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### Homocystinuria a rare cause of low BMD in young patients: A case report with literature review

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#### ABSTRACT

**Background:** Homocystinuria is a rare autosomal recessive disorder in the metabolism of sulfur-containing amino acid caused by mutations in the cystathionine beta-synthase gene which encodes the pyridoxine (Vitamin B6) dependent enzyme cystathionine beta-synthase. It is characterized by significant elevations in plasma and urine homocysteine concentrations, which could be associated with increased risk of fracture.

**Methods:** We describe a case of Homocystinuria who suffered from a low impact patellar fracture with a literature review to highlight the critical relationship between homocysteine level and bone health.

**Results:** We reported a 36-year-old female with a diagnosis of Homocystinuria due to pyridoxine (B6) unresponsive severe Cystathionine Beta-Synthase deficiency. After a minor knee injury she developed a right patellar fracture and her X-ray revealed osteopenia. On examination, she has severe scoliosis in the spine with bilateral aphakia (absence of the lens of the eye). Her labs showed, persistent high Homocysteine above 100 umol/L, Methionine: 383 umol/L (10-42), Vitamin D 12 ng/ml. Her spine X-ray revealed very severe scoliosis with osteopenia but no vertebra fracture. Her DXA scan showed her Z-Score was within the expected range for her age in hip, spine and 1/3 radius areas, however her ultra-distal radius Z-Score was -4.0. Her Homocystine level was mostly higher than 100 due to non-compliance with dietary advice and treatment. High homocysteine levels in Homocystinuric patients impair the function of bone cells that regulate bone remodeling as well as bone material properties such as collagen cross-linking. This imbalance between bone

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formation and resorption may lead to a low BMD and fracture in patients with homocystinuria. Interestingly, even in general population hyperhomocystinemia with a plasma level of more than > 13 nmol/ml has been found to be associated with low BMD and an increased risk of fractures that is independent of BMD. Deficiencies in vitamin B6, B12, or folate can lead to increased serum levels of Homocysteine as these vitamins act as co-factors for various enzymes involved in homocysteine metabolism. This can be easily rectified with dietary intervention.

**Conclusion:** In young patients with a fracture or low bone mineral density, hyperhomocystinemia could play an important role in the pathogenesis. This should be included in the work up for secondary causes for osteoporosis for this age-group. Simple dietary measures and vitamin B6, folate and B12 supplement should be considered as adjuvant therapeutic option for any patient with osteoporosis and fractures, if deficient. Possibly the BMD of the ultra-distal radius is the most sensitive to detect bone changes in these patients.

## INTRODUCTION:

Clinical manifestations of Homocystinuria include developmental delay, Marfanoid appearance, osteoporosis, ocular abnormalities, thromboembolic disease, and severe premature atherosclerosis<sup>1</sup>.

High homocysteine levels are associated with low bone mineral density (BMD) and osteoporotic fractures<sup>2, 3, 4</sup>. The role of homocysteine levels as an independent risk factor for fracture was previously established<sup>5</sup>. Here we are reporting a case of Homocystinuria with low bone mineral density with a literature review highlighting the critical relationship between homocysteine level and bone health.

## CASE REPORT:

Here we present the case of a 36-year-old Saudi lady who was diagnosed with a classical Homocystinuria, with pyridoxine (B6) unresponsive severe Cystathionine beta-synthase (CBS) deficiency. There was no family history of a similar condition.

She was referred to our rheumatology clinic from orthopaedics because of a low trauma fracture for her right patella (figure 1). She gave a history of minor trauma to the right knee, and her X-ray

revealed small fissures of the right patella, with osteoporotic looking bones. She was under the care of orthopaedics because of her spinal deformity (figure 2). She has no family history of similar condition.

She has abysmal compliance with the recommended diet and the medications for her condition. On examination, there was severe scoliosis in the spine, and bilateral aphakia (absence of the lens of the eye). Her latest labs showed, Homocysteine: 46 umol/L (4-10), but most of the times it was above 100 umol/L and sometimes more than 250, Methionine: 383 umol/L (10-42), Vitamin D 12 ng/ml (30-80). Her spine X-ray revealed very severe scoliosis, with the osteoporotic architecture of the imaged bone with no evidence of vertebra collapse. She has been prescribed Alendronic acid in combination with vitamin D once a week, and she was noncompliant to both medications and referred to us.

Because of her pathologic fracture of the patella and the X-ray findings and the Homocystinuria, DXA scan has been done.

DXA scan revealed BMD of left femur neck with 0.771g/cm<sup>2</sup> with a T score of -1.9 and Z score -

1.4 (figure 3) and of lumbar spine T-Score -1.1 and Z-Score -0.7 with VFA revealed the deformity but with no fractures (figure 4 & 5). Interestingly the T-score for ultra-radius was very low at -4.0 and the Z-Score -4.0 which represent mainly cancellous bone, but the 33% radius T-Score was normal at -0.1 and Z-Score

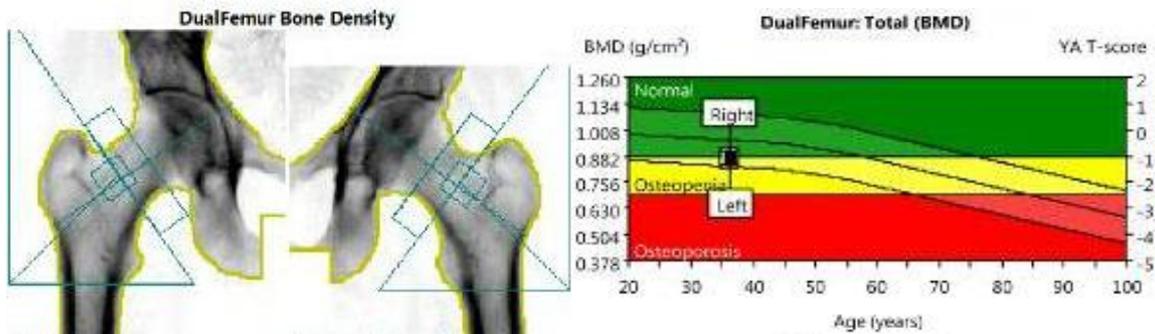
0.1 which represent cortical bone (figure 6). Accordingly, she has a significant low bone mass density for her age. She was started on vitamin D3 10,000 international unit twice a week and calcium. The plan is to try to maintain her homocysteine levels below 100umol/L.



Figure 1: fracture right patella.



Figure 2: Severe scoliosis and osteopenic bones.



Densitometry: USA (Combined NHANES/Lunar)			
Region	BMD (g/cm <sup>2</sup> )	YA T-score	AM Z-score
Neck Left	0.771	-1.9	-1.4
Neck Right	0.836	-1.4	-0.9
Neck Mean	0.804	1.7	-1.1
Neck Diff.	0.065	0.5	0.5
Total Left	0.861	-1.2	-0.8
Total Right	0.878	-1.0	-0.6
Total Mean	0.870	-1.1	-0.7
Total Diff.	0.017	0.1	0.1

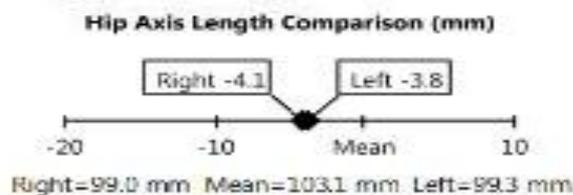
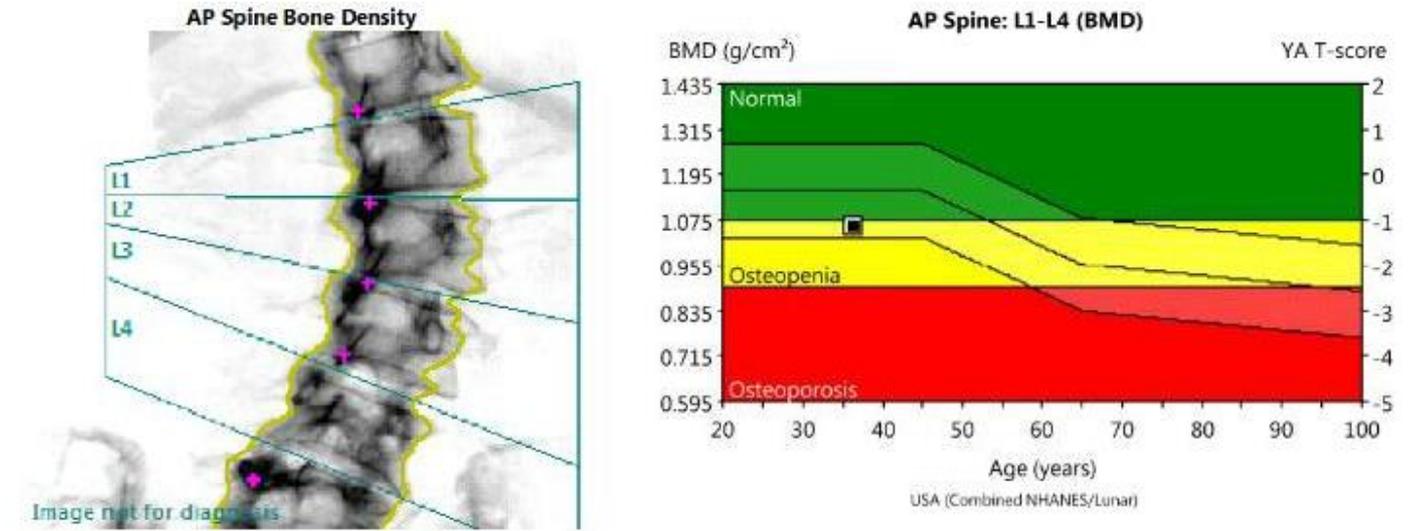


Figure 3: BMD for hips



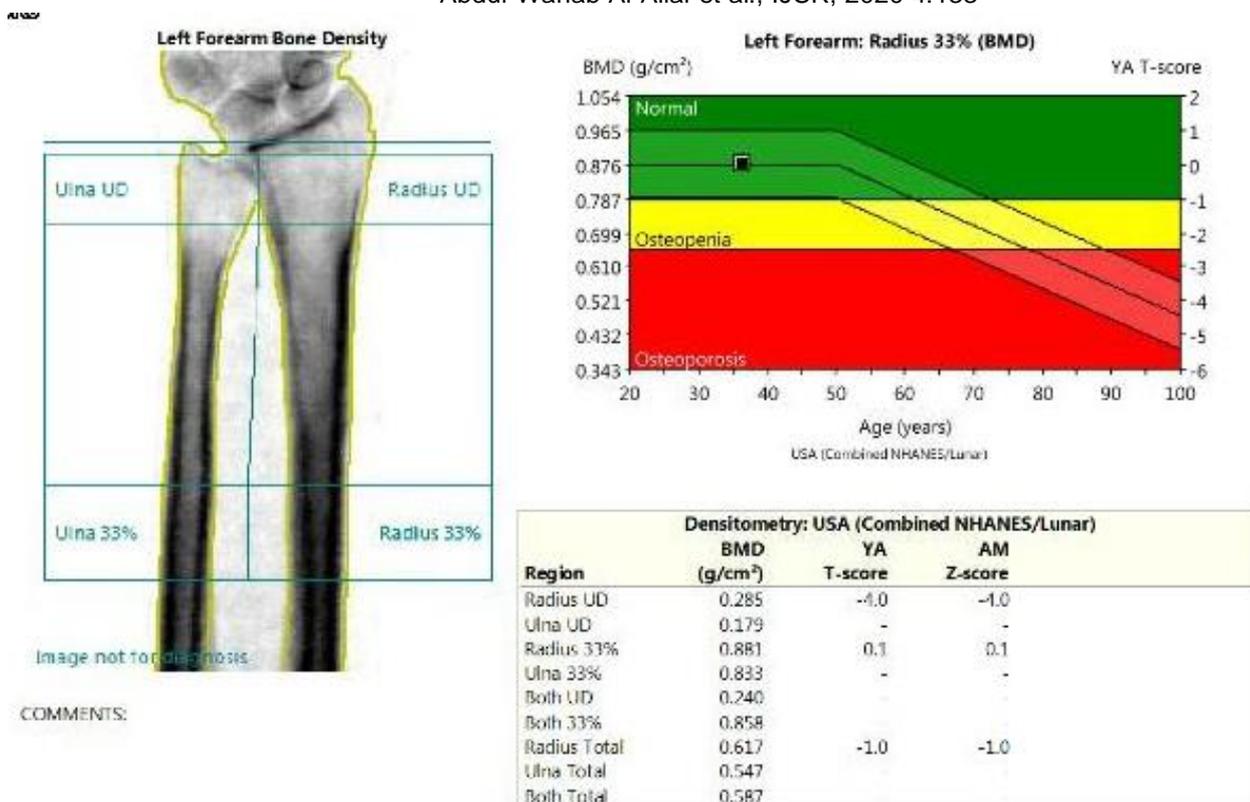
**ANCILLARY RESULTS: AP Spine**

Region	BMD (g/cm <sup>2</sup> )	YA (%)	YA T-score	AM (%)	AM Z-score	BMC (g)	Area (cm <sup>2</sup> )	Width (cm)	Height (cm)
L1	1.053	92	-0.7	96	-0.4	11.97	11.37	4.3	2.67
L2	1.097	91	-0.9	94	-0.6	13.57	12.37	4.3	2.88
L3	1.048	87	-1.3	90	-1.0	14.14	13.48	4.4	3.06
L4	1.051	87	-1.3	90	-1.0	14.81	14.09	4.7	2.97
L1-L2	1.076	92	-0.8	95	-0.5	25.54	23.74	4.3	5.54
L1-L3	1.066	90	-0.9	93	-0.6	39.68	37.23	4.3	8.61
L1-L4	1.062	89	-1.1	92	-0.7	54.49	51.32	4.4	11.58
L2-L3	1.072	88	-1.2	91	-0.8	27.71	25.86	4.4	5.94
L2-L4	1.064	88	-1.2	91	-0.9	42.52	39.95	4.5	8.91
L3-L4	1.050	87	-1.3	90	-1.0	28.95	27.57	4.6	6.04

**Figure 4: BMD for the spine**



**Figure 5: VFA Spine**



**Figure 6: BMD for the forearm.**

## DISCUSSION

Interestingly in our case, we found that the ultra-distal radius has the lowest BMD with a Z-score of -4.0 with normal radius 33% with low MBD of the hip and to less extent the spine. We suggest that possibly the ultra-radius may be the most sensitive site for changes in BMD in such patients. We also suggest that we cannot rely on the spine findings due to the deformity

Homocystinuria is an autosomal recessive disorder in the metabolism of sulfur-containing amino acid caused by mutations in the cystathionine beta-synthase (CBS) gene which encodes the pyridoxine (Vitamin B6)-dependent enzyme CBS<sup>1</sup>. Deficient cystathionine beta-synthase activity disrupts methionine metabolism and results in accumulation of Homocysteine and MethionineMethionine in the blood and urine. Clinical manifestations are variable and can include developmental delay, intellectual disability, Ocular defects (ectopia lentis, myopia), thromboembolism, and skeletal abnormalities. The skeletal features of Homocystinuria include scoliosis, vertebral

changes, genu varum, metaphyseal widening, sternal deformities, arachnodactyly and reduced bone density<sup>6-12</sup>.

Therapeutic reduction of homocysteine levels via MethionineMethionine or protein-restricted diet and betaine or pyridoxine administration can improve clinical outcomes<sup>13, 14</sup>.

The severity of complications primarily depends on two main factors: the age, at which the patient is initially diagnosed, and the amount of the residual cystathionine beta-synthase activity. Roughly half of the Homocystinuria patient population clinically responds to high doses of pyridoxine (vitamin B<sub>6</sub>), a precursor of Pyridoxal 5-Phosphate (PLP), which increases residual cystathionine beta-synthase activity. This could result, in a limited number of cases, to the normalization of plasma metabolites. In the remaining patients, however, metabolic control can be achieved only by MethionineMethionine (protein)-restricted diet with cysteine supplementation. The diet of Homocystinuria patients often combined with betaine, which serves as a methyl donor for an alternative, liver-

dependent conversion of Homocysteine back to Methionine via betaine homocysteine methyltransferase <sup>15</sup>.

Most Homocystinuria (HCU) patients diagnosed in adulthood have severe osteoporosis, and frequently Homocystinuria is mentioned as a cause of osteoporosis <sup>16</sup>. Although not evident at birth and during infancy, young children skeletal abnormalities are among the most striking phenotypical features in HCU patients <sup>17</sup>. Notably, a thinning and lengthening of the long bones result in tall and thin individuals with an appearance similar to that of Marfan's syndrome <sup>18</sup>. However, osteoporosis, particularly of the spine, which is associated with scoliosis, is one of the distinguishing features of the disease and the most consistent skeletal change in HCU patients <sup>18</sup>. It has been described as early as at the age of one year with a frequency often as high as 90%–100% among homocystinuria individuals thus allowing initial diagnosis solely based on a radiological examination <sup>19</sup>. A natural history study showed that half of the untreated HCU patients have radiological evidence of spinal osteoporosis by 15 years of age <sup>18</sup>. DXA measurement in late-diagnosed HCU patients showed similar findings of osteoporosis in the spine and femur for both younger and older patients regardless of the severity of the disease <sup>20</sup>.

If Homocystinuria is well controlled in children, bone mineral density (BMD) will be in the normal range <sup>16</sup>. In contrast, moderate Hyperhomocysteinemia induced by short-term dietary methionine overload alters the bone microarchitecture and collagen features during growth <sup>21</sup>. Homocysteine affects both BMD and material properties such as collagen post-translational modification. Even without a congenital abnormality in cystathionine beta-synthase, mildly elevated serum levels of Homocysteine in the general population (plasma homocysteine level > 13 nmol/mL) are associated with an increased risk of vertebral and hip fractures that is independent of BMD <sup>5</sup>. The relation of elevated total plasma

homocysteine levels and hip fracture was studied in a group of older adults who were enrolled in the Framingham study. It was found that plasma total homocysteine concentrations, an easily modifiable factor through dietary intervention, were associated with increased risk of hip fracture in both men and women <sup>2</sup>. In the general population, deficiencies in vitamin B6, B12, or folate cause increased serum levels of Homocysteine because these vitamins act as co-factors for various enzymes involved in homocysteine metabolism. The enzyme 5-methyltetrahydrofolate-reductase (MTHFR), whose coenzyme is vitamin B12, plays a vital role in homocysteine metabolism. A decrease in MTHFR activity increases the serum level of Homocysteine. Significant determinants of MTHFR activity include genetic polymorphisms and vitamin B12 deficiency. The MTHFR polymorphism C677T (Ala/Val) is characterized by a cytosine-to-thymidine substitution at nucleotide 677, which in turn causes an alanine-to-valine substitution in the amino acid chain. This change decreases the heat stability of the enzyme, substantially decreasing its activity <sup>22</sup>. Thus, high homocysteine levels might impair the function of bone cells that regulate bone remodelling as well as bone material properties such as collagen cross-linking <sup>23</sup>.

In vitro studies showed that high homocysteine levels could modulate the bone remodelling process by increasing osteoclast activity <sup>24-26</sup>; inducing Apoptosis in bone marrow stromal cells <sup>27-29</sup>, osteocytes <sup>30</sup>, and osteoblasts <sup>31</sup>; and inhibiting osteoblastic differentiation <sup>2, 22</sup>. Homocysteine induces Apoptosis in bone marrow cells via the action of reactive oxygen species and NF-kappa B <sup>27</sup>. The intracellular reactive oxygen species generated by Homocysteine stimulate osteoclast formation <sup>24</sup>. Because the antioxidant N-acetyl cysteine blocks such adverse effects on bone cells <sup>24</sup>, an increase in reactive oxygen species induced by Homocysteine may play an essential role in the increase in bone resorption in Hyperhomocysteinemia. Homocysteine also

induces Apoptosis in osteoblastic MC3T3-E1 cells via the induction of intracellular reactive oxygen species in a homocysteine dose-dependent manner<sup>31</sup>. In previous studies, an increased homocysteine level appears to be a strong and independent risk factor for osteoporotic fractures in older men and women<sup>3</sup>.

This imbalance between bone formation and resorption may cause low BMD in patients with Homocystinuria and in the general population of individuals who exhibit mildly elevated Hyperhomocysteinemia.

### CONCLUSION:

In young patients with a fracture or low bone mineral density, Homocystinuria should be considered. More attention should be given to the measurement of homocysteine concentration in the young general population with fracture and or low bone mineral density. Simple dietary measures and drug intervention can alter the prognosis for these patients. Possibly the BMD of the ultra-radius is the most sensitive to detect bone changes in these patients.

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