

**Urinary B2- Microglobulin in hepatitis c
patients: Effect of interferon and ribavirin**

Thesis

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**تأثير فيروس سي والعلاج بالإنترفيرون والريبافيرين علي
نسبة بيتا-2- ميكروجلوبولين في البول**

دراسة

للحصول علي درجة الماجستير في الباطنة العامة

بواسطة

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INTRODUCTION

Hepatitis c is an infectious disease primarily affecting the liver, caused by the hepatitis c virus. The infection is often without any symptoms, but chronic infection can lead to scarring of the liver and ultimately to cirrhosis, which is generally apparent after many years. In some cases, those with cirrhosis will go on to develop liver failure or other complication, including liver cancer or gastric varices and esophageal varices. The hepatitis c virus is spread by blood-to-blood contact. Most people have few, if any, symptoms after the initial infection, yet the virus persists in the liver in about 85% of those infected (*Ryan KJ, Ray CG; 2004*).

An estimated 180 million people worldwide are infected with hepatitis c (*Houghton M; 2009*), and more than 350,000 people die from hepatitis c related diseases each year. Countries with particularly high rates of infection include Egypt (22%), Pakistan (4.8%) and China (3.2%) (*WHO Hepatitis c: 2011*).

Persistent infection can be treated with medication; interferon and ribavirin are the current standard therapy. Overall, between 51-80% of treated patients are cured. Those who develop

cirrhosis or liver cancer may require a liver transplant, and the virus universally recurs after transplantation. The treatment may be physically demanding, particularly for those with a prior history of drug or alcohol abuse. A substantial proportion of people will experience panoply of side effects ranging from a flu-like syndrome to severe adverse events including anemia, cardiovascular events and psychiatric problems. Responses can vary by genotype. Approximately 80% of hepatitis c patients in the United States have genotype 1, and genotype 4 is more common in the Middle East and Africa (**Poordad, F .et al; 2011**).

Hepatitis c virus infection is associated with signs and symptoms in organs besides the liver, such as porphyria cutanea tarda, sicca syndrome (an autoimmune disorder), thrombocytopenia, lichen planus, diabetes mellitus and B-cell lymphoproliferative disorders (**Zignego AL, et al;2007**). HCV infection is associated with severe renal diseases including mixed essential cryoglobulinemia, membranoproliferative glomerulonephritis and less frequently, membranous nephropathy and crescentic glomerulonephritis (**Perico N, et al; 2009**). Hepatitis c virus infection is a significant cause of glomerulopathy in countries with a high prevalence of HCV infection (**Lo KY, et al; 2009**).

B2-Microglobulin one of tubular proteins in the kidney and considered as early marker of tubular injury. B2M normally is filtered out of the blood by the kidney's glomeruli, only to be partially reabsorbed back into the blood when it reaches the kidney's tubules. In glomerular kidney disease, the glomeruli can't filter it out of the blood, so level increase in the blood and decrease in the urine. In tubular kidney disease, the tubules can't reabsorb it back into the blood, so urine level rise and blood level fall. Increased urinary level is found in people with tubular damage caused by exposure to heavy metals as cadmium and mercury. B2M level also rise during infection with some viruses, including cytomegalovirus and HIV; (*Lehman, et al; 2008*).

Aim of the study

The aim of the study is to evaluate the relation between hepatitis c virus infection and urinary beta 2- microglobulin as a sign of tubular damage and aim to detect the effect of treatment by interferon and ribavirin on urinary beta -2- microglobulin.

Chapter (1) Hepatitis C virus infection

INTRODUCTION:

HCV is one of several viruses that cause hepatitis. Up to 85% of individuals who are initially (acutely) infected with HCV will fail to eliminate the virus and will become chronically infected. HCV is spread most commonly through inadvertent exposure to infected blood. Blood transfusion is the most common mode of transmission. The risk of acquiring HCV through sexual contact is low. Generally, patients do not develop symptoms of chronic infection with HCV until they have extensive scarring of the liver (cirrhosis). Some individuals however, may have fatigue and other non-specific symptoms in the absence of cirrhosis. A minority of patients with HCV have symptoms from organs outside of the liver. Infection with HCV is the most common cause of chronic hepatitis and the most common reason for liver transplantation (*Suresha Rajaguru; 2009*).

Hepatitis C infection is an infection of the liver caused by the hepatitis C virus (HCV). It is difficult for the human

immune system to eliminate HCV from the body, and infection with HCV usually becomes chronic. Over decades, chronic infection with HCV damages the liver and can cause liver failure. An estimated 180 million people worldwide are infected with hepatitis c and more than 350,000 people die from hepatitis c related diseases each year. Countries with particularly high rates of infection include Egypt (22%), Pakistan (4.8%) and China (3.2%). **(Houghton M; 2009)**

When the virus first enters the body, however, there usually are no symptoms, so these numbers are estimates. Up to 85% of newly-infected people fail to eliminate the virus and become chronically infected. Infection is most commonly detected among people who are 40 to 60 years of age. HCV infection is the leading cause of liver transplantation and is a risk factor for liver cancer. **(WHO, Hepatitis c: 2011).**

The nature (biology) of the hepatitis C virus:

'Hepatitis' means inflammation of the liver. HCV is one of several viruses that can cause hepatitis. It is unrelated to the other common hepatitis viruses (for example, hepatitis A or hepatitis B). HCV is a member of the Flaviviridae family of viruses. Other members of this family of viruses include those that cause yellow fever and dengue.

Viruses belonging to this family all have ribonucleic acid (RNA) as their genetic material. All hepatitis C viruses are made up of an outer coat and contain enzymes and proteins that allow the virus to reproduce within the cells of the body, in particular, the cells of the liver. Although this basic structure is common to all hepatitis C viruses, there are at least six distinctly different strains of the virus which have different genetic profiles (genotypes). Approximately 80% of hepatitis c patients in the United States have genotype 1, and genotype 4 is more common in the Middle East and Africa (**Poordad, F .et al; 2011**). Genotyping is important to guide treatment because some viral genotypes respond

better to therapy than others. The genetic diversity of HCV is one reason that it has been difficult to develop an effective vaccine since the vaccine must protect against all genotypes.

How does liver damage occur in hepatitis C infection?

The presence of HCV in the liver triggers the human immune system, which leads to inflammation. Over time (usually decades), prolonged inflammation may cause scarring. Extensive scarring in the liver is called cirrhosis. When the liver becomes cirrhotic, it fails to perform its normal functions, (liver failure), and this leads to serious complications and even death. Cirrhotic livers also are more prone to become cancerous. (*Jaw w.; 2011*).

Spread of hepatitis C virus. ;

HCV is spread (transmitted) most efficiently through exposure to infected blood.

- The most common route of transmission is needles shared among users of illicit drugs.

- Accidental needle-sticks in health care workers also have transmitted the virus. The average risk of getting HCV infection from a stick with a contaminated needle is 1.8% (range 0% to 10%)
- Prior to 1992, some people acquired the HCV infection from transfusions of blood or blood products. Since 1992, all blood products have been screened for HCV.
- HCV infection also can be passed from mother to unborn child. Approximately 4 of every 100 infants born to HCV-infected mothers become infected with the virus.
- A small number of cases are transmitted through sexual intercourse. The risk of transmission of HCV from an infected individual to a non-infected spouse or sexual partner without the use of condoms over a lifetime has been estimated to be between 1% and 4%.
- Finally, there have been some outbreaks of HCV when instruments or exposed to blood have been re-used without appropriate cleaning between patients (***Mary D Nettleman 2010***).

Transmission of HCV can be prevented in several ways;

- Prevention programs have been aimed at avoiding needle sharing among drug addicts.
- Among healthcare workers, safe needle-usage techniques have been developed to reduce accidental needle-sticks. Newer syringes have self-capping needle systems that avoid the need to manually replace a cap after drawing blood and reduce the risk of needle-sticks.
- There is no clear way to prevent transmission of the HCV from mother to child.
- If one partner is infected, monogamous couples should consider the low risk of transmission of HCV infection when deciding whether to use condoms during intercourse. Some couples may decide to use them and some may not.
- Screening tests for blood products have almost eliminated the risk of transmission of HCV infection through transfusion, estimated by the CDC to be less than one in two million transfused blood products.

- People with HCV infection should not share razors or toothbrushes with others.
- It is critical that physicians and clinics follow manufacturer's directions for sterilizing/cleaning instruments and disposable instruments be discarded properly.

It is important to realize that HCV is not spread by casual contact. Thus, shaking hands, kissing, and hugging are not behaviors that increase the risk of transmission (**Suresha Rajaguru, et al; 2010**).

Symptoms of HCV infection;

About 75% of people have no symptoms when they first acquire HCV infection. The remaining 25% may complain of fatigue, loss of appetite, muscle aches or fever. Yellowing of the skin or eyes (jaundice) is rare at this early stage of infection.

Over time, people with chronic infection may begin to experience the effects of the persistent inflammation of the

liver caused by the immune reaction to the virus. Blood tests may show elevated levels of liver enzymes, a sign of liver damage, which is often the first suggestion that the infection may be present. Patients may become easily fatigued or complain of nonspecific symptoms (*Shiffman ML, Sulkowski et al; 2004*).

As cirrhosis develops, symptoms increase and may include:

- Weakness and loss of appetite.
- Weight loss, breast enlargement in men and a rash on the palms.
- difficulty with the clotting of blood, and
- Spider-like blood vessels on the skin.

Increased pressure in the blood vessels of the liver (portal hypertension) may cause fluid to build up in the abdominal cavity (ascites) and result in engorged veins in the swallowing tube (esophageal varices) that tear easily and can bleed suddenly and massively. Portal hypertension also can cause kidney failure or an enlarged spleen resulting in a

decrease of blood cells and the development of (anemia), or the development of low platelets (thrombocytopenia), which can promote bleeding. In advanced cirrhosis, liver failure causes decreased production of clotting factors. Patients with advanced cirrhosis often develop jaundice because the damaged liver is unable to eliminate a yellow compound, called bilirubin that is formed from the hemoglobin of old red blood cells. (*Jay W. Marks, 2011*).

Most of the signs and symptoms of HCV infection relate to the liver. Less commonly, HCV infection causes conditions outside of the liver.

- HCV infection can cause the body to produce unusual antibodies called 'cryoglobulins'. These cryoglobulins cause inflammation of the arteries (vasculitis) which may damage the skin, joints, and kidneys. Patients with cryoglobulinemia (cryoglobulins in the blood) may have joint pain, arthritis, a raised purple rash on the legs, generalized pain or swelling. In addition, these patients may develop Raynaud's phenomenon in which the fingers and toes turn color (white, then