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*Case Report*

# Hypophosphatemic osteomalacia induced by prolonged low-dose adefovir dipivoxil therapy for CHB: two cases report and literature review

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**Abstract:** *Background:* Adefovir dipivoxil (ADV) is a nucleotide used as a long-term therapy for chronic hepatitis B (CHB). Low-dose ADV therapy (daily dose of 10 mg) to treat patients with CHB has been reported to be safe. However, there are cumulative reports describing that the long-term use of low-dose ADV triggers proximal renal tubular dysfunction and causes hypophosphatemic osteomalacia. *Methods:* We reported two CHB cases of low-dose ADV-induced hypophosphatemic osteomalacia who presented initially with bone pain. Literature review revealed other 33 cases of hypophosphatemic osteomalacia induced by low-dose (10 mg daily) ADV and we also performed the literature review of the main characteristics from all the included 35 cases. *Results:* The first patient was a 46-year-old man with a 3-year history of bone pain involving low back, lumbar spine, rib cage, cervical vertebra, both knees, ankles without antecedent trauma. The patient had been receiving adefovir for 10 years before the confirmation of hypophosphatemia. Bone scintigraphy revealed multiple ribs, cervical vertebra, clavicle, humerus, sacrum, both posterior iliac bones, ankles and calcaneus, which were suggestive of metabolic bone disorder. Laboratory investigations showed hypophosphatemia, hypocalcemia, hypouricemia, increased level of alkaline phosphatase (ALP) and decreased 25-hydroxyvitamin D level. After ADV was replaced with entecavir, with supplementation of phosphate, calcium carbonate, calcitriol, bone pain was significantly reduced within 7 months. The second patient was a 62-year-old man who presented with a 4-year history of bone pain of the heel bone, knee and breast bone. The patient had been taking ADV for approximately 24 months before the development of bone pain. Laboratory data revealed hypophosphatemia, hypouricemia, hyperglycemia, increased level of ALP and vitamin D deficiency. Bone scintigraphy showed increased uptake in cervical vertebra, clavicle, sacrum, posterior iliac bones, lateral condyle and upper tibia. The symptoms improved by changing the antiviral agent from adefovir to entecavir within 6 months. Follow-up examination after 14 months showed his serum level of phosphate and bone densitometry to be normal. *Conclusion:* Hypophosphatemic osteomalacia and renal Fanconi syndrome can be induced by long-term low-dose ADV therapies. The symptoms and the hypophosphatemia improved after discontinuation of ADV coupled with supplementation with phosphate in most cases and replacing ADV with entecavir may be a better alternative. CHB patients taking long-term ADV therapy (daily dose of 10 mg) daily should receive regular monitor of the renal function and serum phosphate level. Clinicians prescribing ADV over a long period of time should be aware of the late onset of hypophosphatemic osteomalacia and renal Fanconi syndrome.

**Keywords:** Hypophosphatemic, osteomalacia, ADV

## Introduction

Adefovir dipivoxil (ADV) is a nucleotide analogue of adenosine monophosphate commonly used as the therapeutic agent against human immunodeficiency virus (HIV) or wild-type and lamivudine-resistant hepatitis B virus (HBV). ADV was initially used with high dose (60-120 mg per day) to treat the HIV infection [1]. Unfortunately, the high-dose ADV therapy can cause the nephrotoxicity, whereas low-dose ADV therapy (daily dose of 10 mg) to treat patients with HBV infection has been reported to be safe [2-7].

However, there are cumulative reports describing that the long-term use of low-dose ADV trig-

**Table 1.** Baseline and follow-up laboratory data after discontinuation of ADV (Case 1/Case 2)

| Case 1/Case 2 | Baseline | The first follow-up | The nearest follow-up |
|---|---|---|---|
| Serum | | | |
| Phosphate (mmol/L) | 0.45/0.76 | 0.83/0.72 | 0.86/1.06 |
| Calcium (mmol/L) | 2.07/2.25 | 2.19/2.34 | 2.25/2.33 |
| Ionized calcium (mmol/L) | 1.05 | 1.09 | 1.13 |
| Potassium (mmol/L) | 3.75/3.98 | 3.79/4.15 | 3.70/4.24 |
| Sodium (mmol/L) | 143.7/139.4 | 136.9/145.0 | 139.7/137.5 |
| Alkaline phosphatase (U/L) | 201/301 | 311/191.0 | 61/42.3 |
| Aspartate aminotransferase (U/L) | 18/18.7 | 45/24.8 | 25/16 |
| Alanine aminotransferase (U/L) | 24/23.7 | 78/28.4 | 47/19 |
| Glucose (mmol/L) | 4.07/7.38 | 4.36/6.21 | 4.59/5.13 |
| Uric acid (μmol/L) | 116.6/113.6 | 153.4/102.5 | 195.4/417.6 |
| BUN (mmol/L) | 3.7/6.2 | 4.9/6.3 | 7.2/4.8 |
| Creatinine (μmol/L) | 102.5/97.4 | 84.1/98.3 | 104.7/63.9 |
| Intact parathyroid hormone (pg/ml) | 16.8/16.2 | 57.0/55.9 | 39.5/38.1 |
| 25-Hydroxyvitamin D (nmol/L) | 36.7/26.5 | 36.9/NA | NA/NA |
| Urine | | | |
| Urine glucose | Positive/Positive | NA | NA |
| Urine protein (g/24 h) | 1.01/2.23 | 0.93 | NA |
| Urine microalbumin (mg/L) | NA | NA | 13.8 |
| Urine creatinine (mmol/24 h) | 6.08 | NA | 19.9 |
| Urine calcium (mmol/24 h) | 20.69 | 4.81 | NA |
| Urine phosphorus (mmol/24 h) | 13.37/15.2 | 28.6 | NA |

gers proximal renal tubular dysfunction and causes hypophosphatemic osteomalacia with systemic pain, a feature of Fanconi's syndrome, particularly in populations of China and other regions of East Asian [8-32]. The most common clinical symptoms of osteomalacia are undefined or uncharacteristic bone pain and polyarthralgia [18], due to the dysfunctions of the proximal renal tubule leading to hypophosphatemia, hypouricemia, proteinuria and glycosuria [33]. These early signs are often misdiagnosed as other disease such as polymyalgia rheumatica, arthritis, or fibromyalgia. Moreover, there are numerous clinical, laboratory, and radiographic tests which need been utilized together for diagnosis of osteomalacia, no single diagnostic blood test or radiographic finding specific for osteomalacia. Therefore, the diagnosis of osteomalacia induced by long-term use of low-dose ADV was usually delayed.

Here we reported two cases of low-dose ADV-induced hypophosphatemic osteomalacia who presented initially with severe dorsal back pain and chest wall pain. Other 33 cases previously reported in the literature are also reviewed.

### Ethics approval and consent from the patients

This study was approved by the Institutional Ethics Committee of Infectious Hospital of Wuxi, Affiliated to Jiangnan University (No: WXIH2016-016), and was in compliance with the national legislation and the Declaration of Helsinki guidelines. Written consents were obtained from the patients according to the institutional guidelines.

### Case 1

A 46-year-old man was admitted to hospital in April 2012 with a 3-year history of bone pain, persistent and dull, involving low back, lumbar spine, rib cage, cervical vertebra, both knees, ankles without antecedent trauma, and was accompanied by difficulty of positional change during sleep and walking since July 2010. And then, the patient began to experience weakness in his limbs muscles, and recognized the progressive exertional and generalized bone pain. The patient came to hospital due to severe bone pain. The patient had a history of chronic hepatitis B infection and liver cirrhosis, and had received Adefovir dipivoxil (ADV) (10

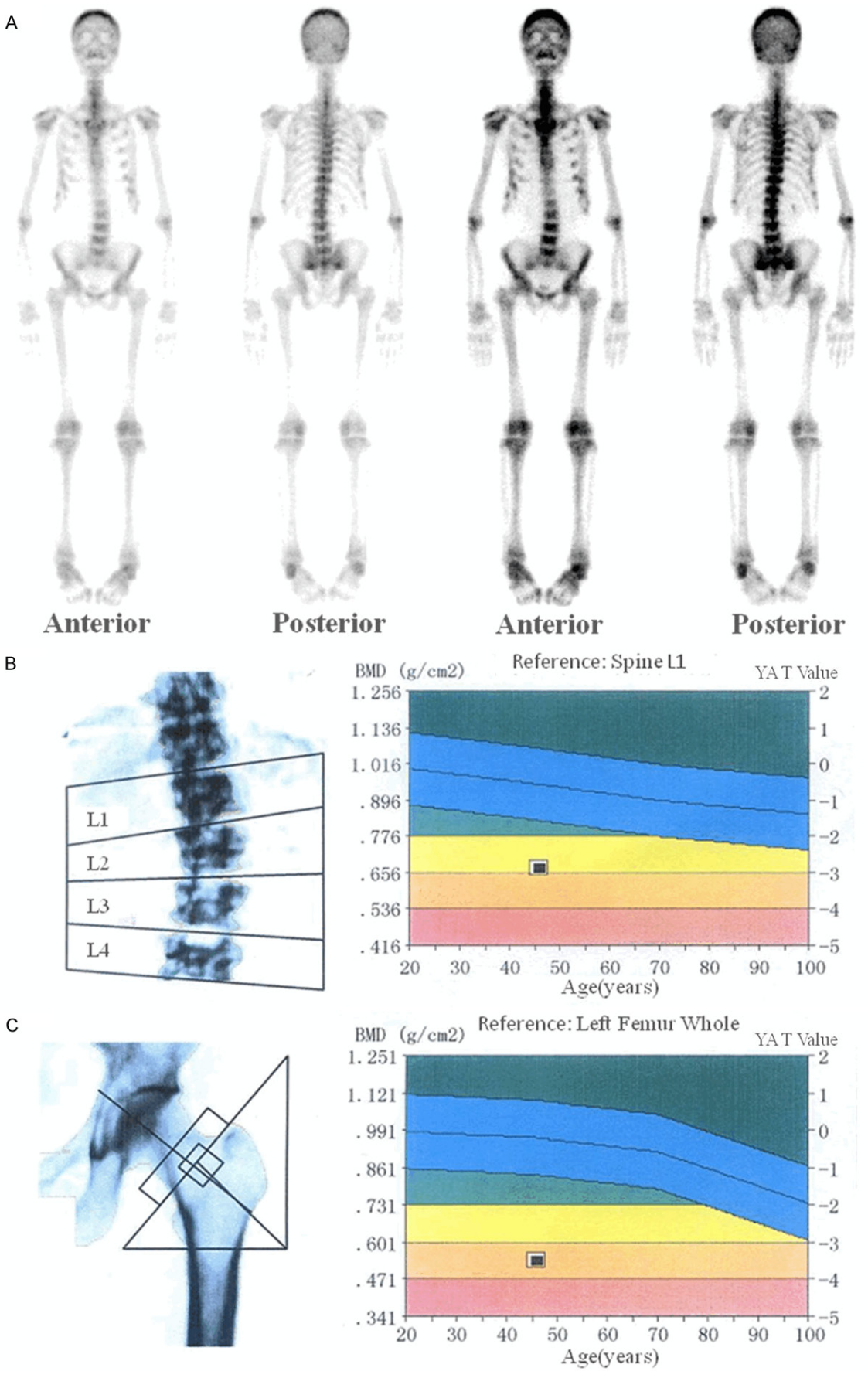

A
Anterior
Posterior
Anterior
Posterior
B
L1
L2
L3
L4
BMD (g/cm2)
Reference: Spine L1
YAT Value
1.256
1.136
1.016
.896
.776
.656
.536
.416
2
1
0
-1
-2
-3
-4
-5
20 30 40 50 60 70 80 90 100
Age(years)
C
BMD (g/cm2)
Reference: Left Femur Whole
YAT Value
1.251
1.121
.991
.861
.731
.601
.471
.341
2
1
0
-1
-2
-3
-4
-5
20 30 40 50 60 70 80 90 100
Age(years)

**Figure 1.** Radiographic findings of case 1. A. Whole-body 99mTc-methylene diphosphonate bone. B. Bone mineral density of spine. C. Bone mineral density of left femur.

**Table 2.** The bone mineral density measurement of Case 1

| Region | Baseline | | | The first follow-up | | | The nearest follow-up | | |
|---|---|---|---|---|---|---|---|---|---|
| | BMD ($g/cm^2$) | T-score | Z-score | BMD ($g/cm^2$) | T-score | Z-score | BMD ($g/cm^2$) | T-score | Z-score |
| L1-4 spine | 0.654 | -3.6 | -2.9 | 0.927 | -1.3 | -0.7 | 1.067 | -0.1 | 4 |
| Neck | 0.534 | -3.4 | -2.7 | 0.642 | -2.6 | -2 | 0.865 | -0.9 | -0.2 |
| Upper femoral neck | 0.425 | - | - | 0.546 | - | - | 0.756 | - | - |
| Trochanter | 0.388 | -3.7 | -3.1 | 0.594 | -2 | -1.5 | 0.874 | 0.4 | 0.9 |
| Femoral shaft | 0.647 | - | - | 0.891 | - | - | 1.124 | - | - |
| Total hip | 0.536 | -3.5 | -3.3 | 0.734 | -2 | -1.8 | 0.986 | 0 | 0.2 |

mg/day) since 2002, with normal liver function and HBV DNA < 500 copies/ml. He was 56.0 kg in weight and 165 cm in height and had a body mass index of 21.4 $kg/m^2$. His heart rate was 80 bpm and his blood pressure was 140/100 mmHg. On a physical examination, he had generalized bone tenderness, especially on the lumbar spine, rib cage and both knees. There is no history of trauma, bone metabolic disorder and chronic diarrhea. No familial renal disease. No history of organic poison or close contact with heavy metals. No observation on the motion and sense losses was found with the neurologic examination.

Laboratory investigations showed hypophosphatemia, hypocalcemia, hypouricemia, increased level of alkaline phosphatase (ALP) and decreased 25-hydroxyvitamin D level (**Table 1**). Serum aspartate aminotransferase, alanine aminotransferase, sodium, and potassium were normal (**Table 1**). Urinalysis showed positive albumin and glucose in the absence of hyperglycemia and a history of diabetes mellitus (**Table 1**). The initial 24-h urinalysis showed hypercalciuria and a decreased level of urinary phosphorus and creatinine (**Table 1**).

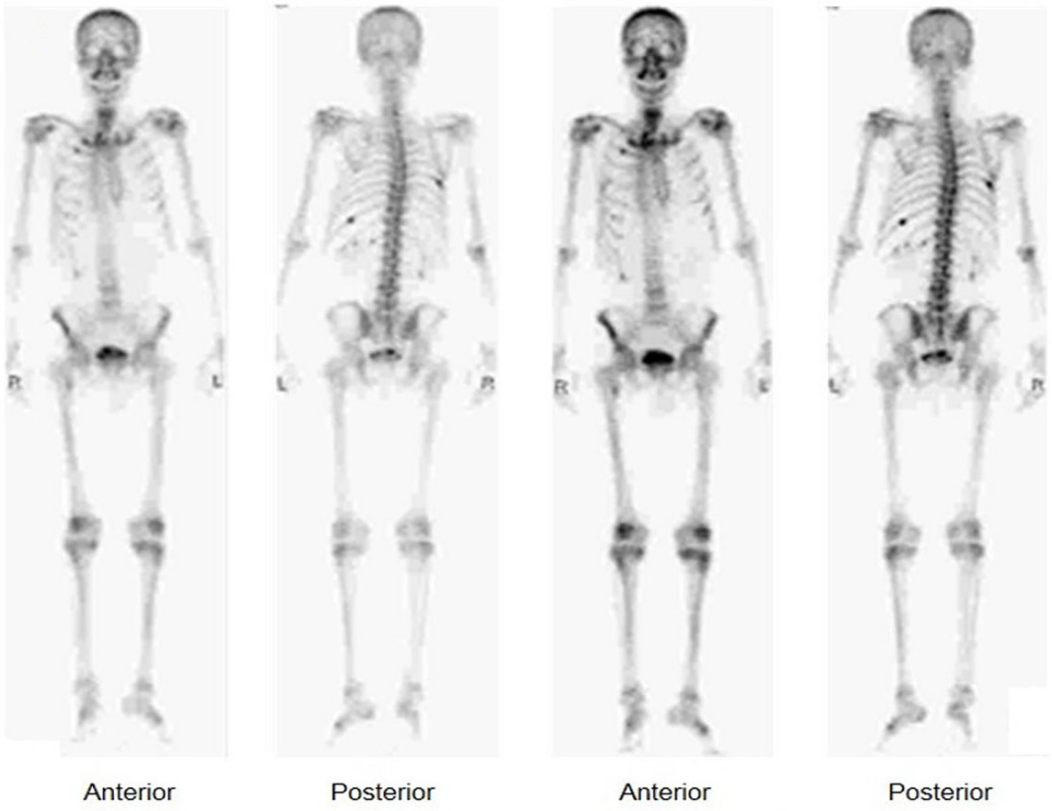
Bone scintigraphy using technetium-99m methylene diphosphate (99mTc-MDP) showed increased uptake in multiple ribs, cervical vertebra, clavicle, humerus, sacrum, posterior iliac bones, ankles and calcaneus (**Figure 1A**). Bone densitometry showed abnormally low bone mineral density with a mean lumbar (L1-L4) T-score of -3.6 standard deviations and a mean lumbar Z-score of -2.9 standard deviations (lowest at L3 with a T-score of -3.9), with a mean neck T-score of -3.4 standard deviations and a mean lumbar Z-score of -2.7 standard deviations, and with a mean total hip of T-score (-3.5) and Z-score (-3.3) (**Table 2** and **Figure 1B**).

It was diagnosed that the osteroporosis appeared due to the hypophosphatemia secondary to adefovir therapy based on the hypophosphatemia, ALP increase, and increased uptake in multiple sections of bone scintigraphy and low bone mineral density. After adefovir was replaced with entecavir, with supplementation of phosphate, calcium carbonate, calcitriol, the patient reported symptomatic improvement within 7 months. This was accompanied by normalization of phosphate level and decrement of high uptakes on bone scintigraphy. Bone pain was markedly ameliorated, although still felt weakness of double lower limbs after activity. Follow-up physical examination in May, 2015 showed his serum level (phosphate 0.86 mmol/L, ALP 61 U/L, Uric acid 195.4 μmmol/L) was nearly normal, at the same time, Bone densitometry showed a mild decrease only in the neck.

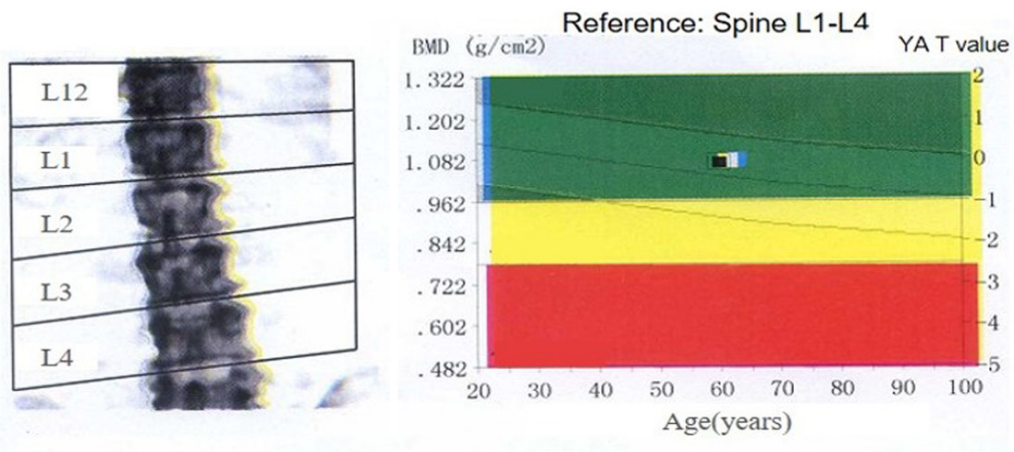
### Case 2

A 62-year-old man presented in March 2014 with a 4-year history of bone pain, which originated from heel bone in the absence of antecedent trauma in January 2009. He came to a hospital and diagnosed as lumbar disc herniation by the department of orthopaedics. But after 6 month, he also felt bone pain of knee and breast bone, and then he recognized the progressive exertional and generalized bone pain accompanied by difficulty of positional

A


Anterior
Posterior
Anterior
Posterior

B


L12
L1
L2
L3
L4
Reference: Spine L1-L4
BMD (g/cm2)
YA T value
1.322
1.202
1.082
.962
.842
.722
.602
.482
2
1
0
-1
-2
-3
-4
-5
20 30 40 50 60 70 80 90 100
Age(years)

C

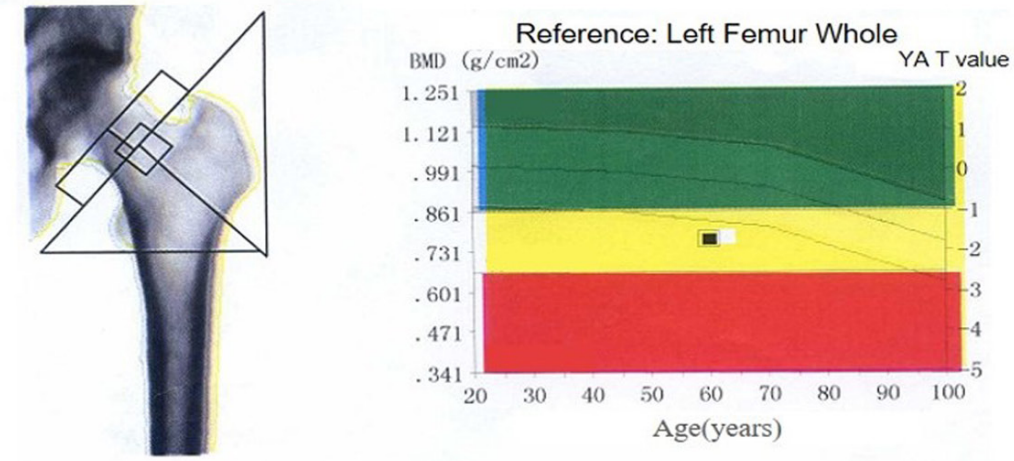

Reference: Left Femur Whole
BMD (g/cm2)
YA T value
1.251
1.121
.991
.861
.731
.601
.471
.341
2
1
0
-1
-2
-3
-4
-5
20 30 40 50 60 70 80 90 100
Age(years)

**Figure 2.** Radiographic findings of case 2. A. Whole-body 99mTc-methylene diphosphonate bone. B. Bone mineral density of spine. C. Bone mineral density of left femur.

**Table 3.** The bone mineral density measurement of Case 2

| Region | Baseline | | | The nearest follow-up | | |
|---|---|---|---|---|---|---|
| | BMD ($g/cm^2$) | T-score | Z-score | BMD ($g/cm^2$) | T-score | Z-score |
| L1-4 spine | 1.070 | -0.2 | 0.1 | 1.203 | 1.0 | 1.6 |
| Neck | 0.787 | -1.5 | -0.7 | 0.943 | 0.3 | 0.7 |
| Upper femoral neck | 0.562 | | | 0.679 | | |
| Trochanter | 0.601 | -1.9 | -1.5 | 0.780 | 0.4 | 0 |
| Femoral shaft | 0.907 | | | 0.956 | | |

change and walking. Hence, he changed to another hospital. Plain radiographs revealed multiple rib fractures and bone densitometry prompted severe osteoporosis. With therapy of taking calcium gluconate D3 and calcitriol therapy, the bone pain was not ameliorated. Finally, the patient was admitted to our hospital in March 2014. The patient had a history of chronic hepatitis B infection and abnormal liver function from June 2006, and had received Adefovir dipivoxil (ADV) (10 mg/day) since February 2007. Due to HBV DNA was constantly above 2000 copies/ml, lamivudine (LAM) was combined with ADV in January 2009 and HBV DNA level was less than 500 copies/ml after 3 months. On a physical examination in March 2014, he had generalized bone pain, especially compression on thorax, multiple ribs, both knees and ankles without trauma, bone metabolic disorders.

Laboratory investigations showed hypophosphatemia, hypouricemia, hyperglycemia, increased level of alkaline phosphatase (ALP) and decreased 25-hydroxyvitamin D level (**Table 1**). Serum aspartate aminotransferase, alanine aminotransferase, sodium, calcium, and potassium were normal (**Table 1**). Urinalysis showed positive protein and glucose in accordance with hyperglycemia (**Table 1**).

Bone scintigraphy using technetium-99m methylene diphosphate (99mTc-MDP) showed increased uptake in cervical vertebra, clavicle, sacrum, posterior iliac bones, lateral condyle and upper tibia (**Figure 2A**). Bone densitometry showed lightly low bone mineral density with a mean neck T-score of -1.5 standard deviations and a mean trochanter T-score of -1.9 standard deviations (**Table 3** and **Figure 2B**).

It was also diagnosed as Hypophosphatemic Osteomalacia induced by prolonged low-dose ADV therapy based on the hypophosphatemia, ALP increase, and increased uptake in multiple sections of bone scintigraphy and low bone mineral density. Therefore, ADV was replaced with entecavir (0.5 mg/d), combined with supplementation of phosphate, calcium carbonate, calcitriol. One month later, the bone pain had not markedly ameliorated accompanied by low serum phosphate (0.72 mmol/L). After 6 months later, the patient reported symptomatic improvement of bone pain. Follow-up physical examination in July, 2015 showed his serum level (phosphate 1.06 mmol/L, ALP 42.3 U/L, Uric acid 417.6 μmmol/L). Bone densitometry showed to be normal in October, 2015.

## Discussion

Osteomalacia is a metabolic bone disorder caused by impaired bone mineralization due to inadequate levels of available phosphate, calcium, and vitamin D. Hypophosphatemic osteomalacia, vitamin D-related osteomalacia, and osteomalacia with hypophosphatasia (low ALP) are the three main types of osteomalacia [30]. ADV, a nucleotide analog commonly used as an antiviral agent for the treatment of patients with chronic hepatitis B, displays a dose-dependent nephrotoxicity related to dysfunctions of the proximal renal tubule leading to phosphate wasting and osteomalacia.

The mechanisms associated with proximal renal tubule damage caused by ADV are not comprehensively understood. As known, ADV is transported and excreted mainly by proximal renal tubule, through the human renal organic anion transporter-1 (hOAT-1) and multidrug resistance protein 2 (MRP2) of renal tubular epithelial cells. Large doses or prolonged application of ADV can result in extensive intracellular ADV accumulation within renal tubular epi-

**Table 4.** Literature review of the patients with Hypophosphatemic Osteomalacia Induced by Low-dose Adefovir Therapy for CHB

| Ethnicity | Sex | Age (yr) | Duration of ADV use to | | Baseline serum/Follow-up serum | | | | | | | Treatment | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Onset symptoms (months) | Find hypophosphatemia (months) | Phosphate (mmol/L) | Creatinine (μmol/L) | Ca (mmol/L) | PTH (pg/ml) | 1,25(OH)2D3 (pmol/L) | 25(OH)D (nmol/L) | BMD (L spine) (T-score) | | |
| China | Male | 33 | > 24 | 48 | 0.38/1.24 | 84/98 | 2.1/2.43 | 11.6 | NA | 31.9 | NA | Switched with entecavir, phosphate supplementation | [8] |
| China | Male | 35 | > 24 | 84 | 0.6 | 116 | 2.24 | 27.4 | NA | 14.6 | NA | Switched with entecavir, phosphate supplementation | [8] |
| China | Female | 34 | > 24 | 36 | 0.64/1.04 | 127/76 | 2.21/2.24 | 38.4 | NA | 29.1 | NA | Switched with entecavir, phosphate supplementation | [8] |
| China | Female | 58 | > 24 | 24 | 0.53/1.05 | 119/129 | 2.03/2.37 | 68.6 | NA | 35.4 | NA | Switched with entecavir, phosphate supplementation | [8] |
| China | Female | 45 | > 24 | 72 | 0.58/0.92 | 116/87 | 2.11/2.31 | 95.3 | NA | 51.4 | NA | Switched with entecavir, phosphate supplementation | [8] |
| China | Male | 59 | 24 | 42 | 0.4 | 84 | 2.17 | 40.4 | NA | 13.5 | -3.4 | Switched with entecavir, phosphate supplementation | [9] |
| China | Male | 48 | 54 | 68 | 0.32/0.78 | 91.1/94.5 | 2.09/2.24 | 77.4/47.1 | NA | 49/48.5 | -4.8/-3.3 | ADV cessation | [10] |
| China | Female | 74 | 48 | 48 | 0.49 | 80 | 2.29 | 30 | 75.4 | NA | NA | ADV reduction | [11] |
| China | Male | 48 | 12 | 37 | 0.77/0.98 | 118 | 2.21 | 25.9 | NA | NA | NA | Switched with entecavir | [12] |
| China | Male | 22 | 38 | 48 | 0.37 | NA | 2.14 | 50.9 | NA | NA | NA | Switched with entecavir, phosphorus, cholecalciferol supplement | [13] |
| Chinese Cambodian | Female | 53 | 89 | 95 | 0.49/0.96 | NA | 1.94 | 86.5 | 17/118 | 29/132 | -3.8 | ADV cessation, phosphate supplementation | [14] |
| Chinese Cambodian | Male | 40 | 24 | 29 | 0.65 | NA | 2.2 | 39 | 57 | 61 | -3.5 | Switched with entecavir, phosphate supplementation | [14] |
| Korean | Male | 42 | 6 | 18 | 0.38/0.74 | 88.4 | 2.51 | 3.7 | 109.2 | NA | -2.8 | ADV cessation, phosphate supplementation | [15] |
| Korean | Male | 66 | 36 | 36 | 0.54/0.74 | 106.1 | 2.08 | 24.2 | 129.2 | NA | NA | ADV cessation, phosphate supplementation | [16] |
| Korean | Male | 47 | 32 | 38 | 0.42/0.64 | 119.4/81.3 | 2.1 | 20 | 49.6 | NA | -3.4 | ADV cessation, phosphate supplementation | [17] |
| Korean | Male | 62 | 48 | 72 | 0.23/0.58 | 131.7 | 2.1 | 28.2 | NA | NA | -1.9 | Switched with entecavir, phosphorus supplement | [18] |
| Korean | Male | 54 | 41 | 59 | 0.36 | 99 | 2.3 | 17.4 | NA | NA | -2.2 | ADV cessation, phosphorus, calcitriol supplement | [18] |
| Korean | Male | 61 | 53 | 56 | 0.61 | 114.9 | 2.28 | 14.7 | 140.9 | NA | -3.3 | ADV cessation | [19] |
| Korean | Male | 43 | 48 | 84 | 0.32 | 106.1 | NA | NA | NA | 27.5 | -4.86 | Switched with entecavir, supplementation of phosphate, calcium carbonate and vitamin D3 | [20] |
| Korean | Male | 43 | NA | NA | 0.51 | 114.9 | 2.43 | 42.9 | 133.9 | NA | -5.1/-1.8 | Switched with entecavir, alendronate | [21] |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Korean | Male | 42 | 81 | 84 | 0.52 | 141.4 | 2.4 | 21.1 | 80 | NA | -2.1/0.75 | Switched with entecavir, alendronate | [21] |
| Japanese | Female | 57 | 9 | 14 | 0.61 | 77.8 | NA | NA | NA | NA | NA | ADV reduction, phosphorus supplement | [22] |
| Japanese | Male | 48 | 20 | 50 | 0.45/0.96 | 97.3/114.9 | 1.98 | 85 | 55.3 | NA | NA | ADV reduction, phosphorus supplement | [23] |
| Japanese | Female | 70 | 12 | 30 | 0.48 | 84 | 2.15 | 24 | 34.5 | NA | -3.7 | Switched with entecavir, alphacalcidol | [24] |
| Japanese | Male | 60 | 36 | 18 | 0.54 | 118.5 | 2.25 | 28.6 | 62.3 | NA | -2 | Phosphate supplementation, alphacalcidol | [24] |
| Japanese | Male | 48 | 36 | 36 | 0.64/0.74 | 141.1 | NA | NA | 43.5 | NA | NA | ADV reduction, calcitriol | [25] |
| Japanese | Male | 62 | 47 | 60 | 0.64/NA | 61.9 | NA | 19 | 100 | NA | NA | Switched with entecavir, eldecalcitol | [26] |
| Japanese | Male | 56 | NA | 48 | 0.71/NA | 132.6 | NA | NA | NA | NA | NA | ADV reduction | [27] |
| Japanese | Male | 58 | 71 | 88 | 0.44/0.99 | 93.7/93.7 | 2.41 | 26 | 116 | NA | NA | ADV reduction, phosphate, alfacalcidol | [28] |
| Japanese | Male | 64 | 36 | 96 | 0.45/0.77 | 114 | NA | 59 | 35 | NA | NA | ADV reduction, eldecalcitol and bicarbonate | [29] |
| Unspecified | Male | 68 | 20 | 38 | 0.72 | 132.6 | NA | 20 | NA | NA | -4.8/-3.8 | Switched with entecavir, phosphate, cholecalciferol | [30] |
| Singapore | Male | 53 | 56 | 59 | 0.64 | 57 | 2.11 | 38 | NA | 58.8 | NA | ADV reduction | [31] |
| Unspecified | Male | 58 | 8 | 8 | 0.3 | 166.4 | NA | NA | NA | NA | NA | ADV cessation | [32] |
| China (our case) | Male | 46 | 84 | 120 | 0.45/0.86 | 102.5/104.7 | 2.07/2.25 | 16.8/39.5 | NA | 36.7/36.9 | -3.6/-0.1 | Switched with entecavir, supplementation of phosphate, calcium carbonate and vitamin D3 | |
| China (our case) | Male | 60 | 24 | 134 | 0.76/1.06 | 97.4/63.9 | 2.25/2.33 | 14.3/38.1 | NA | NA | -2.9/0.9 | Switched with entecavir, supplementation of phosphate | |

thelial cells [34, 35]. The high concentration of ADV can inhibit mitochondrial DNA synthesis in the proximal tubular epithelium, leading to renal tubular damage and nephrotoxicity [36, 37].

Literature review revealed 33 other cases of hypophosphatemic osteomalacia induced by low-dose (10 mg daily) ADV [8-32] (**Table 4**). The age of these 35 patients including two cases of us varied from 22 to 74 years, with a mean of 51.9 years. The gender ratio of male and female patients was 4:1. Most cases (32/35) involved subjects of East-Asian ethnicity, including Chinese, Korean, Japanese, and Cambodian [8-29]. The one of other three cases was from Singapore and the rest two cases did not specify ethnicity [30-32].

Symptoms of 28 cases became clinically evident after a median 36 months (range 6-89 months) of ADV treatment. Major symptoms began with generalized bone-pain and muscle-weakness, and then deteriorated to mobility difficulties. These early signs of osteomalacia are often misdiagnosed as other disease such as polymyalgia rheumatica, arthritis, or fibromyalgia. Hypophosphatemia usually takes longer to find (median 48 months of ADV treatment, range 8-134 months). The median serum phosphate was 0.51 mmol/L on diagnosis ranged from 0.23 to 077. Most of these cases had several characteristics of renal Fanconi syndrome, including low serum level of calcium (median 2.17 mmol/L, range 1.94-2.51 mmol/L) (27/35) and PTH (median 27.8 pg/ml, range 3.7-95.3 pg/ml) (32/35). Hypophosphatemia and hypocalcemia can lead to a generalized defect in bone mineralization, causing excessive accumulation of under mineralized bone matrix and a lack of structural support for the periosteum. This generalized softening of the bone may explain aches and pains in bones, muscles, and joints.

Bone scintigraphy using 99mTc-MDP showed increased uptake in the calvarium, mandible and anterior rib are highly suggestive of underlying metabolic disorder. Bone densitometry of 17 cases showed abnormally low bone mineral density with a median lumbar T-score of -3.4 (range -1.9 to -5.1). The radiological findings help to the diagnosis of ADV-induced hypophosphatemic osteomalacia. Although these features are not specific for osteomalacia and may be seen in other metabolic disorders, including renal osteodystrophy and primary hyperparathyroidism, the combination of lab findings and radiological features on bone scintigraphy are diagnostic of underlying hypophosphatemic osteomalacia.

After cessation or reduction of ADV, serum phosphate level improved to median 0.92 mmol/L (range 0.58-1.24 mmol/L), and clinical symptoms significantly improved in all cases with obvious improvement in other serum parameters and BMD T/Z-score. Therefore, the damage of proximal renal tubule induced by low-dose ADV may be reversible. However, serum phosphate level of some patients remained under the normal range after discontinuation of ADV. Almost without exception, these patients just stopped or reduced using ADV instead of transforming to entecavir [15-18, 25, 29]. Long-term follow-up of phosphate metabolism after discontinuation of ADV and entecavir replacement needs further study. Undoubtedly, discontinuation of ADV offers the best chance of recovery from ADV-induced hypophosphatemic osteomalacia and replacing ADV with entecavir may be a better alternative.

Hypophosphatemic osteomalacia and renal Fanconi syndrome can be induced with long-term low-dose ADV therapies. The symptoms and the hypophosphatemia improved after discontinuation of ADV coupled with supplementation with phosphate in most cases and replacing ADV with entecavir may be a better alternative. CHB patients taking long-term ADV therapy (daily dose of 10 mg) daily should receive regular monitor of the renal function and serum phosphate level. Clinicians prescribing ADV over a long period of time should be aware of the late onset of hypophosphatemic osteomalacia and renal Fanconi syndrome.

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## Disclosure of conflict of interest

None.

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