

The effect of co-infection with hepatitis B and hepatitis C viruses on the prevalence of proteinuria and loss of renal function: a single-center experience

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Introduction and aim of the work

Patients infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) are at increased risk of renal disease. This study compares factors associated with proteinuria and doubling of serum creatinine level in patients who were infected with HCV or HBV alone with those who were coinfecting with HCV and HBV.

Materials and methods

The study was performed on 1243 patients who were diagnosed with HBV and/or HCV at the Cairo University Hospitals. All the included subjects underwent urine analysis for proteinuria and serum creatinine level. Clinical characteristics were recorded at baseline and at last follow-up.

Results

Of 1243 patients, 293 (23.6%) patients had proteinuria. Subset analysis of the patients with proteinuria showed that 10.6% were HBV infected, 63.8% were HCV infected, and the remaining 25.6% were coinfecting with both HBV and HCV. Overall, coinfection with both viruses ($P=0.01$), lower serum albumin ($P=0.001$), hypertension ($P=0.01$), and diabetes ($P=0.001$) were associated with an increase in risk of proteinuria. Coinfection ($P=0.001$), presence of HBV ($P=0.001$), and increasing HCV RNA level in patients with HCV and in coinfecting patients ($P=0.05$) was associated with doubling of serum creatinine level.

Conclusion

The patients coinfecting with HBV and HCV are at greater risk of clinically significant proteinuria and loss of renal function owing to complex virological profile. Progressive loss of renal function in that population is associated with markers of viral activity such as proteinuria and increasing HCV RNA levels among HCV-infected patients.

Keywords:

co-infection, creatinine, hepatitis, proteinuria

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Introduction

In Egypt, ~15% of the population is infected with hepatitis C virus (HCV) and 8% is infected with hepatitis B virus (HBV). Both viruses represent a major endemic medical health problem in our country [1,2]. They are not only associated with end-stage liver disease and hepatocellular carcinoma, the most frequent causes of death in patient with liver disease, but also with various extrahepatic manifestations [3–7]. In addition to symptomatic disease, clinically silent glomerular disease has been described in these patients in the form of elevated serum creatinine, microscopic hematuria, and/or proteinuria [8,9]. Proteinuria has been shown to be an early diagnostic marker of kidney damage and can predict the progression of renal disease. Protein overload can upregulate complement cascade and various proinflammatory, vasoactive, and fibrogenic genes in proximal tubular cells leading to apoptosis

of proximal tubules [10–20]. Many studies, such as the ALLHAT [21], INSIGHT [22,23], and LIFE [24], have shown that increasing proteinuria and deterioration of renal function are associated with poorer outcomes from vascular disease, higher incidence of cardiovascular events, and fatal and nonfatal stroke in both diabetic and nondiabetic patients. Microalbuminuria is also associated with a failure of nocturnal dipping in blood pressure, insulin resistance, and abnormal vascular responses to various stimuli [25–27]. Therefore, reducing proteinuria is a well-known renoprotective approach in nephrology. Proteinuria is a modifiable risk factor and can be managed by treating its cause. In this line of

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concept, the Kidney Disease Improving Global Outcomes clinical practice guidelines recommend screening for kidney disease at the time of HCV diagnosis [28,29]. Complex virological profiles may be present in infected patients, and dually infected patients are an extremely heterogeneous population [30]. This study assesses factors associated with proteinuria and doubling of serum creatinine level among patients infected with HBV or HCV alone or coinfecting with both viruses.

Materials and methods

This is a prospective study conducted at the Cairo University Hospitals, Egypt, over 2 years. Ethical and Research Committee of the National Research Centre approved the study protocol. A total of 1243 patients who were diagnosed with viral hepatitis (HCV or HBV alone or coinfecting with both) were enrolled. All patients had agreed to take part in the study and signed a declaration of informed consent form.

Clinical characteristics were recorded at baseline and at last follow-up. Co-morbid conditions such as diabetes mellitus and hypertension were recorded. Type 2 diabetes was diagnosed using the criteria proposed by the American Diabetes Association. Fasting and 2-h postprandial glucose levels in venous blood were measured with an autoanalyzer (Automated Beckman analyzer Au 680; Beckman Coulter Diagnostics Company, USA). Hypertension was defined as mean systolic blood pressure greater than or equal to 140 mmHg, mean diastolic blood pressure greater than or equal to 90 mmHg, a diagnosis of hypertension, or current use of antihypertensive medications. Serum creatinine (mg/dl) and albumin (g/dl) were measured by creatinine kinetic Jaffe uncompensated method and albumin BCP method, respectively, by using serum sample with an autoanalyzer (Automated Beckman analyzer Au 680). A serum albumin level less than 3.5 g/dl was considered 'low'.

Urine analyses were done in all subjects using reagent-strip tests (AlbustixTM; McGuff Company (McGuff), USA). Patients were considered proteinuric if the reading was equal to or greater than 1. Patients were included in the analyses if they had at least two creatinine measures obtained at a minimum of 3 months apart. Patients were included if they had urine analysis for proteinuria at entry and on last seen visit. The serum samples were analyzed for hepatitis B surface antigen (HBsAg) and anti-HCV antibody using commercially available fourth generation ELISA kits (Dialab, Wiener Neudorf,

Austria). The specificity of the kit is 99.87% and sensitivity is 100%. The test is very simple and cost-effective. HCV-infected patients who were positive for HCV antibody were further confirmed for the presence of HCV RNA by PCR as per the routine methodology used in our hospital.

Statistical analyses

Continuous data are expressed as means \pm SD. Characteristics for patients were compared using either χ^2 -test or Student's *t*-test. Multivariate binary logistic regression assessed the association between clinical variables, the presence of proteinuria, and doubling of serum creatinine level. For non-normal data, a Mann-Whitney *U*-test was performed. *P* less than 0.05 was considered statistically significant. All statistics were carried out using SPSS, version 16 (SPSS; SPSS Inc., Chicago, Illinois, USA).

Results

Proteinuria in the study population

Of the 1243 patients, 79% were males, with a mean age of 39.2 \pm 8.4 years. A total of 293 (23.6%) patients had proteinuria at both initial and follow-up urine analyses studies. The remaining patients (950) with positive virology but without proteinuria were considered the control group. Their age and sex were comparable to patients with positive virology and proteinuria. The prevalence of proteinuria was the highest among patients infected with HCV alone (63.8%), followed by coinfection (25.6%) and HBV alone (10.6%) (Table 1).

Factors associated with proteinuria

Results of multivariate logistic regression analyses on independent factors associated with proteinuria in patients with viral hepatitis are shown in Table 2. In proteinuric patients, coinfection with both viruses further increased the risk of proteinuria when compared with mono infection. The odds of having proteinuria in coinfecting state was 1.20 when compared with HBV alone (*P*=0.08, not statistically significant) and 1.50 when compared with HCV alone (*P*=0.01, statistically significant). Low serum albumin level had a significant overall effect on proteinuria with

Table 1 Proteinuria in patients with viral hepatitis

Patients	N (%)
Total patients screened	1243 (–)
Total patients with proteinuria	293 (23.6)
Patients with proteinuria and HBV alone	31 (10.6)
Patients with proteinuria and HCV alone	187 (63.8)
Patients with proteinuria and both HCV and HBV	75 (25.6)

HBV, hepatitis B virus; HCV, hepatitis C virus.

Table 2 Factors associated with increasing proteinuria in the 293 patients

Association	OR	Confidence interval	P value
Coinfection versus HBV alone	1.20	1–1.4	0.08
Coinfection versus HCV alone	1.50	1.3–1.7	0.01
Low serum albumin	1.96	1.6–2.2	0.001
Low serum albumin and HBV alone	1.6		0.01
Low serum albumin and HCV alone	2.4		0.001
Low serum albumin and coinfection	1.9		0.001
Presence of hypertension	1.50	1.2–1.7	0.01
hypertension and HBV alone	1.4		0.01
hypertension and HCV alone	1.6		0.01
Hypertension and coinfection	1.5		0.01
Presence of diabetes	3.2		0.001
DM and HBV alone	2.8		0.01
DM and HCV alone	3.6	2.9–3.6	0.001
DM and coinfection	3.4		0.001

DM, diabetes mellitus; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio. Bold values means its statistically significant, $P < 0.05$.

an odd ratio (OR) of 1.96. When serum albumin level was compared against the type of infection, neither HBV alone nor coinfection influenced the OR significantly from the overall OR (1.6 and 1.9, respectively); however, such comparison showed an OR of 2.4 for HCV alone. Hypertension had an overall OR of 1.5, but the type of infection did not alter the OR significantly. Diabetes was the most significant factor associated with proteinuria (OR=3.2), and again, the type of infection did not alter the OR significantly from the overall OR.

Factors associated with doubling of serum creatinine level

HBV infection, with or without HCV coinfection, was associated with serum doubling ($P < 0.001$; Table 3). Hypertension in HCV-infected patients with or without HCV coinfection was associated with an increased risk of doubling of creatinine level (OR=2.70); it was not found to be statistically significant. Increasing HCV RNA also had significant association with serum creatinine doubling in HCV-infected patients and in coinfecting patients ($P=0.05$) (Table 3).

Discussion

Proteinuria and renal diseases are often associated with diabetes mellitus and hypertension, but when we talk about endemic countries of hepatitis, we must also consider HCV and HBV as causative factors of proteinuria and kidney functions deterioration [31]. Approximately one-fourth of our cases in this study

Table 3 Factors associated with doubling of serum creatinine level in patients with proteinuria

Association	OR	Confidence interval	P value
All HBV-infected patients (with or without HCV)	12.5	12.2–12.7	0.001
HBV alone	11.5		0.001
HBV/HCV coinfection	13.5		0.001
Hypertension in HCV-infected patients (with or without coinfection)	2.7	2.1–2.9	0.06
Hypertensive HBV-infected patients (without HCV)	1	0.9–1.2	0.3
Increasing HCV RNA in HCV-infected patients (with or without coinfection)	1.0002	0.9–1.1	0.05

HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio. Bold values means its statistically significant, $P < 0.05$.

(23.6%), infected with either HCV or HBV alone or with both viruses, had proteinuria. This result was expected as it has been known that chronic HCV had a well-recognized association with renal and extrahepatic manifestations [3]. In addition, HBV infection is also associated with renal disease, and treatment of HBV improves renal outcome [32]. Proteinuria is thought to be caused by either the deposition of immune complexes or the presence of the virus itself. In our study, the prevalence of proteinuria was higher in patients infected with HCV. The prevalence of nephropathy in HBV infection is reported to be 3–20%, and in HCV infection, it is ~38% [33]. A study from an endemic area of southern Taiwan demonstrated a significant association between proteinuria and HCV (10.2%) but not HBV infections [34].

In our study, 25.6% of our patients (293 patients) had coinfection and proteinuria. Coinfection is not uncommon in endemic countries because of the shared modes of transmission, and the prevalence of dual infection varies from country to country. In Egypt, the dual infection prevalence is reported to be 0.7% whereas in India, it is 16%. In Turkey, it is 2.6%, and data from Spain, Italy, Japan, Taiwan, and Iran, have demonstrated that ~10–15% of patients with chronic HBV infection are also infected with HCV, and ~2–10% of anti-HCV-positive patients are also HBsAg positive [35–40]. These patients with dual infection have a higher risk of progression of their renal disease and increasing proteinuria owing to various patterns of viral replication and great variations of immune profiles.

Our study showed that, in patients with viral hepatitis, diabetes mellitus is the most significant factor associated with proteinuria followed by low serum albumin and hypertension. Coinfection is associated

with 1.5 times the risk of proteinuria compared with HCV mono infection and 1.2 times the risk of proteinuria compared with HBV mono infection. This comes in agreement with different studies analyzing factors associated with proteinuria [34–41].

In our cases, patients infected with HBV with concurrent infection with HCV (coinfection) or even without HCV were associated with an increased risk of proteinuria and doubling of creatinine levels. Proteinuria in HBV can be mediated by immune reactions, for example, glomerular deposition of immune complexes, or virus-induced specific immunological effector mechanisms (specific T-lymphocyte or antibody), or indirect effects from virus-induced cytokines/mediators on renal tissue.

HBV antigens are also expressed in renal tubular epithelial cells [42]. They can upregulate complement-mediated inflammatory pathways and contribute to the pathogenesis of nephropathy. Finally, HBV infection has been shown to induce apoptotic damage to the renal tubular cells [42–44].

The work by Chen *et al.* [45] on 17 758 patients with chronic HBV infection and randomly selected 71 032 matched controls without HBV to assess the risk of ESRD found significant associations of end stage renal disease (ESRD) with HBV in men of any age and women younger than 60 years and concluded that HBV-infected patients should have targeted monitoring for the development of ESRD.

However, our results are in partial agreement with the study by Lee *et al.* [46] that found HCV infection, but not HBV infection, was associated significantly with prevalence and CKD stage, and are in agreement with another study that found HCV was associated with 40% greater risk of renal insufficiency among persons who had a positive HCV antibody test as compared with those who had a negative one [47].

Increasing HCV RNA level in HCV-infected patients and in coinfecting patients was associated with an increasing risk of doubling of creatinine level. This can be explained by renal parenchymal expression of CD81 and SR-B1 receptors that allow the binding of HCV to the cell surface and endocytosis of HCV RNA and related proteins found in mesangial cells, tubular epithelial cells, and endothelial cells of glomerular and tubular capillaries causing direct mesangial injury. In addition, toll-like receptors may have a role in recognizing molecular patterns associated with microbial pathogens like HCV RNA and induce an immune response [48].

Another explanation is kidney injury owing to systemic immune response that is mediated by cryoglobulins [49].

Finally, the non-immunological aspects of HCV-related kidney injury cannot be ruled out because HCV-positive patients often have insulin resistance and hyperinsulinemia, and a higher prevalence of diabetes, which itself causes proteinuria. The HCV core protein directly reduces expression of insulin receptor substrate proteins 1 and 2 and increases the expression of tumor necrosis factor- α in hepatic cells, which upregulate the expression of angiotensin II type 1 receptors in mesangial cells, thus enhancing the deleterious effects of angiotensin II in the kidney [44].

Hypertension in HCV-infected patients was associated with risk of doubling of serum creatinine level. This can be explained by the use of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, which are commonly used in arterial hypertension treatment and can cause elevation of serum creatinine level above the patient's baseline level. Angiotensin II constricts both the afferent and efferent arterioles, but it preferentially increases efferent arteriole resistance. This lowers intraglomerular pressure and reduces the glomerular filtration rate [50].

Conclusion

Patients coinfecting with HBV and HCV are at a greater risk for clinically significant proteinuria and loss of renal function. Progressive loss of renal function is associated with markers of viral activity such as proteinuria among HBV-infected patients and increasing HCV RNA levels among HCV-infected patients. Thus, a careful evaluation of the HBV and HCV viremia levels is mandatory for a correct diagnosis and proper therapeutic approach.

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Conflicts of interest

There are no conflicts of interest.

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