The Value of Cystatin-c Serum Level as a Marker of Renal Dysfunction in Patients with Liver Cirrhosis

Thesis

Submitted for Partial Fulfillment of Master Degree

in ***Internal Medicine***

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2007

Abstract

This study is carried out to evaluate the advantage of serum cystatine C as a marker of renal dysfunction over the routine renal function tests in cirrhotic patients and whether it has a correlation with degree of liver affection while using Pugh's modification of child's classification as a marker of degree of liver affection.

The result of this study showed and confirmed that in patients with cirrhosis, particularly in patients with Child-Pugh class C, cystatin C determination is a valuable tool for the diagnosis of moderately impaired renal function.

Key Words:

Anti Diuretic Hormone – Blood Urea Nitrogen

Acknowledgements

First and foremost, my deep gratefulness and indebtedness is to ***Allah.***

I am honored to express my deep gratitude to ***Prof. Dr. Emad El Moetasem Bellah Amin,*** *Professor of Internal Medicinen , Faculty of Medicine. Cairo University, for his sincere guidance and support, he sat the plan of this work and offered brillinat ideas from the start to the end .*

I wish to express my great thanks to ***Dr. Mohammed Hamdy Fathy El Akad,*** *Assistant Professor Of Internal Medicine, Faculty of Medicine, Cairo University, for his encouragement and valuable suggestion .*

I wish to express my great thanks to ***Dr. Shahira Morsy El Shafie,*** *Assistant Professor of Clinical Pathology, Faculty of Medicine, Cairo University, for her laboratory work and her encouragement and valuable suggestion.*

I would like to express my thanks and best hopes for all patients included in this study.

I also thank every person who helped me during this work.

Waleed Mohammed Abd El Haleem

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List of Abbreviations

ADH…….anti diuretic hormone.

ANP…….atrial natruretic peptide.

AUC…….area under curve.

AVP…… argenine vasopressin.

BUN…….blood urea nitrogen.

Ccr…….creatinine clearance.

CNS…….central nervous system.

COX. …….cyclo oxygenase enzyme.

CSF…….. cerebrospinal fluid.

FENA……fractional excretion of sodium.

GFR……..glomerular filteration rate.

HCCAA….hereditary cystatin-c amyloid angiopathy.

HRS……..hepatorenal syndrome.

MW……molecular weight.

NADP….. nicotinamide adenine dinucleotide phosphate.

NO……..nitric oxide.

NSAID…. Non-steroidal anti-inflammatory drugs.

P.value…….. probability value.

PGS……... prostaglandins.

RAAS….. renin angiotensine aldosterone system.

ROC…….receiver operator characteristic curve.

SD……..standard deviation.

SNS……sympathetic nervous system.

-PV……..negative predictive value.

+PV…… positive predictive value.

Introduction

The evaluation of renal function in patients with decompensated cirrhosis is important for prognosis, dosage assessment of potentially nephrotoxic drugs and recognition of changes in glomerular filtration rate (GFR) to decide paracentesis and diuretic therapy ***(Bernardi et al., 1994).***

Cirrhosis of the liver is often accompanied by functional renal failure, which means that they are not accompanied by morphological changes and in the early stages can be reversed by medical intervention ***(Moller and Henriksen ,1999)***. The extreme stage of this renal failure , the hepatorenal syndrome , is rarely reversible, and liver transplantation is the only established therapy ***(Gerbes et al. ,1998).***

Patients with functional renal failure of cirrhosis are particularly sensitive to decreases in plasma volume. Therefore, monitoring renal function is pivotal. On diagnosis of deterioration in renal function, appropriate measures such as volume expansion can be taken to avoid further impairment and development of hepatorenal syndrome ***(Bernardi et al., 1994).***

Various endogenous substances are being investigated as potential reliable markers of renal function. Creatinine clearance is regarded as the "gold standard" for evaluating glomerular filtration rate (GFR), but technical difficulties preclude its routine use in clinical practice ***(Papadakis and Arieff , 1999)***.

Serum creatinine concentrations should be interpreted with caution as a filtration marker in liver cirrhosis because they do not adequately reflect renal dysfunction ***(Whelton et al. , 2000).*** Increased tubular secretion and muscle wasting account for the disparity between creatinine concentrations and GFR in cirrhotic patients. Thus, GFR has been demonstrated repeatedly to be overestimated by serum creatinine ***(Randers and Erlandsen ,2000).***

Cystatin C values in serum have been proposed as a marker for GFR ***(Price and Finney , 2001)***. cystatin C, a low-molecular-weight protein produced at a constant rate by all nucleated cells, is freely filtered across the glomerular membrane and is neither secreted nor reabsorbed along the nephron. Because cystatin C is almost completely catabolized in the proximal tubule, its renal clearance cannot be measured, but its concentration in serum or plasma reflects the GFR. Several studies have reported that the reciprocal of cystatin C correlates better with GFR than does the reciprocal of creatinine. An advantage of cystatin C over creatinine is that the concentration of the former in serum is independent of sex, muscle mass, and age, so that the same reference interval applies to the whole population ***(Randers and Erlandsen , 2000).***

Aim of the Study

This study aim to evaluate the advantage of using cystatin C serum level as a marker of renal function in cirrhotic patients over the routine renal function tests while using creatinine clearance as the gold standard of renal function testing and whether it has a correlation with degree of liver affection while using Pugh's modification of Child's classification as a marker of degree of liver affection.

Renal Dysfunction in Liver Cirrhosis

Cirrhosis of the liver is often accompanied by functional renal failure, which means that they are not accompanied by morphological changes and in the early stages can be reversed by medical intervention ***(Arroyo et al., 1999).***

A unique feature of cirrhosis is that renal dysfunction occurs in the absence of significant abnormalities in kidney structures. The normalization of kidney function after liver transplantation confirms the functional origin of these disturbances of kidney function. The mechanisms leading to renal dysfunction in cirrhosis are not completely understood. Several factors including several extra renal and intra renal vasoactive and sodium- and water-retaining systems, abnormalities in systemic and splanchnic hemodynamics, and the diseased liver causing portal hypertension and hepatic failure, probably play a contributory role ***(Moller and Henriksen, 1999).***

Patients with cirrhosis and portal hypertension develop circulatory dysfunction characterized by disturbances in systemic and renal hemodynamics; it has been shown that the severity of circulatory dysfunction correlates with the severity of cirrhosis ***(Arroyo and Jimenez, 2000).***

In compensated cirrhosis (i.e., cirrhosis without ascites),

the systemic hemodynamics is normal in the upright position, but become hyperdynamic in the supine position - that is, cardiac output increases and systemic vascular resistance decreases. This is thought to be due to volume expansion secondary to subtle sodium retention in the upright position. The renal circulation is frequently vasodilated with glomerular hyperfiltration ***(Wong et al., 1995).***

With disease progression, circulatory dysfunction worsens, manifested as vasodilatation and relative intravascular under filling. There is increased activity of the sympathetic nervous and renin-angiotensin systems in order to maintain hemodynamic stability. Peripheral edema and ascites can occur as a result of worsening sodium retention despite an increase in natriuretic substances ***(Grossman, 1994).***

Despite activation of various vasoconstrictor systems, renal perfusion and glomerular filtration rate **(GFR)** in the early stages of ascites may be normal or only moderately decreased as a result of increased renal production of prostaglandin E2 ***(Pozzi et al., 2001).***

Nitric oxide and **prostacyclin** have also been shown to counteract vasoconstrictors to maintain renal perfusion. At this stage of disease, hypersecretion of antidiuretic hormone **(ADH**) results in decreased free water excretion. Concurrently, increased **prostaglandin E_2** synthesis by the collecting tubules antagonizes **ADH** and preserves renal excretion of free water;

therefore, hyponatremia is not common in early ascites ***(Salo et al., 1995).***

Hepatorenal syndrome is the end of spectrum of functional renal abnormalities in cirrhosis and is due to a severe vasoconstriction of the renal circulation. Patients with marked sodium and water retention are at high risk of developing hepatorenal syndrome ***(Gines Ginès and schrier , 1997).***

Mechanisms Responsible for Renal Functional Abnormalities:

Several intrarenal and extra renal systems have been proposed as potential mediators of functional renal abnormalities in cirrhosis. A concise review of these systems is provided below:

(1) Extra renal Systems:

Most cirrhotic patients with ascites show an over activity of the two major vasoconstrictor and antinatriuretic systems, the renin-angiotensin-aldosterone system **(RAAS),** and the sympathetic nervous system **(SNS)** ***(Gines Ginès and schrier, 1997).***

A large body of evidence indicates that the activation of these systems plays a major role in the increased tubular reabsorption of sodium in cirrhosis ***(Salo Sal' et al., 1995).***

However, other antinatriuretic mechanisms may also

participate because a small proportion of cirrhotic patients with ascites have sodium retention in the setting of normal activity of **RAAS** and **SNS** ***(Claria Clària et al., 1991).***

The activation of these two systems is particularly intense in patients with **HRS**, which suggests that they participate in the pathogenesis of vasoconstriction of the renal circulation. Another important vasoconstrictor factor that is frequently increased in cirrhosis with ascites is anti-diuretic hormone **(ADH)**. Increased plasma levels of this hormone enhance water reabsorption in the collecting ducts and contribute to water retention and dilutional hyponatremia ***(Arroyo et al., 1996).***

The pharmacological interruption or blockade of the effectors of these three major vasoconstrictor systems **(angiotensin II, norepinephrine, and AVP)** in human or experimental cirrhosis results in marked reduction of total systemic vascular resistance and arterial hypotension, which suggests that these systems are activated as a homeostatic response to maintain arterial pressure within normal limits ***(Claria Clària et al. , 1991).***

The circulating levels of endothelin, an endothelial-derived peptide with potent vasoconstrictor effect, are also increased in cirrhosis ***(Asbert et al. , 1993).***

These increased levels are probably due to an enhanced release of the peptide from the hepatic and/or splanchnic circulation ***(Moller et al. , 1995).***