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Original Article

Renal hypophosphatemia and osteomalacia during long-term therapy of adefovir dipivoxil in patients with chronic hepatitis B

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Abstract: Cases have been reported about hypophosphatemia and osteomalacia induced by long-term use of adefovir dipivoxil (ADV) in patients with chronic hepatitis B (CHB). However, a systemic introduction of clinical characteristics, treatment strategy and prognosis lacks. In this study, clinical features of diseases above were evaluated, individualized treatments based on multiple parameters were explored and implemented, as well as a follow-up study on the prognosis. All 61 patients showed mild to moderate hypophosphatemia. Most of the patients also showed renal dysfunction characterized by decreased estimated glomerular filtration rate (eGFR), elevated serum cystatin C and urinary albumin-to-creatinine ratio. Elevated serum creatinine was shown in a few patients. Osteoporosis and osteopenia were found in two-thirds of patients, most of which had elevated serum alkaline phosphatase (ALP) and complained bone pain. Changing of antivirals and supplement of phosphate were given according to history of antiviral resistance, mutation loci, renal function, severity of hypophosphatemia and bone pain. Entecavir, tenofovir disoproxil fumarate and telbivudine were used for etiological treatment. After ADV cessation or dose reduction, normalization of serum phosphate and bone pain relief were observed within a few months. Significantly increased eGFR was obtained in a small proportion. The bone mineral density increased but not significantly. A disappearance in isotope uptake was shown on repeated whole body bone scintigraphy. Hypophospatemia and osteomalacia develops in some CHB patients with long-term use of ADV, which is partially reversible by ADV cessation or dose reduction. Monitoring serum phosphate and renal function is prudent during ADV therapy.

Keywords: Adefovir dipivoxil, hypophosphatemia, osteomalacia, chronic hepatitis B

Introduction

Hepatitis B virus (HBV) infection affects approximately two billion people worldwide, of which about 350 million people are chronically infected [1]. To achieve sustained HBV DNA suppression and persistent disease remission, long-term use of oral nucleoside or nucleotide analogues (NAs) is recommended by current guidelines [2, 3]. Six NAs have been approved as antiviral agents for chronic hepatitis B (CHB) patients at present. Although entecavir (ETV) and tenofovir disoproxil fumarate (TDF) have been recommended as first-line therapeutic options for CHB treatment by guidelines worldwide [2, 4], adefovir dipivoxil (ADV) is still being used in CHB patients. Overall, all NAs have infrequent adverse reactions, we should pay attention to drug safety in long-term therapy. Although a dose-related (60 and 120 mg daily) nephrotoxicity of ADV was reported in HIV infected patients, studies showed that ADV was safe at the dose of 10 mg per day for the treatment to patients with CHB [5, 6].

In previous studies, only 3% of patients receiving ADV 10 mg per day after 144-week treatment performed increases in serum creatinine level of ≥ 0.5 mg/dL, hypophosphatemia was not found while on ADV therapy [6]. However, during the long-term treatment with low-dose ADV, some cases have been reported as renal dysfunction characterized by decreases in serum phosphate with or without osteomalacia [7-13], especially in Asian areas. In present study, we reported the clinical characteristics,

potential resolution and prognosis of CHB patients with the evidence of hypophosphatemia and hypophosphatemic osteomalacia on long-term low-dose ADV therapy in real-life setting.

Material and methods

Patients

Sixty-one consecutive inpatients and outpatients with CHB infection treated with ADV (10 mg/day) alone or combined with lamivudine (LAM) or ETV were included in this study from October 2013 to December 2016. Hypophosphatemia (normal range: 0.81-1.45 mmol L^{-1}) were confirmed on two consecutive occasions in all patients with or without cirrhosis. The following cases should be excluded, drinking, treated with drugs affecting bone metabolism like corticoid, abnormality of parathyroid hormone, phosphorus deficient or malabsorption. The study protocol was approved by the ethics committee at the Second Hospital of Shandong University.

Serum and urine monitoring during therapy

Ages, gender, body weight, antiviral drugs application and drug resistance, clinical diagnosis and manifestation were recorded when the diagnosis of ADV-induced hypophosphatemia and hypophosphatemic osteomalacia were comfirmed. At baseline, blood samples were analyzed for calcium, phosphate, and serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total and direct bilirubin, albumin, total protein, renal function indexes including serum creatinine (SCr), cystatin C (Cys-C), uric acid and beta-2-microglobuline (β2-MG). Then creatinine clearance rate (Ccr) were calculated. Estimated glomerular filtration rate (eGFR) was calculated based upon SCr, Cys-C and age with the CKD-EPI creatinine-cystatin C calculation. First urine samples for routine test and a urinary albumin-to-creatinine ratio (UACR) were collected after overnight fasting, a 24-hour urinalysis was also ordered at baseline. At each clinic visit (week 2, months 1, 3, 6, 9 and 12), all tests above were done and recorded. A urinary α1 microglobulin (α1-MG) testing (normal range: ≤ 12 mg/L) was ordered after individual interventions.

The eGFR level of ≥ 90, 60-89, 30-59, 15-29, and < 15 mL/min/1.73 m^2 were defined as normal, mild decreased, moderate decreased, severely decreased and kidney failure, respectively [14].

Bone mineral density and whole-body bone scan

A dual energy X-ray absorptiometry (DEXA) scan was ordered at baseline and every 3 months (T score: > -1 revealed normal, < -2.5 osteoporsis, osteopenia was between -1 and -2.5). We ordered a whole-body bone scan using technetium-99m methylene diphosphate (^{99m}Tc-HMDP) for the diagnosis of osteomalacia especially for patients suffered bone pain.

Grading of hypophosphatemia

Hypophosphatemia is categorized as mild (serum phosphate level of 0.66 to 0.81 mmol/L), moderate (serum phosphate level of 0.32 to 0.65 mmol/L) and severe (< 0.32 mmol/L) [15].

Statistical analysis

The variable data was presented as median values (range). A two-tailed *P*-value less than 0.05 was considered to be statistically significant. Comparison of continuous variables was performed using Student's t-test, or Wilcoxon test, as required. All analyses were performed using SPSS (version 22.0; SPSS, Chicago, IL, USA).

Results

Patient characteristics

Forty-one men and twenty women with a median age of 54 (27-76) years were diagnosed with ADV-induced hypophosphatemia or hypophosphatemic osteomalacia between 2013 and 2016, among which 27 had cirrhosis before diagnosis. The total duration of ADV therapy ranged from 18 to 116 months and median duration was 68 months, 43 (70.5%) patients had 3 to 8 years therapy. Twenty-seven patients (44.2%) had received ADV monotherapy with no antiviral resistance, other 34 patients had received ADV in combination with ETV or LAM because of antiviral resistance or virological breakthrough. Detailed history of antiviral agents was showed in **Table 1**.

Clinical manifestations

Twenty-five (41%) patients complained of a median of 9.5-month (range: 1-24) history of

Table 1. Detailed history of antiviral drugs

Antiviral drugs	Number (%), total = 61
ADV monotherapy	27 (44.2)
ADV and LAM previously	15 (24.6%)
ADV in combination with LAM	16 (26.2%)
ADV in combination with entecavir (ETV)	3 (5%)

bone pain involving both knees, ankles, heels, hips and bilateral rib cage. Two of them were treated by surgery because of femoral neck fracture.

Abnormally low bone mineral density with a median lumbar T-score of -3 (-5 to -1.1) standard deviations was found in 45 (73.8%) patients. Among those 45 patients, 25 patients had osteoporosis. Multiple foci of increased radiotracer uptake in the scapula, the rib cage, the lumbar spine, the knees and the ankles were shown in 10 patients suffered severe bone pain who accepted the whole-body bone scan as recommendations, however, one of those ten patients had normal bone mineral density.

Clinical parameters

Mild to moderate hypophosphatemia were noted in all 61 patients, the median serum phosphate level was 0.67 (range: 0.41-0.79) mmol L^{-1}. Hypocalcemia was found in 10 patients. Thirty-five patients had abnormally elevated ALP, twenty-three of them suffered with bone pain, which had lasted for 9.5 months (range: 1-24 months). Mild and moderate deceased eGFR level was diagnosed in 27 and 16 patients, respectively. No patients had a severely deceased eGFR or kidney failure. A reduced serum uric acid was found in 20 patients (median level: 103 mmol L^{-1}, range: 72-119 mmol L^{-1}). Forty-nine patients agreed to have a UACR test, among which 37 patients had elevated UACR with a median level of 89.6 mg g^{-1} (range: 16.7-499.9). Twenty-three patients had proteinuria (> 1+ on a fasting, spot urine sample), three of which had glucosuria (> 1+ on a fasting, spot urine sample) without a diagnosis of diabetes mellitus. Aberrant elevated SCr was found in 10 patients with a median level of 126.75 μmol L^{-1} (range: 116-232). All patients had a normal range of HBV DNA (< 500 copies mL^{-1}), ALT and AST. These clinical parameters were described in **Table 2**.

Treatment and prognosis

Etiological treatment including switching ADV to ETV or telbivudine (LdT), adding on LdT with or without dose reduction of ADV from 10 mg every day to every other day was taken to all patients except two based on following several conditions, which involved in patients' choices, diagnosis (cirrhosis or chronic hepatitis), history of antiviral resistance and mutation loci, renal function and bone mineral density. Detailed adjustments of antiviral drugs were shown in **Table 3**. Regular phosphate supplementation was commenced when moderate to severe hypophosphatemia, complicated with bone pain and/or osteoporosis were found, calcium supplementation was given when patients achieved normal phosphate level. Calcitriol was prescribed to patients with osteoporosis, and patients with osteopenia who suffered bone pain. Twenty-nine patients received calcitriol, among which 19 received phosphate supplementation and calcium supplementation subsequently.

Fifty-four patients agreed to be followed. Serum phosphate level increased to normal within 1 (0.25-12) months in all patients except one who refused to be treated. There were 54, 53, 49, 46 and 45 patients to be followed at month 1, 3, 6, 9 and 12, respectively. Patients reported that symptoms of bone pain began to alleviated in 1 (0.25-3) month, and completed improved in 3 (1.5-6) months.

Decreased ALP levels were observed in 17, 17, 18, 20, 25 patients after 1, 3, 6, 9, 12 months therapy, respectively. There were 5 patients had arising ALP within 3 months, but there was no statistically significant elevations (213 (126-369) *vs.* 175 (66-538), P = 0.073, Wilcoxon signed-rank test). Compared with baseline level, abnormally elevated ALP declined in both 6 (213 (126-369) *vs.* 149 (102-379), P = 0.019, Wilcoxon signed-rank test) and 12 months (213 (126-369) *vs.* 97 (45-233), P = 0.00, Wilcoxon signed-rank test) respectively. There were 6 patients who had abnormally elevated ALP after 12 months therapy still needed longer observation.

Five and thirteen patients obtained improved eGFR after 6 and 12 months intervention, respectively. Significant increased eGFR was

Table 2. Clinical parameters in patients with hypophosphatemia and hypophosphatemic osteomalacia

Features	Number of abnormality (proportion %)	Median values (range)
Age (years)		54 (27-76)
Duration of ADV use (month)		68 (18-116)
Abnormal ALP (U L^{-1})	35 (57.4)	213 (126-369)
With bone pain	23 (37.7)	238 (135-369)
Without bone pain	12 (19.7)	153 (126-273)
Serum creatinine (μmol L^{-1})	10 (16.4)	126.75 (116-232)
Cys-C (mg/L)	29 (47.5)	1.27 (1.07-1.8)
Serum phosphate (mmol L^{-1})	61 (100)	0.67 (0.41-0.79)
Serum potassium (mmol L^{-1})	7 (11.5)	3.28 (3.0-3.46)
Serum calcium (mmol L^{-1})	9 (14.7)	2.03 (1.9-2.07)
eGFR (< 90 mL min^{-1})	43 (70.5)	64.56 (38-88.1)
(< 60 mL min^{-1})	16 (26.2)	52.71 (38-59.0)
Proteinuria (trace or greater)	23 (37.7)	+ to ++
Blood uric acid (μmol L^{-1})	19 (31.1)	104 (75-119)
Urinary ACR (mg g^{-1})	37/49 (75.5)	89.6 (16.7-499.9)

obtained after 12-month intervention in patients who had eGFR less than 60 mL/min/1.73 m^2 before intervention (P = 0.028). SCr became normal in 30% (3 of 10) 12 months after withdrawal or reduction of ADV. Serum uric acid returned to normal in 57.9% (11 of 19) and 89.5% (17 of 19) after 1 and 3 months therapy, respectively. Serum Cys-C gradually deceased, and proteinuria gradually disappeared in 2 and 3 patients after 6 and 12 months therapy, respectively.

A urinary α1 microglobulin (α1-MG) testing (normal range: ≤ 12 mg/L) was done in 30 patients followed up. Normalized urinary α1 microglobulin was observed in 11 patients, but not in another 19 patients in which a median level of 50.8 mg/L (range: 13.2-187.1) were obtained. The urinary α1 microglobulin was related to patients' age (r = 0.434, P = 0.017, Spearman rank correlation analysis). There was no difference in patients with or without cirrhosis (Z = -1.402, P = 0.172, Wilcoxon signed-rank test).

The bone mineral density appeared to be no significantly improved within 12 months. However, it showed a disappearance in isotope uptake on repeated whole body bone scintigraphy in 12 months in 10 patients, respectively.

Discussion

This 61 CHB patients' study, combining with earlier published case reports, confirmed the occurence of hypophosphatemia and osteomalacia in a proportion of patients after long-term therapy of ADV, which were characterized by mild to moderate hypophosphatemia, decreased eGFR level, increased ALP level, general bone pain, decreased BMD and abnormally isotope uptake in multiple bones by a whole-body bone scan. Meanwhile, abnormally elevated SCr is infrequent. ADV withdrawal or dose reduction or LdT adding-on were the key resolution. Hypophosphatemia and related symptoms can be fully improved, however, decreased eGFR level and BMD cannot be fully reversed.

Early diagnosis of ADV related renal hypophosphatemic osteomalacia was still lacking. Whereas, there was a median of 9.5-month (range: 1-24) of bone pain in nearly half of our patients (25/61) before they were diagnosed with ADV related renal hypophosphatemic osteomalacia. In previous reports [7-13, 16, 17], the duration was a median of 12-month (range: 3-36), respectively. Low rate of ADV related renal dysfunction and insufficient attention to serum phosphate level might be two major reasons. In our study, the duration of ADV therapy was 3 to 7 years in 75% of patients with mean age of 54 years old. Combined with duration of bone pain, physicians should pay more attention to older patients receiving ADV treatment for more than 2 years. Serum phosphate level combined with SCr and Cys-C, should be monitored to evaluate the risk of ADV related renal dysfunction.

Hypophosphatemic ostomalacia is a metabolic bone disorder leading to low BMD. Significant hypophosphatemia, generalized bone pain, and elevated level of ALP were the major characteristics in patients with diagnosis of ADV related hypophosphatemic osteomalacia. Although DEXA scan is reliable in detecting osteoporosis, it is not directly related with osteomalacia because there is increased bone volume [18]. Regarding to an up-to-50% occurence of osteoporosis in patients with chronic liver diseases

Table 3. Adjustments of antiviral drugs

Adjustments of antiviral drugs		Number
ADV withdrawal	Switched to LdT 600 mg per day	23
	Switched to LdT 600 mg per 2 days or 3 days	3
	Switched to ETV 0.5 mg per day	16
	Cessation criterion	3
	ETV 0.5 mg per day	2
	Switched to tenofovir 300 mg per 2 days combined with LdT 600 mg per day	3
ADV reduction to 10 mg per 2 days	Combined with LdT 600 mg per day	8
ADV	Combined with LdT 600 mg per day	1
	Refused interventions	2

[19], a whole-body bone scan rather than a DEXA scan is preferred for diagnosis and follow-up in patients with ADV related renal hypophosphatemic osteomalacia.

The resolution of ADV related renal hypophosphatemia and osteomalacia were not completely explained in previous studies. In this study, adjustment of antiviral drugs was a primary treatment when the diagnosis of ADV related hypophosphatemia and osteomalacia were made. Based on current researches, ADV-related hypophosphatemia and osteomalacia were induced by proximal renal tubular dysfunction, resulting in urinary phosphate wasting. Therefore, ADV cessation or reduction, rather than supplementation of phosphate, was more essential in order to reach serum phosphate normalization.

In this study, ADV was switched to ETV or LdT, the later was not ever involved in former studies. Recent study showed that long-term LdT therapy could improve renal function [20]. Therefore, ADV was switched to LdT in patients with lower eGFR levels and ADV monotherapy history without liver cirrhosis. Meanwhile, LdT adding on ADV or TDF with or without dose reduction, showed effective in patients who had mild hypophosphatemia or multidrug resistance. In this study, 3 patients switched ADV to TDF (300 mg per 2 days) combined with LdT and 1 patient adding on LdT without ADV reduction, reaching serum phosphate level normalization and the abnormalities did not recur as well.

Calcium carbonate and calcitriol were both recommended in former studies. However, there was not unified opinion about elemental phosphate supplement [21, 22]. Not all the patients in this study received phosphate supplement. Patients with moderate to severe hypophosphatemia, complicated with bone pain and/or osteoporosis received elemental phosphate supplement. Also, serum phosphate level normalization was observed in all patients in this study.

Unlike the normalization of serum phosphate, not all abnormally increased SCr and Cys-C, and decreased eGFR and CCr levels reached normal after 12 months intervention. Only a few patients improved in the abnormal indexes above. Therefore, ADV induced renal dysfunction, mainly glomerular function, might be partially reversible.

The urinary α1-MG is used as a marker of proximal tubular damage. A slower normalization was observed in older patients in our study. It was revealed that patients with long-term therapy of ADV should be monitored, especially older patients [23]. It might take longer recovery for older patients with ADV related renal hypophosphatemia and hypophosphatemic osteomalacia.

It is clear that renal phosphate wasting causes the low serum phosphate level. However, it has not been fully understood how this happen in some patients on long-term therapy of lower-dose ADV. ADV is actively absorbed from blood to proximal tubular cell by basolateral membrane human organic anion transporter 1 (hOAT-1) and transported through luminal membrane by multiple drugs resistance protein 2 (MRP-2) [24]. It has been reported that extensive ADV accumulation in proximal tubular cell is associated with ADV nephrotoxicity [24]. Most patients reported with ADV related renal dysfunction came from Asian areas, there may

be relationship between single nucleotide polymorphisms (SNPs) in genes encoding hOAT-1 and MRP-2 and ADV nephrotoxicity.

In spite of lower incidence of renal hypophosphatemia and osteomalacia [25], TDF has the same risk of renal function decline. There was only 1.5% of patients with serum phosphate < 2 mg/dL up to seven years of TDF [26]. In clinical practice, some cases with TDF related Fanconi syndrome have been reported [27-29]. Because of their closely related structures of TDF and ADV, studies of the early diagnosis, treatment and pathogenesis of ADV related renal dysfunction are needed.

This study has a few limitations. As a retrospective study, baseline data when patients began antiviral treatment as well as a control group was lacking, which some risk factors could be found. Future prospective study will be needed to resolve the problem above.

In conclusion, renal hypophosphatemia and hypophosphatemic osteomalacia develop in some CHB patients with long-term therapy of ADV, which is partially reversible by switching ADV to other antivirals and/or ADV dose reduction. ^{99m}Tc-HMDP whole-body bone scan is more specific to diagnose osteomalacia. We recommend regular monitoring for serum phosphate, ALP, SCr, Cys-C and urine test during long-term ADV therapy, and personal adjustment of antiviral drugs based on history of antiviral resistance, mutation loci and renal function.

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Disclosure of conflict of interest

None.

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