Association between osteoporosis and acute leukaemia: a single centre study from Baghdad

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ABSTRACT

INTRODUCTION: Osteoporosis is a major growing public health with significant impact that crosses medical, social, and economic lines.

OBJECTIVE: To study the possible association between osteoporosis and acute leukaemia .

METHODS: This case control conducted out-patient consultation clinic of Department of Haematology and Unit of Rheumatology in Baghdad Teaching Hospital in Baghdad City, Iraq from July 2013 to July 2014. The study included 100 patients who were newly diagnosed with acute leukaemia before starting treatment and 50 healthy controls, who were age and sex matched with the patients. Dual Energy X ray absorptiometry were performed.

RESULTS: The mean age of patients was 30.49 ± 7.76 years and for controls was 27.30 ± 5.87 years.

The results of BMD of femur and lumbar in patients was less than in control. Z-score lumbar spines of patients versus control were normal in 40, osteopenia in 48 and osteoporosis in 12. While in control all 43 control are normal, 7 osteopenia. Z-score neck of femur in patients versus control was normal in 34, osteopenia in 55 and osteoporosis in 11. While in control all 45 control were normal, 5 osteopenia.

CONCLUSION: Osteoporosis was relatively frequent and significantly associated with acute leukaemia at lumbar spine and femoral neck.

Key words: Osteoporosis, Acute leukaemia, Bone mineral density, Leukaemia.

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INTRODUCTION

Osteoporosis is a silent condition where the bones are weak and prone to fracture, characterized by low bone density and a deterioration of bone microarchitecture that reduces bone strength and increases the risk of fracture. WHO defines osteoporosis as a T score ≤ -2.5. Severe osteoporosis is defined as T score ≤ -2.5 plus the presence of at least one fracture. Globally, osteoporosis is by far the most common metabolic bone disease, and it is estimated to affect over 200 million people worldwide.[1] An estimated 75 million people in Europe, the United States and Japan have osteoporosis.[2] Approximately 1 in 2 women and 1 in 5 men older than 50 years will eventually experience osteoporotic fractures.[3] Many risk factors have been reported to be associated with osteoporosis.[4]

Osteoporosis is silent because there are no symptoms. When osteoporosis is established, a fracture can occur even after a minor injury, such as a fall. The most common fractures occur at the spine, can produce loss of height, pain, dowager's hump, and increased risk of fracture and hip fractures, in particular, may lead to chronic (long-term) pain and disability,and even death. The biomechanical consideration in hip and spine fractures is important explanation. The Low bone mineral density is strongly associated with hip and vertebral fractures, but not

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foot fracture. Most fractures of the hip result from a fall, whereas smaller proportions of fractures vertebrae follow a fall. Frail people are likely to fracture their hip or proximal humerus, while healthy, active people tend to fracture their distal forearm.[5]

Dual-energy x-ray absorptiometry (DEXA) is the most widely used bone mass measurement technique. DEXA affords a fast, reliable, accurate measurement of bone mineral density (BMD) that involves low radiation exposure. DEXA is currently the "gold standard" for both patient care and clinical investigation in osteoporosis.[6]

Osteoposrosis is diagnosed according to the World Health Organization (WHO) Criteria for osteoporosis. If age of the patient is 45 years and below, then the Z score will be considered for diagnosis of osteoporosis. If Z scores equals to -2.0 or lower, then the patients will be considered to have osteoporosis. If the age of the patient more than 45 years, then the T score will be considered for diagnosis of osteoporosis. If the T score is ≤–2.5, then the patient is osteoporotic. However if patients age above 45 years and T The World Health Organization (WHO) ≤–2.5 with the presence of at least one fracture then the patient is considered to have severe osteoporosis.[7]

Acute leukaemia (AL) is the result of a malignant events occurring in an early haematopoietic precursor. The affected cell gives rise to progeny that fail to differentiate but continue to proliferate in an uncontrolled fashion, As a result, immature myeloid cells in acute myeloid leukaemia (AML) or lymphoid cells in acute lymphoblastic leukaemia (ALL) — often called blasts— rapidly accumulate and progressively replace the bone marrow, diminishing the production of normal red cells, white cells, and platelets, With time, the leukaemic blasts pour out into the blood stream and eventually occupy the lymph nodes, spleen and other vital organs.[8]

Anaemia is present at diagnosis in most patients and causes fatigue, pallor, and headache. Thrombocytopenia is usually present, usually in the form of petechiae, ecchymoses, bleeding gums, epistaxis, or haemorrhage. Enlargement of lymph nodes, liver, and spleen are common at diagnosis. Bone pain, thought to result from leukaemic cell infiltration of the periosteum or expansion of the medullary cavity, is a common complaint, particularly in children with ALL. Leukaemic cells sometimes infiltrate the skin and result in a raised, non-pruritic rash, a condition termed Leukaemia cutis.[12]

In literature, the reduced bone mineral density (BMD) has been largely reported at diagnosis and during treatment of AL. Possible explanation might be related to the disease process itself, steroid therapy, intensive chemotherapy, lesion of endocrine organs that control bone accretion, immunosuppressive agents after haemopoietic stem cell transplant , poor nutrition, and decreased physical activity.[9] In leukaemia , invasion of leukaemia cells results in osteopenia mediated by an expansion of osteoclasts causing increased bone resorption and a concomitant reduction of osteoblastic activity.[10] Because Osteoporosis is a major growing public health problem with impact that crosses medical, social, and economic lines, and up to the best of our knowledge there is no previous study that assessed osteoporosis among Iraqi patients with acute leukaemia, This study was designed to evaluate the possible association between osteoporosis and acute leukaemia among sample of Iraqi patients diagnosed with acute leukaemia.

METHODS

Setting and Study Design: A case control study was conducted at out-patient consultation clinic of Department of Haematology and Unit of Rheumatology in Baghdad Teaching Hospital in Baghdad City, Iraq from July 2013 to July 2014.

Ethical Consideration: The study protocol was conducted according to the regulation of the Iraqi Ministry of Health in Iraq. Ethical approval was obtained from Ethics committee of Baghdad University College of Medicine, Medical Department. Written consent was obtained from each participant in the study after explaining all relevant details of the study.

Definition of the cases, inclusion and exclusion criteria: Patients who were diagnosed at the department of haematology as acute leukaemia according to their protocol during the studied period were enrolled in this study. We included only patients who were between 20-50 years and were newly diagnosed and did not used any medications for their leukaemia. Patients with

the following condition were excluded from the study in order not to affect the interpretation of the results:

1. Diabetes mellitus.
2. Cushing syndrome.
3. Thyrotoxicosis.
4. Rheumatological conditions like rheumatoid arthritis or ankylosing spondolytis.
5. History of gastrectomy.
6. History of bilateral oophorectomy.
7. History of fractures spine or hip and other sites.
8. History of using the following drugs; corticosteroid, thyroxin, anticoagulant, contraception, rifampicin, anticonvulsant, antiacid.
9. Family history of metabolic disease.
10. History of smoking, alcohol drinking, eating diet rich with calcium.
11. History of prolonged immobility.

The study included 100 patients with newly diagnosed acute leukaemia before starting treatment, and 50 healthy controls, who are age and sex matched with the patients. Patients age ranged between 20 to 50 years.

Sampling method: a convenient sample of consecutive patients with acute leukaemia and apparently healthy controls were involved in this study.

Outcome: Those who fulfilled the inclusion and exclusion criteria have sent for the assessment of MBD by dual X-ray absorptiometry (DEXA scan) and osteoporosis was determined according to the WHO Criteria. Also, the fracture of hip and spine was evaluated by X-ray of hips and lateral dorso-lumbar spine read by an expert radiologist blinded to the result of DEXA. A similar protocol was applied for participants in the control group.

Controls selection: Apparently healthy, aged and gender matched persons has been selected from the relatives of other patients who were attending the rheumatology Unit. A good history taking and proper clinical examination with relevant investigations whenever indicated have been done for all participants in the control group. Those who tend to have similar excluding conditions mentioned for the patients group were excluded from the control group.

Procedure: Height of patients was measured by tape measure from the side of the patient without shoes in standing position; weight was taken by electronic scale and the patient in standing position.

Methods of data monitoring: Blood samples were aspirated for complete blood count, fasting blood sugar, serum calcium, serum phosphorus, serum alkaline phosphatase, erythrocyte sedimentation rate, thyroid function test, and parathyroid hormone. X-ray of hips and lateral dorso-lumbar spine for fracture. Dual energy X-ray absorptiometry (DEXA scan) The DEXA type is DXA STRATOS, fixed type, K14015D418, French. Request was sent to take T-score at spine L1-L4, right femur neck, Z-score of both.

Statistic: Statistical package for social science version 18 (SPSS18) was used for both data entry and data analysis. Continuous variable presented as mean ± SD and discrete variable presented as number (%). Student t- test was

Table 1: Comparison of BMD results of cases versus control.

Parameters	Cases	Control	P-value*
BMD (gm/cm2) lumber	0.99 ± .16	1.35 ± .19	<0.001
BMD (gm/cm2) femur	0.85 ± .14	.98 ± .30	0.001

* Student t-test was used; BMD= bone mineral density

Table 2: Comparison of Z score of lumbar spine of cases versus control.

	Parameters	Cases (%)	Control (%)	P value*
Z score lumber (L1-L4)	Normal	40 (40)	43(86)	<0.001
	Osteopenia	48 (48)	7 (14)	
	Osteoporosis	12 (12)	0 (0)	
Total		100	50	

Odds ratio of lumbar spine osteoporosis in cases compared to controls = 26.85 p= 0.02
Odds ratio of lumbar spine osteopenia incases compared to controls =7.37 p<0.0001
* Fisher's Exact Test was used

Table 3: Comparison of Z score of neck of femur of cases versus control.

	Parameters	Cases (%)	Control (%)	P-value*
Z score neck of femur	Normal	34 (34)	45 (90)	<0.001
	Osteopenia	55 (55)	5(10)	
	Osteoporosis	11 (11)	0 (0)	
	Total	100	50	

* Fisher's Exact Test was used
Odds ratio of neck of femur osteoporosis in cases compared to controls=30.33 p=0.02
Odds ratio of neck of femur osteopenia in cases compared to controls=14.56 p<0.0001

used to test the significance of association of continuous variable and Fisher exact test was used for discrete variable. p< 0.05 was statistically significant.

RESULTS

A total of 100 patients involved in this study, 62(62%) were males and 38(38%) were females. Mean age of patients were 30.49 ± 7.76 years, and BMI 20.87 ± 1.37 kg/m^2, Total number of controls in this study was 50, of them 21 (42%) were male, and 29 (58%) were females. Mean age of controls was 27.30 ± 5.87 years, and mean BMI was 24.43 ± 3.44 kg/m^2.

BMD femur and lumber in patients is significantly less than controls (P value <0.05, **Table 1**)

Z-score lumbar spines of patients versus control were normal in 40, osteopenia in 48 and osteoporosis in 12. While in control all 43 control were normal, 7 osteopenia, so there was strong relationship between leukemia and decrease in Z-score (lumber) (P value<0.05). (**table 2**)

Z-score neck of femur in patients versus control was normal in 34, osteopenia in 55 and osteoporosis in 11. While in control all 45 control were normal, 5 osteopenia. So, there was strong relationship between leukaemia and decrease in Z-score (neck of femur) (P value<0.05). (**table 3**).

DISCUSSION

After searching the available literature, we could not find a similar case control study that assesses the possible association between osteoporosis and acute leukaemia among adult Iraqi patients.

In this study, 12% of the adult patients with acute leukaemia had osteoporosis at the time of diagnosis. The low BMD at time of diagnosis of these patients may be related to the Leukaemic cell infiltration to the spongious tissue of the bone, or the paracrine excretion of lymphokines and parathormone-related peptides, or parathormon excreted from leukaemic cells or ectopically produced.[11]

A similar result was reported by Rayar et al[12] who found that 11% of children with acute leukaemia had osteoporosis at time of diagnosis. Donmez et al[13] evaluated bone health by measuring BMD after ALL treatment in children and found 7.7% of the patients had osteoporosis. The lower prevalence in that study possibly is due to lower sample size and they assessed patients after treatment not at time of diagnosis.

Ruchlemer et al[14] performed a pilot study to identify bone loss in haematological malignancies in adults. They found that Adult patients with haematological malignancies have significant bone loss compared to a normal age-matched population and stated that osteoporosis in Acute leukaemias was 20% the difference in prevalence could be due to the lager sample size used in that study in addition to the treatment used.

The main limitation of this study was first the small sample size. Second, we did not follow up the patient to see the impact of medications on the BMD. Third, the short duration of the study. However, the current study is the first study among adult Iraqi patients with leukaemia that evaluated BMD at time of diagnosis with strict inclusion and exclusion criteria.

CONCLUSION

Osteoporosis was relatively frequent and significantly associated with acute leukaemia at lumbar spine and femoral neck among adult Iraqi patients.

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Abbreviation list: Acute Leukaemia (**AL**), Acute Lymphoblastic Leukaemia (**ALL**), Acute Myeloid Leukaemia (**AML**), Body Mass Index (**BMI**), Bone Mineral Density (**BMD**), Dual-Energy x-ray Absorptiometry (**DEXA**), Kilogram per square meter (**kg/m²**), Statistical Package for Social Science Version 18 (**SPSS18**), Standard Deviation (**SD**), World Health Organization (**WHO**).

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