Scintigraphic Evaluation of Renal Function in Patients with Hepatitis B Virus Infection

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SUMMARY

Aim: Chronic hepatitis B virus (HBV) infection can induce nephropathy and major HBV antigens (HBcAg, HBeAg, HBsAg) and immune complexes responsible for its pathogenesis. The purpose of our study was to assess the renal function of patients with HBV infection by means of technetium diethylenetriamine pentaacetic acid (Tc99m DTPA) scintigraphy, in order to detect any early renal dysfunction, which might be related to nephropathy associated with HBV infection.

Methods: Nineteen patients (10 male and 9 female with a mean age of 37.11±11.34 years, age range 25−62 years) with the diagnosis of HBV infections, and 16 healthy controls (8 male and 8 female with a mean age of 33.50±11.56 years, age range 24-55 years) were enrolled into the study. All subjects had no history of renal disease and treatment of HBV infection including interferon-alfa, pegylated interferon-alfa, lamivudine and adefovir. Blood urea nitrogen (BUN), urea and creatinine were analyzed. The renal perfusion, concentration and excretion were evaluated by Tc99m DTPA scintigraphy. The time to peak (TTP), peak activity (counts/second) (PA), clearance half time ($T_{1/2}$) and percent contribution of each kidney to total function (differential function) were calculated. The glomerular filtration rate (GFR) was determined simultaneously by 3 methods; gamma camera uptake method (Gates, GFR), predicted creatinine clearance method (Cockcroft-Gault, CG-GFR), and Modification of Diet in Renal Disease (MDRD). The variables were compared between groups.

Results: The mean values of patients' parameters were as follows; right TTP:5.73±3.14 min, left TTP:5.52±2.09 min, right PA:884.78±214.85 cts/sec, left PA:889.52±252.68 cts/sec and right $T_{1/2}$:17.84±6.89 min, left $T_{1/2}$:14.51±8.59 min. Differential functions were 50.27±3.39% on the right side and 49.72±3.39% on the left side. In study group, Gates GFR value was 125.63±25.84 ml/min, CG-GFR:124.05±24.32 ml/min, MDRD-GFR:113.15±24.70 ml/min/1.73 m^2, BUN:14.57±5.05 mg/dl, urea: 27.37±10.24 mg/dl, and creatinine:0.73±0.18 mg/dl. The mean values of control group were as follows; right TTP:4.05±1.87 min, left TTP:2.93±1.14 min, right PA:819.25±260.48 cts/sec, left PA:796.75±176.94 cts/sec, and right $T_{1/2}$:12.25±3.19 min, left $T_{1/2}$:12.25±5.49 min. In control group, Gates GFR value was 109.75±39.03 ml/min, CG-GFR:104.62±39.67 ml/min, MDRD-GFR:89.68±34.15 ml/min/1.73 m^2, BUN:11.37±4.47 mg/dl, urea:24.75±5.54 mg/dl, and creatinine:0.78±0.17 mg/dl. There were a statistical difference between patients and controls groups at right TTP value and left TTP value ($p<0.020$ and $p< 0.000$, respectively). Glomerular filtration rate and clearance half time increased in patients with HBV as compared with control group, but there were no statistical difference. However, 18 patients had stasis in different localization and degree. In three patients, stasis was spontaneously drained, and washout of radioactivity was obtained by intravenous diuretic application in the other patients with stasis.

Conclusion: We concluded that Tc99m DTPA scintigraphy is a non-invasive and practical method to evaluate renal functions quantitatively or semi-quantitatively in patients with nephropathy possibly secondary to HBV infection. But further studies in large series are needed.

Key words: Hepatitis B virus, Tc99m DTPA scintigraphy, renal function.

Hepatit B Virus Enfeksiyonlu Hastalarda Renal Fonksiyonların Sintigrafik Değerlendirilmesi

ÖZET

Amaç: Kronik hepatit B virus (HBV) enfeksiyonu nefropatiyi indüklemektedir ve patogenezinden major HBV antijenleri (HBcAg, HBeAg, HBsAg) ile immun kompleksler sorumlu tutulmaktadır. Çalışmamızın amacı, HBV enfeksiyonu ile ilişkili olabilecek herhangi bir böbrek fonksiyon bozukluğunu erken tespit etmek için, teknesyum dietilentriamin pentaasetik asid (Tc99m DTPA) sintigrafisi ile HBV enfeksiyonlu hastaların renal fonksiyonlarını değerlendirmekti.

Metod: Çalışmamıza, HBV enfeksiyon tanılı 19 hasta (10 erkek, 9 kadın, yaş ortalaması: 37.11±11.34 yıl, yaş aralığı:25−62 yıl) ve 16 sağlıklı kontrol grubu (8 erkek, 8 kadın, yaş ortalaması: 33.50±11.56 yıl, yaş

aralığı:24−55 yıl) dahil edildi. Tüm deneklerde böbrek hastalığı ve interferon-alfa, pegylated interferon-alfa, lamivudine ve adefovir içeren HBV enfeksiyon tedavisi öyküsü yoktu. Kan üre nitrojeni (BUN), ure ve kreatinin analiz edildi. Böbrek perfüzyonu, konsantrasyonu ve ekskresyonu Tc99m DTPA sintigrafisi ile değerlendirildi. Pik zamanı (TTP), pik aktivite (kaunt/saniye) (PA), Yarılanma zamanı ($T_{1/2}$) ve diferansiyel böbrek fonksiyonları hesap edildi. Glomeruler filtrasyon oranı (GFR) eş zamanlı olarak 3 metod ile belirlendi; gamma kamera uptake metodu (Gates, GFR), Kreatinin klerens metodu (Cockcroft-Gault, CG-GFR) ve böbrek hastalığında modifiye diyet metodu (MDRD). Değişkenler gruplar arasında karşılaştırıldı.

Bulgular: Hastalara ait parametrelerin ortalama değerleri; sağ TTP:5.73±3.14 dak, sol TTP:5.52±2.09 dak, sağ PA:884.78±214.85 kts/sn, sol PA:889.52±252.68 kts/sn ve sağ $T_{1/2}$:17.84±6.89 dak, sol $T_{1/2}$:14.51±8.59 dak. Diferansiyel funksiyonlar sağda % 50.27±3.39 ve solda %49.72±3.39 idi. Çalışma grubunda, Gates GFR:125.63±25.84 ml/dak, CG-GFR:124.05±24.32 ml/dak, MDRD-GFR:113.15±24.70 ml/dak/1.73 m^2, BUN:14.57±5.05 mg/dl, urea: 27.37±10.24 mg/dl ve kreatinin:0.73±0.18 mg/dl idi. Kontrol grubuna ait parametrelerin ortalama değerleri; sağ TTP:4.05±1.87 dak, sol TTP:2.93±1.14 dak, sağ PA:819.25±260.48 kts/sn, sol PA:796.75±176.94 kts/sn ve sağ $T_{1/2}$:12.25±3.19 dak, sol $T_{1/2}$:12.25±5.49 dak. Kontrol grubunda, Gates GFR:109.75±39.03 ml/dak, CG-GFR:104.62±39.67 ml/dak, MDRD-GFR:89.68±34.15 ml/dak/1.73 m^2, BUN:11.37±4.47 mg/dl, urea:24.75±5.54 mg/dl ve kreatinin:0.78±0.17 mg/dl idi. Sağ TTP ve sol TTP değerlerinde hasta ve kontrol grupları arasında istatistiksel farklılık vardı (sırasıyla, $p<0.020$ ve $p< 0.000$). Glomeruler filtrasyon oranı ve klerens yarılanma zamanı HBV enfeksiyonlu hastalarda kontrol grubu ile karşılaştırıldığında yüksekti, fakat istatistiksel fark yoktu.

Sonuç: HBV enfeksiyonuna sekonder gelişebilecek nefropatili hastalarda renal fonksiyonların kantitatif ve semikantitatif değerlendirilmesinde, Tc99m DTPA sintigrafisi girişimsel olmayan ve pratik metodtur. Fakat daha geniş serilerde çalışmaya ihtiyaç duyulmaktadır.

Anahtar kelimeler: Hepatit B virus, Tc99m DTPA sintigrafi, böbrek fonksiyonu

INTRODUCTION

Hepatitis B virus (HBV) is a small DNA-containing virus belonging to the family Hepadnaviridae (1). Infection with HBV leads to the emergence of three major antigens; HBcAg, HBeAg, HBsAg. HBV is a cause of viral hepatitis in humans. Aside from hepatitis, this virus causes several extrahepatic manifestations such as reactive arthritis, skin rashes, vasculitis, and nephropathy (2). The disease affects both adults and children who are chronic carriers of hepatitis B virus, with or without a history of overt liver disease (3). Almost all major renal manifestations of HBV including membranous nephropathy, membranoproliferative glomerulonephritis, mesangial proliferative glomerulonephritis, minimal change disease, IgA nephropathy, focal segmental glomerulosclerosis, have been described (4). Although treatment, renal failure can be seen in HBV associated nephropathy (5).

Currently accepted methods of assessment of renal function include creatinine, glomerular filtration rate (GFR), measurement of proteinuria, assessment of tubular function and radiologic imaging (6). Technetium diethylenetriamine pentaacetic acid (Tc99m DTPA) scintigraphy is a non-invasive and practical method to evaluate renal functions quantitatively or semiquantitatively. Tc99m DTPA is excreted exclusively by glomerular filtration; no tubular secretion occurs (7). The scintigraphically measured percentage dose uptake of Tc99m DTPA by the kidneys and the plasma clearance of Tc99m DTPA have been reported to correlate well with inulin clearance (8). Both renographic parameters and GFR can be measured by means of Tc99m DTPA (9).

The aim of the study was to evaluate the estimation of renal function of patients with HBV infection using Tc99m DTPA scintigraphy.

MATERIAL AND METHOD

Two groups were included in our study, first group was 19 patients (10M, 9F) with chronic HBV infection whom taking any medical treatment such as interferon-alpha, PEG-interferon-alpha, lamivudin and adefovir; the other group was 16 healthy and voluntary person (8M, 8F). There was no any condition or systemic diseases like hypertention, diabetes mellitus, etc that might effect renal function of patients. Routine laboratory tests including complete blood count, urinalysis (proteinuria), blood urea nitrogen (BUN), urea, creatinine (clearance), serum total protein, albumin, alanine aminotransferase (ALT), alchalyn phosphatase (ALP), and HBV DNA were

analyzed. HBV-DNA parameters were studied by RT-PCR (Artus, Germany).
Tests for HBsAg, anti-HBs, and anti-HBc were performed using an enzyme immunoassay (Diapro, Italy).
The study was approved by the Medical Ethics Committee of Afyon Kocatepe University School of Medicine.

GFR were calculated as follows

1. Cockcroft-Gault (CG) GFR (10) : CrCl x (body surface area)/1.73 m^2
   a. For men: CrCl = [(140−Age) x Weight (kg)]/SCr x 72
   b. For women: CrCl= ([(140−Age) x Weight (kg)]/SCr x 72) x 0.85
2. Modification of Diet in Renal Disease (MDRD) GFR (11): 186 x [serum creatinin concentration (mg/dl)]$^{-1.154}$ x [Age]$^{-0.203}$ [0.742 if patients is female]

Tc99m DTPA renography

Before the study all subjects was hydrated with 500 ml of water. Patient data such as height, weight, age, total injected dose was noted in all fields on patient information page for calculating Gates GFR. Tc99m DTPA was prepared 30 min prior to injection using a DTPA kit (TechneScan® DTPA Turkey). Static pre-syringe and post-syringe counts were obtained for 60 seconds in a 64×64 matrix. A dose of 10 mCi (370 MBq) Tc99m DTPA was injected as a bolus in an antecubital vein and computer acquisition was initiated at the time of injection. Data were collected by means of a large field gamma camera (Philips Medical Systems Gamma Diagnost, Holland) which included a low energy general purpose collimator. Dynamic renal images were obtained from a posterior view and perfusion images of one second duration for one minute, followed by 60 second function images for a total 30 minutes in a 64×64 matrix with 1.00 zoom factors. In the end of the study, when renal stasis occured, 20 mg furosemid intravenous injection was applied, and dynamic image was continued during 10 minutes and delayed static image was acquired to evaluation of the diüretic effect. A region of interest (ROI) was drawn over the renal cortex such that the activity in the collecting system was excluded. Radioactivity was corrected for radionuclide decay and the renogram curves were generated based on data corrected for extrarenal-background activity.

The scintigrams were evaluated; visually, quantitatively and semiquantitatively. Quantities analysis for time to peak (TTP), peak activity (counts/second) (PA), clearance half time ($T_{1/2}$) and percent contribution of each kidney to total function (differential function) were calculated by obtaining renogram curve of the both renal ROI. Camera based GFR estimated from Tc99m DTPA renography was named Gates GFR. Gates GFR calculated using commercially available software. For GFR calculation, whole kidney ROI was used.

Statistical analysis

All parametric results were expressed as mean ± standard deviation for each group. The Chi−Square test was performed comparing the gender between groups. Comparisons of the between groups subjects were performed using the Mann−Whitney U test. Correlation analyses were done by spearman correlation analysis. A p-value less than 0.05 was considered to be statistically significant.

RESULT

The study population consisted of 19 patients (10 M, 9 F; mean age: 37.11±11.34 years, age range 25–62 years) with cronically HBV infection, and 16 healthy controls (8 M, 8 F; mean age: 33.50±11.56 years, age range 24–55 years).

Clinical, biochemical and scintigraphic findings of patients and control group are presented in Table 1.
When we compared the patient and control groups, there was no difference in age, gender and body mass index value. The level of HBsAg(+), AntiHBs(-), HBV DNA level was below the 10^4 kopya/ml in all patients. Complete blood count, urinalysis, serum total protein, albumin, ALT and ALP were normal. We found that mean degree of BUN, urea, CG-GFR and MDRD-GFR were high but creatinine clearance degree was low in patients group, and there was no statistical difference.

Quantitative parameters of scintigraphic studies showed that there was delayed TTP in patients group which had

Table 1: Clinical, biochemical and scintigraphic findings of patients and control group

Characteristics	**Patients (n=19)**	**Control (n=16)**	**p value**
Age	37.11±11.34	34.75±01.66	0.101
Gender (M/F years**)**	10/9	8/8	0.877
BMI (kg/m^2**)**	27.05±3.83	25.43±2.36	0.099
BUN (mg/dl)	14.57±5.05	11.37±4.47	0.103
Urea (mg/dl)	27.37±10.24	24.75±5.54	0.765
Creatinin (mg/dl)	0.73±0.18	0.78±0.17	0.481
TTP (min)			
Right	5.73±3.14	4.05±1.87	**<0.020**
Left	5.52±2.09	2.93±1.14	**<0.001**
PA (cts/sec)			
Right	884.78±214.85	819.25±260.48	0.289
Left	889.52±252.68	796.75±176.94	0.289
$T_{1/2}$ (min)			
Right	17.84±6.89	12.25±3.19	**0.005**
Left	14.51±8.59	12.25±5.49	0.894
Differential function (%**)**			
Right	50.27±3.39	52.00±3.33	**0.041**
Left	49.72±3.39	47.87±3.48	**0.038**
Gates GFR (ml/min)	125.63±25.84	109.75±39.03	0.407
CG-GFR (ml/min/1.73 m^2)	124.05±24.32	104.62±39.67	0.274
MDRD-GFR (ml/min/1.73 m^2)	113.15±24.70	89.68±34.15	0.057

meaningful statistical difference when compared with control group. Although there was high degree in PA in patients group, there was no statistical difference. There was minimal delay in T1/2 degree and when we compared with control group we found statistical difference in right kidney. There was statistical difference in both kidneys by the differential function.

There was increase in the degree of Gates GFR, CG-GFR and MDRD-GFR in patients group according to control group but this was not statistically different (Table 1).

However, 18 patients had stasis in different localization and degree. In three patients, stasis was spontaneously drained, and washout of radioactivity was obtained by intravenous diuretic application in the other patients with stasis. An example scintigraphic image and renogram curve is presented in Figure 1.

There was meaningful correlation between Gates GFR value measured by Tc99m DTPA versus CG-GFR and MDRD values ($r=0.860$, $p<0.001$ and $r=0.597$, $p<0.001$, respectively). Figure 2 demonstrates correlation between Gates GFR and CG-GFR.

DISCUSSION

Epidemiological, clinical and immunological evidence suggest a causal association between HBV carriage and the development of nephropathy. The pathogenetic mechanisms by which individuals with chronic HBV infection develop nephropathy are not clearly defined, and in fact not result from the direct effects of the virus (4).

It is estimated that HBV effect the kidney by some pathway and disturb the function of it. The most widely accepted mechanism associated with nephropathy is the deposition of immune complexes of viral antigen and host antibody (4,12), and other mechanisms could induce renal tissue injury by HBV as following; cytopathic effect induced by virus infection of the cell, virus-induced specific immunological effector mechanisms which damage the kidney, and indirect effects on renal tissue mediated via virus-induced cytokines or mediators (4).

Histopathologic study revealed deposition of HBcAg, HBeAg, antibody (anti-HBe), IgG, C3, and on electron microscopy, virus-like particles along glomerular capillary walls (13-18). Circulating immune complexes and HBsAg are deposited principally in the

mesangial regions and subendothelial space (2,4). And those processes give rise to glomerular injury (19).

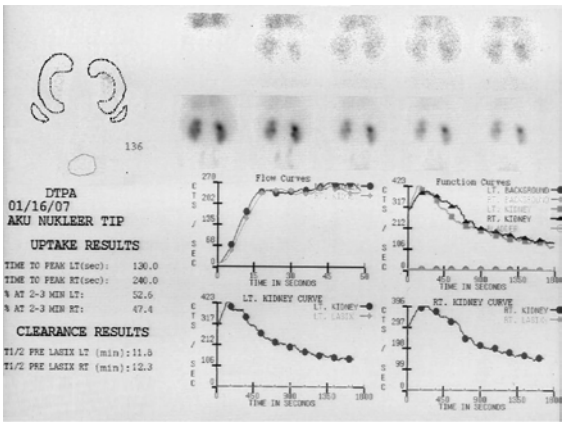

Figure 1: A 28-years-old man with HBV infection of 3-years duration. Cr=0.80 mg/dl, BUN=11 mg/dl, Urea=30 mg/dl, CG-GFR=110 ml/min/1.73 m^2, MDRD-GFR=91 ml/min/1.73 m^2, Gates GFR=111 ml/min. Image demonstrated right kidney upper zone stasis which was spontaneously drained.

When antigen persisted in the serum with low levels of antibody, chronic nephritis with subepithelial deposits developed; the latter are markers of HBV membranous lesions. Infected hepatocytes (by HBV) continually secrete viral specific particles; non-infectious particles consisting of excess viral coat protein (HBsAg), and DNA-containing particles (Dane particles) (4).

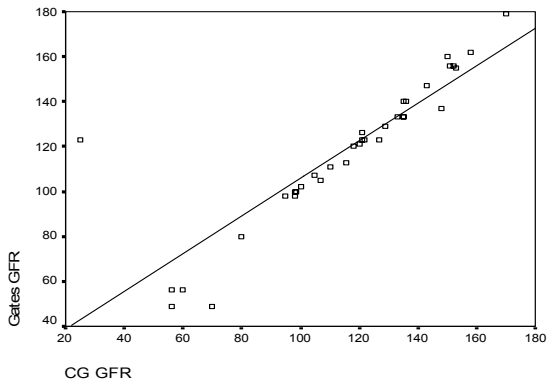

Figure 2: Positive correlation between Gates GFR and CG GFR (r=0.860 and p<0.001) is shown

Recent studies showing expression of HBV viral antigens in kidney tissue and HBV DNA distributed generally in the nucleus and cytoplasm of epithelial cells and mesangial cells of glomeruli, and epithelial cells of renal tubules suggest direct viral-induced pathological alterations and chronic immunologic injury. The analysis implied that the more extensive the existence of HBV DNA in the nephron unit and interstitial tissue, the more severe the clinical manifestation (4,20).

Detection of early renal dysfunction remains a difficult problem because serum creatinine, which is the most common measure of renal function in current clinical practice, is not an accurate index of GFR, as creatinine levels often do not become abnormal until GFR is severely reduced. Camera based Tc99m DTPA clearence appear to provide a more reliable measure of renal function than serum creatinine and creatinine clearance (21,22).

Renal scintigraphy is a valuable way to assess the three phases of renal function. Time-activity curves (radionuclide renogram) reflect these sequential changes in renal function. These three stages of renal function provide a method for quantitatively evaluating kidney function. Quantitative scintigraphic parameters include: TTP, PA, $T_{1/2}$, differential function and GFR (23).

The first phase evaluates perfusion (transit of the tracer through the renal blood vessels). The second phase is the period in which the nephrons extract the tracer from the blood and excrete it by glomerular filtration and/or tubular secretion (the peak point of a time-activity curve reflect renal blood volume, this point reflects maximal extraction of the tracer by the kidney). The third phase is the period during which the tracer drains through the pelvicalyceal system. Radionuclide renograms based on these three stages of renal function provide a method for quantitatively evaluating kidney function (23). Gates found a good correlation between the 2-3-min renal uptake of Tc99m DTPA and renal function (24).

In our study; there was normal renal perfusion in patients with HBV infection. The time of maximal extraction of the tracer by the kidney was delayed in HBV infection compared to control group. And mean counts of the activity was higher than control group. Gates GFR was increased in HBV infection.

And also our results revealed that, in all subjects, estimates of GFR calculated using the MDRD and Cockcroft and Gault formulae correlate well with Gates GFR measured using Tc99m DTPA clearance method.

When evaluation of renal function in HBV infection, hyperfiltration can be together with normal, increased, or decreased GFR (23). It is beter to evaluate GFR with quantitative and semiquantitative analysis of renogram curve.

According to our knowledge there isn't any study of HBV associated nephropathy evaluated by Tc99m DTPA. However, Filler et al. demonstrated that; in their patient who had HBV associated nephropathy, had hyperfiltration with an increased GFR determined by Tc99m DTPA clearance (25).

In our study; we found that there was minimal delay and prolongation in concentration function of kidneys (delayed TTP and increased PA). We thought that this was because of extraction dysfunction of affected nephrons.

Increased production of circulating mediators (such as tumor necrosis factor, interferons, IL-8, and/or other factors) from secondary liver disease in genetically predisposed individuals, may lead to increased glomerular permeability to plasma proteins (26). We conclude that increased GFR is because of increase in glomerular permeability, prolonged T1/2 is because of pelvicalixeal inflammation. And we thought that renal pathology is reversible because pelvicalixeal stasis responded to diuretics. But further studies are neded to confirm our studies. There was difference in differential function of kidneys in both groups but rates were in normal range Normal 50/50−56/44) (27).

In conclusion; evaluation of kidneys with worsened function by immonological processes in HBV infection; Tc99m DTPA scintigraphy showed; delayed TTP, delayed PA, increased GFR and prolongated T1/2 time. Tc99m DTPA scintigraphy is a non-invasive and easy method to evaluate any early renal dysfunction in patients with nephropathy possibly secondary to HBV infection. But further studies in large series are needed.

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