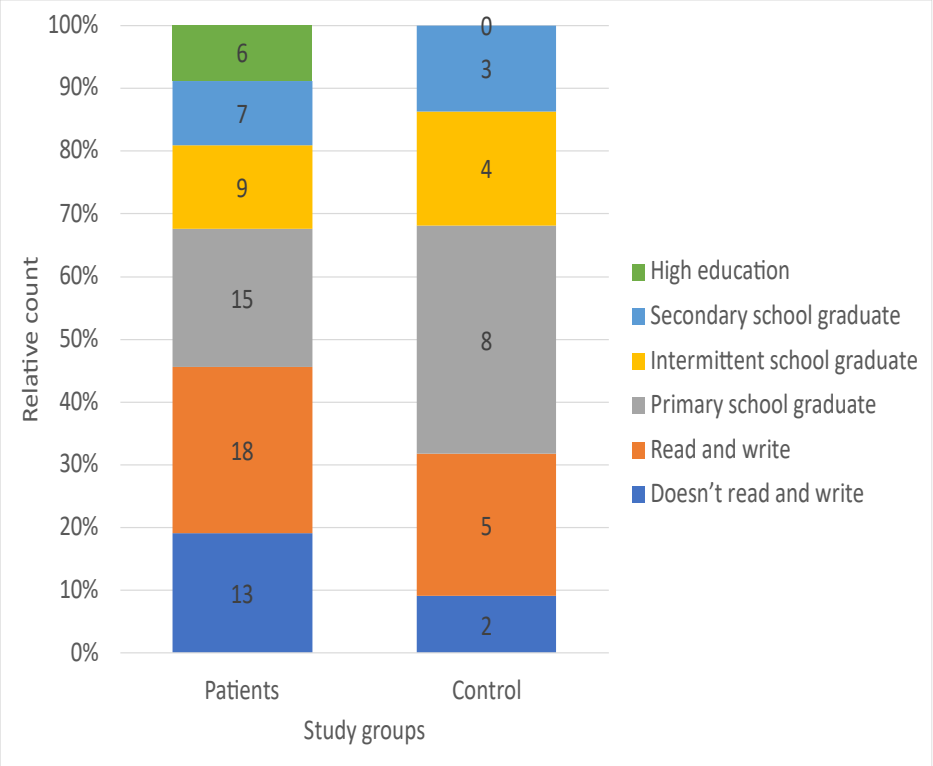

Figure 4.4 Education levels of study groups

Regarding the educational level, in accordance with recent research, it was discovered that the majority of the participants in the study had the ability to read and write (Alkhaqani 2012). Several Iraqi studies have conducted estimations on the prevalence of CKD among patients in various cities. The findings indicate that a significant proportion of the patients have literacy skills (Goh and Griva 2018). This may be attributed to the advanced age of the majority of the research participants, as well as their unfavorable living, social, and cultural circumstances, which hindered their ability to enroll in school or successfully finish their education. Furthermore, this outcome might be attributed to the persistent economic and political turmoil, as well as ongoing conflicts, that our nation has endured from the early 1980s up till the present.

4.1.5 Occupational status of study groups

Table 4.5 Occupational status of patients and control groups

Occupational status	Patients		Control	
	Frequency	Percentage	Frequency	Percentage
Retired	12	17.65%	3	13.64%
Housewife	14	20.59%	6	27.27%
Jobless	29	42.65%	10	45.45%
Disable	13	19.12%	3	13.64%
P value	0.848^{NS}			

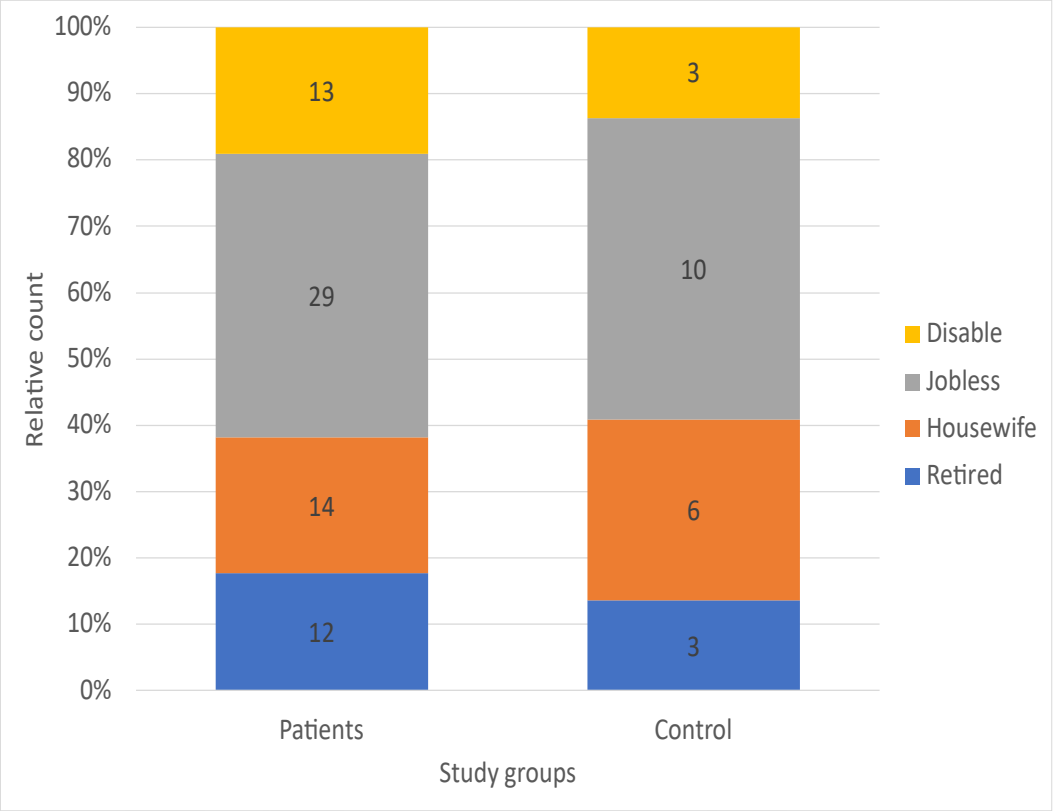

Figure 4.5 Occupational status of patients and control groups

With respect to occupation, the present investigation revealed that the majority of patients were unemployed. Consistent with our findings, a research done by (Alkhaqani 2021) revealed that over 35% of patients were unemployed. The findings are consistent with previous research conducted in Iraq, indicating that the majority of participants in the survey experienced job loss (Anees 2014). This outcome may be attributed to the fact that a majority of the research participants are elderly, rendering them unable to engage in job activities in comparison to younger patients. Perhaps due to the impact of the illness and its treatment on the patient's lifestyle and daily routine. Nevertheless, a prior investigation has shown that individuals with CKD are compelled to either choose a lower-paying occupation or face unemployment, leading to diminished earnings and a decreased standard of living (Goh and Griva 2018).

4.2 Clinical Characteristics of Patients

4.2.1 Disease duration

Table 4.6 Duration of disease among patients

Duration of CKD	Patients	
	Frequency	Percentage
<1 year	7	10.29%
2-3 year	23	33.82%
4-5 year	27	39.71%
>6 year	11	16.18%

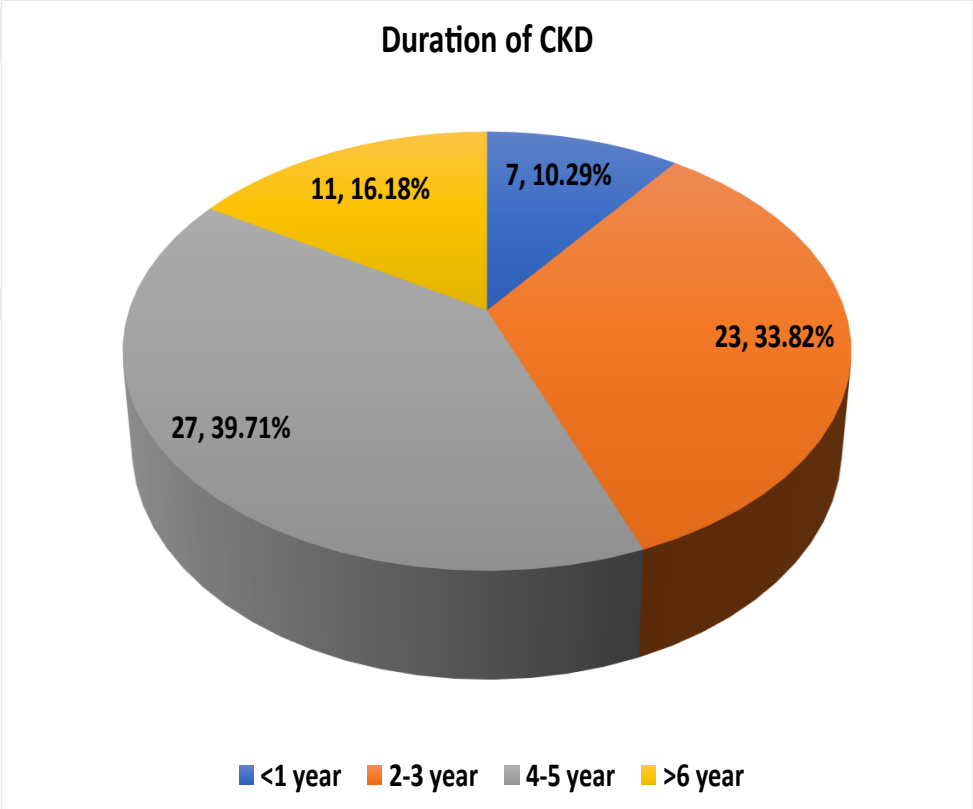

Figure 4.6 Duration of disease among patients

Based on the length of illness, the findings of the present research indicate that the majority of the patients had suffered from CKD for a period of two to three years. This finding is consistent with the prior research performed by (Barbosa 2017) in Iraq, where

they reported that the majority of participants had been diagnosed with CKD for a duration of three years or less. Similarly, a prior research conducted in Iraq revealed that a significant proportion of patients had been afflicted with CKD for a duration of around 2-3 years (Alkhaqani 2021). There is a belief that individuals have experienced detrimental social habits and financial hardships in the last two years, which might perhaps be linked to a rise in instances during this period. Furthermore, the research findings indicate that the majority of the participants in the study were diagnosed with renal failure for a duration of two years or longer. Furthermore, a 2017 research revealed that the majority of patients received a diagnosis of CKD within a timeframe of 2 to 3 years (Al-Nassar 2017).

4.2.2 Family history of patients

The patients with family history of chronic kidney disease 39 (57.35%) were higher than patients without family history 29 (42.65%) as demonstrated in Table 4.7 and Figure 4.7.

Table 4.7 Family history among patients' group

Family history	Patients	
	Frequency	Percentage
NO	29	42.65%
YES	39	57.35%

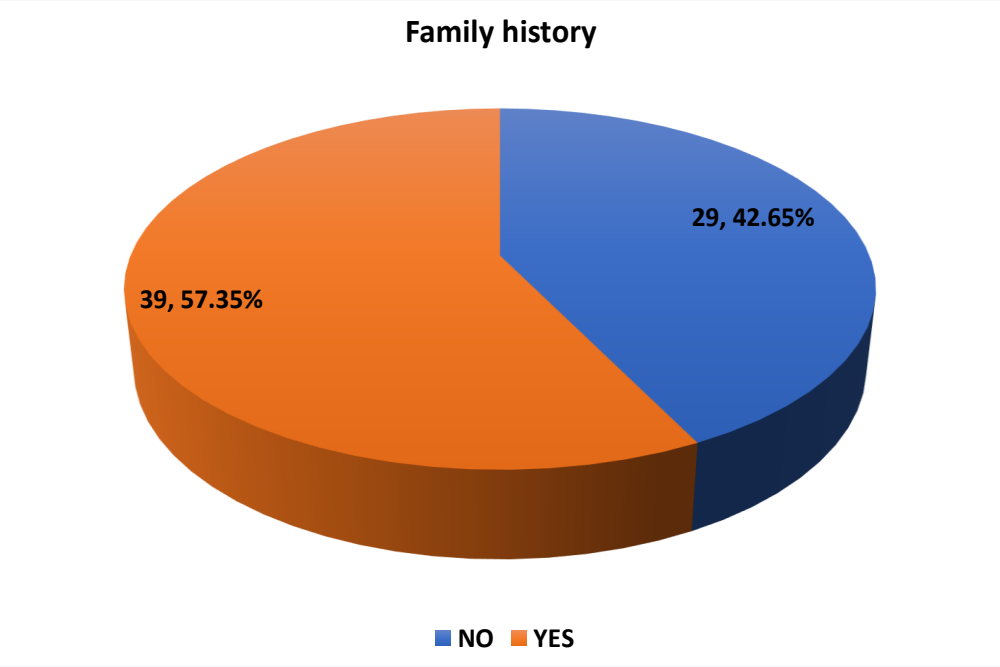

Figure 4.7 Family history among patients' group

The present investigation revealed that a significant proportion of individuals with CKD had a strong familial predisposition to CKD. Consistent with these results, a prior research conducted in Iraq also examined the familial history of CKD in patients and determined that this factor significantly contributes to the development of CKD within the same family (Alkhaqani 2021). The observed outcome may be ascribed to the prevalence of genetic factors in the transmission of various illnesses from parents to offspring, which is often regarded as the primary cause for the development of different diseases in the future, along with other contributing environmental variables.

4.2.3 Diabetes mellitus

The patients with diabetes 47 (69.12%) was higher in comparison with patients without diabetes 21 (30.88%): as shown in Table 4.8 and Figure 4.8.

Table 4.8 Diabetes mellitus among patients' group

Diabetes	Patients	
	Frequency	Percentage
No	21	30.88%
Yes	47	69.12%

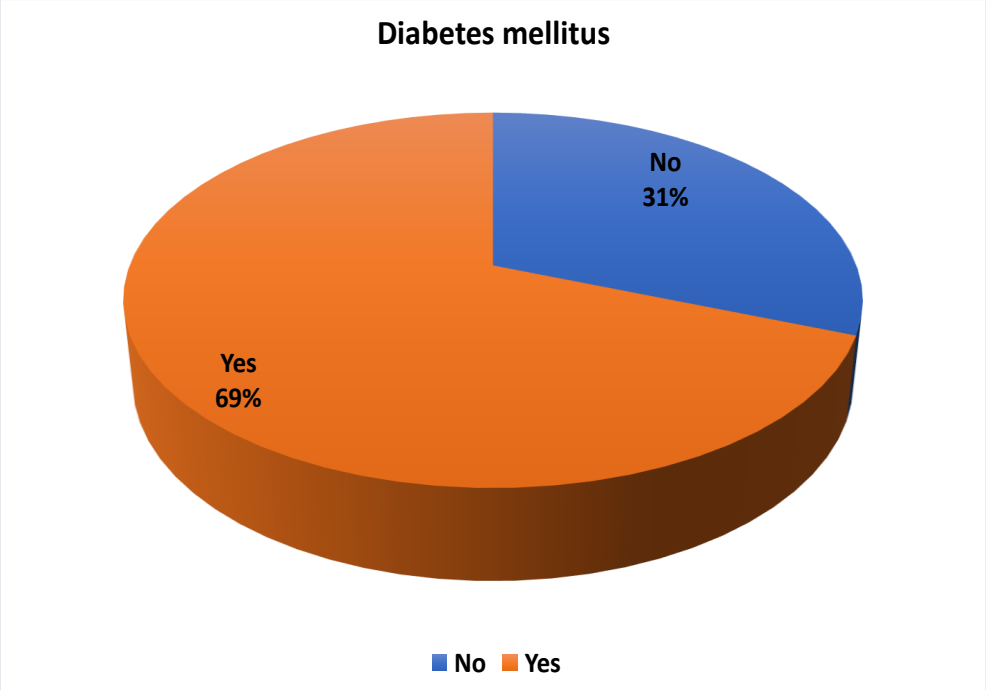

Figure 4.8 Diabetes mellitus among patients' group

The research results suggest that the majority of the patients suffer from diabetes mellitus. This discovery aligns with the results of a prior research conducted in Iraq, which revealed that a significant number of individuals with CKD were linked to diabetes (Alkhaqani 2021). According to a meta-analysis research completed in 2020, diabetes was identified as the primary cause of renal disorders (Shiferaw *et al.* 2020). Moreover, the research also revealed that diabetes mellitus is widely recognized as the primary factor contributing to CKD on a global scale (Copur *et al.* 2020). Diabetes leads to the impairment of the renal microvasculature, resulting in kidney damage and elevated blood pressure (Li *et al.* 2020, Kazancioğlu 2013).

4.3 Matrix Metalloproteinase-10 (MMP-10) Serum Levels

Table 4.9 and Figure 4.9 show that the mean MMP-10 serum level was higher (1632.6±221.7 pg/ml) in the CKD group compared to patients with CKD and HCV (1352.03±119.8 pg/ml) and the healthy control group (574±89.4 pg/ml). In addition, there was a high significance difference among patient groups against control (p value <0.001).

Table 4.9 MMP-10 serum levels among study groups

MMP10 (pg/ml)	CKD group	HCV and CKD group	Control
Mean±SD	1632.6±221.7	1352.03±119.8	574±89.4
P value	<0.001**	<0.001**	
	0.089^{NS}		

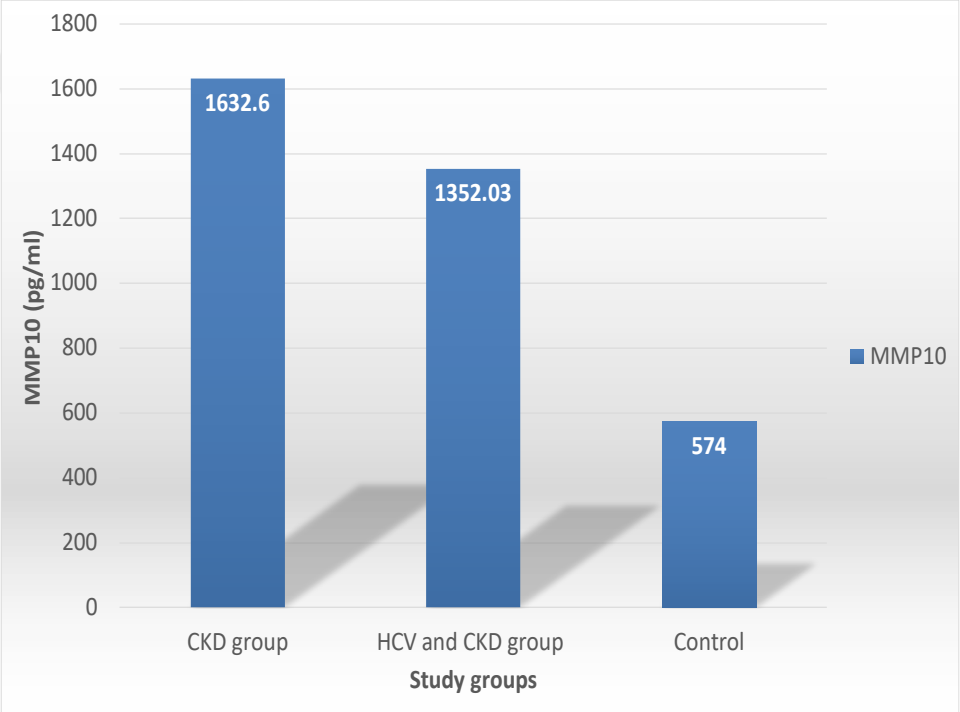

Figure 4.9 MMP-10 serum levels among study groups

Among the several MMPs, MMP10 plays a key role in the regulation of embryogenesis, normal tissue remodeling, wound healing, and angiogenesis. Inflammation, tissue ulceration, malignancy, bone turnover, nephritis, and fibrosis are only few of the illnesses and disorders associated with MMP10. MMP10 was formerly assumed to have a role in the development, maintenance, and resolution of renal, a vital component of blood vessels and the basement membrane (Agewall 2006, Brown *et al.* 1995, Ronco *et al.* 2007). There is evidence that MMP10 expression in the kidney is complex and species-specific, a complete description has yet to be written (Catania *et al.* 2007). Those who suffer from chronic kidney disease (CKD) tend to have higher levels of MMP-10 (stromelysin 2) (Velikova *et al.* 2018). However, the functions of MMPs in nephrogenesis, renal damage, and renal remodeling during CKD are poorly understood since so few research have focused on these processes in the kidney (Nagase and Barrett 1999).

Coll *et al.* (2010) also shown a relationship between the comorbidity of atherosclerosis and MMP-10 levels in individuals with CKD at various stages,it is widely acknowledged that individuals with CKD, especially in the early stages, are more likely to die than the average person due to underlying cardiovascular disease (Lo *et al.* 2009). Contradictory features are present in MMP-10. However, also, it may have a role in the development of atherosclerosis by encouraging the spread of vascular smooth muscle cells into the intima of the artery wall, which in turn leads to the formation of plaque (Ravn and Falk 1999).

However, MMP-10 also contributes to a reduction in plaque size by causing the intima's extracellular matrix to degrade. Ardans *et al.* (2001) this explains why atherosclerotic plaques have less fibrous material. Some investigations have revealed that extremely severe vascular disease, which poses a high risk in people with CKD and is significant for both clinical and public health reasons, is frequently caused by chronic illnesses like CKD (Zoccali and Seck 2010). Additionally, people with CKD are 10–20 times more likely to develop atherosclerosis, particularly those with end-stage renal disease Zoccali and Seck (2010). This is consistent with research showing that CKD patients receiving chroniodialysis have the highest levels of MMP-10. Additionally, Coll *et al.* (2010) demonstrated a correlation between blood levels of MMP-10 and the degree of Heart disease in CKD patients (Coll *et al.* 2010).

Even though the involvement of MMPs in atherosclerosis and proteinuria in the evolution of renal disease are still poorly understood, this theory might clarify the association between MMPs and proteinuria under certain pathological conditions. To begin with, MMPs are assumed may have a role in glomerular basal membrane lysis, subsequently, they may aid in extracellular matrix lysis, this lysis is linked to scarring and fibrosis (Dimas *et al.* 2013). Other investigations have demonstrated that various inflammatory and prothrombotic stimuli may cause human endothelial cells to produce and secrete MMP-10 (Orbe *et al.* 2007). MMPs have been thought of by Zoccali et al. as indicators of angiogenesis prior to the development of proteinuria and of the progression of CKD at advanced stages (Zoccali and Seck 2010)

We point out that increasing the level of MMP10 in patients with chronic kidney disease can be considered a protective factor for the kidneys, as it may enhance the repair of the internal tissues of the kidneys as an attempt to maintain their functions as a result of the deterioration that occurs when they are injured.

4.4 Matrix Metalloproteinase-7 (MMP-7) Serum Levels

Table 4.10 and Figure 4.10 show that the mean MMP-7 serum level was higher (1311±124.9 pg/ml) in the CKD group compared to patients with CKD and HCV (1187±88.5 pg/ml) and the healthy control group (634.7±103.3 pg/ml). In addition, there was a high significance difference among patient groups against control (p value =<0.001).

Table 4.10 MMP-7 serum levels among study groups

MMP7 (pg/ml)	CKD group	HCV and CKD group	Control
Mean±SD	1311±124.9	1187±88.5	634.7±103.3
P value	<0.001**	<0.001**	
	0.233^{NS}		

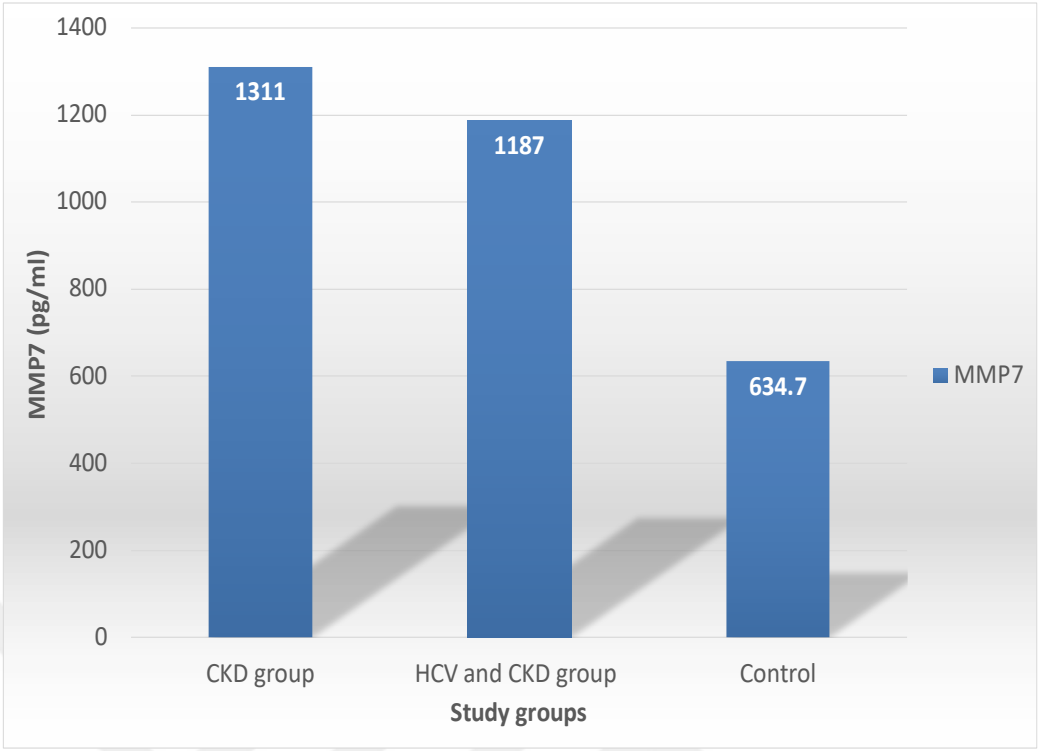

Figure 4.10 MMP-7 serum levels among study groups

The diagnosis of renal problems typically occurs later, and the start of treatment measures is typically postponed. Therefore, there is a pressing need to create new biomarkers for renal illnesses that may be used for prognostication and early identification (Rysz *et al.* 2017). The MMP-7 protein is thought to be secreted into the urine since it is identified in the tubular lumen and epithelial tubules at their tip (Zhou et al. 2017). In certain renal diseases, MMP-7 expression is increased. As a result, the MMP-7 level has the potential in order to act as a biomarker for renal illness that does not need invasive procedures.

Matrix metalloproteinase 7 concentrations (MMP-7) have also been shown to have a positive correlation with renal fibrosis scores and a negative correlation with renal function (He *et al.* 2012). Therefore, MMP-7 levels have the potential to function as a noninvasive biomarker for renal fibrosis, a predictor of CKD outcomes, and a means of tracking the dynamic evolution of fibrosis. It has been shown that persons with human idiopathic pulmonary fibrosis had elevated MMP-7 levels in their peripheral blood, which is in agreement with the results in the kidneys. These measurements might be used as a biomarker to foretell the severity of the disease and the likelihood of death (Nakatsuka *et*

al. 2019). Numerous studies have found that individuals with various kidney diseases have significantly higher urine MMP-7 levels, and that these levels may even be connected linked with the worsening of renal fibrosis (Zhou *et al.* 2019). Since then, MMP-7 has gained prominence as an important indicator of preliminary kidney injury (Liu and Liu 2020). There is a lot of MMP-7 in the urine of CKD patients, in their renal tubular epithelium, and in kidney biopsy samples (He *et al.* 2012). The actual pathogenic mechanism behind MMP-7's function in the production of renal fibrogenesis, however, has to be investigated. The proteolytic degradation of E-cadherin, which is necessary for maintaining the integrity of the tubular epithelium, caused by MMP-7 has been described in a number of studies as causing EMT in sick kidneys (Ke *et al.* 2017). Research has also demonstrated that MMP-7 enhances renal inflammation, which also causes fibrosis, by activating MMP-2 and MMP-9 and by encouraging the production of TNF-alpha (Cheng *et al.* 2017).

This data suggests that MMP-7 has a crucial function in the development of CKD and is elevated in this illness. This elevation of MMP-7 levels in hypertensive patients makes CKD highly likely to develop. As a result, even at an early stage, CKD can develop in any patient with hypertension. Accordingly, the morbidity related to CKD can be reduced by pharmacologically inhibiting MMP-7, according to the study's findings.

Thus, the high level of MMP7 can be considered a type of protection and immune response to kidney cells as a result of the deterioration occurring in the tissues, as it has a role in tissue repair.

5. CONCLUSIONS AND RECOMMENDATION

Conclusions

1- The majority of patients were of advanced age, this indicated that CKD may be considered a disease of age, and its severity is progressing more with age.
2- The frequency of males was higher than females, which indicated that the differences in lifestyle among both genders may play an important role in developing this disease.
3- The majority of patients had a family history of CKD and had diabetes mellitus. These findings indicated that genetic factors and diabetes were considered the most common causes of renal diseases, especially CKD.
4- MMP-7 and MMP-10 levels were higher in patients than in healthy people, and that could be considered a novel marker to predict the severity and tissue damage in patients with CKD.

Recommendations

1- Further studies are needed to evaluate the relationships between elevated levels of MMP-7 and MMP-10 and histopathological changes among patients with CKD.
2- Study the precise relationship between the presence of hepatitis or other viral infection and the progression of the pathogenicity of CKD and the worsening of kidney functions.
3- Investigation of single nucleotide gene polymorphisms as genetic markers and their relationship with developing CKD.
4- Estimated other immunological and biomarkers as non-invasive methods and compared with invasive methods in diagnosis and prediction of CKD.

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CURRICULUM VITAE

Personal Information

Name and Surname : Qabas Fadhil alwan ALANBARY

Education

MSc Çankırı Karatekin University
Graduate School of Natural and Applied Sciences 2020-2023
Department of Biology