SECONDARY OSTEOPOROSIS DUE TO SICKLE CELL ANEMIA: DO SEX STEROIDS PLAY A ROLE?

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ABSTRACT

BACKGROUND: *The exact cause of osteoporosis in patients with sickle cell disease (SCD) is not known, and various hypotheses have been put forward.* ***AIM:*** *To assess the effect of sex steroids on bone mass in SCD patients.* ***Settings and Design:*** *In King Fahd Hospital of the university, Alkhobar, Saudi Arabia, a cross-sectional study was carried out.* ***MATERIALS AND METHODS:*** *All patients known to suffer from SCD attending the hospital between August 2006 and August 2007 were subjects of the study. Blood was extracted for serum level of androgens, gonadotropins, thyroid stimulating hormone (TSH), calcium, phosphorus, and alkaline phosphatase. Measurement of bone mineral density (BMD) of hip and spine was done using dual-energy X-ray absorptiometry (DEXA). All tests were performed using SPSS (Statistical Package for Social Sciences), version 14.0, Chicago, Illinois, with P value of <0.05 being statistically significant with confidence interval (CI) of 95%.* ***RESULTS:*** *One hundred three consecutive patients with an average age of 27.83 years were studied. Forty-five were males; and 58, females. Low bone mass (osteoporotic/osteopenic) was found in 62.2% of the patients in the male group and 67.06% in the female group. In males, testosterone level was not significant between different groups, but total estradiol levels were significantly lower in the osteopenic and osteoporotic patients (P <0.003 and <0.01 respectively). In female patients, estradiol and testosterone levels were lower in osteoporotic patients in comparison to non-osteoporotic patients (P = 0.05 and 0.001).* ***CONCLUSIONS:*** *Our study indicates that sex steroids play a major role in the development of osteopenia and osteoporosis in patients with SCD*

Key words: *Estradiol, osteoporosis, sickle cell disease, testosterone*

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INTRODUCTION

The prevalence of osteoporosis in premenopausal Saudi Arabian women is reported to be 10%; and in postmenopausal women, between 30% and 40%, which is higher in comparison to that in other parts of the world[1-4] In 20% to 30% of

postmenopausal women and in more than 50% of men, osteoporosis is due to secondary causes.[5] Bones are sensitive to diseases, which may cause secondary osteoporosis such as hormonal and due to drugs like steroids and chemotherapeutic agents.[6] Recently SCD has been added to the list of diseases which cause secondary osteoporosis.[7-10]

The importance of testosterone in men with osteoporosis has been challenged now, and reports indicate that in primary osteoporosis, estrogen is the important hormone in the prevention of osteoporosis in both sexes.[11-15] Since the role of sex steroids in secondary osteoporosis in SCD has not been previously studied, the objective of this study was to identify the role of estrogen and testosterone in young men and women with SCD.

MATERIALS AND METHODS

All patients known to suffer from SCD attending the outpatient clinics and admitted to King Fahd Hospital of the university, Alkhobar, Saudi Arabia, between August 2006 and August 2007 were subjects of the study. After obtaining ethical approval from the research and scientific committee of College of Medicine, King Faisal University, Dammam, the study was started. Verbal consent was obtained. The patients had their weight and height measured to calculate the body mass index (BMI). History was taken and clinical examination was done and followed by appropriate investigations to rule out secondary osteoporosis. Patients who were diagnosed and treated for osteopenia and osteoporosis and those patients who were on steroids; had anorexia nervosa, hyperthyroidism, chronic obstructive pulmonary disease, liver and inflammatory bowel disease; or had undergone organ transplantation were excluded from the study. All blood samples were collected before 10 AM for tests which included complete blood picture, hemoglobin, electrophoresis, blood urea nitrogen, creatinine level, calcium, phosphorous, alkaline phosphatase, parathormone level, thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), total estradiol (E2), and total testosterone (Te); and the hormonal assay was done with Architeci 2000 machine using the chemiluminescent microparticle immuno-assay (CMIA). The gonadotropin assays in females were done 21 days from the first day of the cycle. Bone mineral density (BMD) measurement of hip area and lumbar spine (lumbar 1 to lumbar 4 vertebra) using dual-energy x-ray absorptiometry (DEXA) scan, Hologic Inc., Waltham, MA, USA, was performed. Patients with a T score of ≤2.5 SD or below were taken as osteoporotic and those between ≤1 and −2.5 SD were taken as osteopenic for analysis. The reference value of T and Z score was entered in the DEXA machine with software for the Asian values. Secondary osteoporosis was ruled out on the basis of drug history and blood tests which included complete blood picture, serum calcium, phosphorus, alkaline phosphatase, thyroid stimulating hormone, serum estradiol, serum testosterone, and parathormone levels.[16] The data was entered in the database and analyzed using a *t* test to compare means between the non-osteoporotic, osteopenic, and osteoporotic patients. All tests were performed using SPSS (Statistical Package for Social Sciences),[17] version 14.0, Chicago, Illinois, with *P* value of <0.05 being statistically significant with confidence interval (CI) of 95%.

RESULTS

One hundred three patients with homozygous sickle cell anemia had an average age of 27.8±6.7 years. Forty-five were males and 58 were females. Table 1 gives data of the male patients. In the male group, 62.2% of the patients had low bone mass (osteoporotic/osteopenic). In patients who were non-osteoporotic, the BMI was significantly higher compared to that in osteoporotic patients [19±4.1 *vs.* 16.7±4.4; *P* = 0.05 (95% CI, 4.6-6.5)]. Table 2 shows the results of sex steroids and bone mineral density in male patients. Ninety-five percent of the patients had blood transfusion more than once, and 69 (66.9%) patients had bone and joint complications.

There was no statistically significant difference in the levels of testosterone between the non-osteoporotic, osteopenic, and osteoporotic patients (*P* = 0.5). Osteoporotic patients had lower estradiol level (24.5 pg/mL) in comparison to non-osteoporotic patients [30.1 pg/mL; *P* = 0.01 (95% CI, 0.41-11.6)]. In the female group, the BMI was significantly lower in osteopenic and osteoporotic patients [*P* = 0.01 and 0.05 (95% CI, 1.4-7.8 and 4.6-6.5) respectively] [Table 3]. Osteopenia was observed in 31.3% and osteoporosis in 36.3% of the patients, and

Table 1: Demographic data of male patients

Parameter	*Normal (Group 1) Mean ± SD*	*Osteopenia (Group 2) Mean ± SD*	*Osteoporosis (Group 3) Mean ± SD*	*P value Group 1 and 2*	*P value Group 1 and 3*
Number	17 (37.7%)	13 (28.8%)	15 (33.4%)		
Age (Years)	28.5 (20-42)	26.6 (22-36)	27.7 (18-41)	NS	NS
BMI kg/M^2	19 ± 4.1	17.1 ± 4.0	16.7 ± 4.4	0.08	0.05
Hemoglobin 'S' (%)	87.3 ± 4.4	84.9 ± 4.3	86.3 ± 4	NS	NS
Hemoglobin Concentration (g/l)	9.5 ± 0.9	9.4 ± 0.9	9.7 ± 1.2	NS	NS
BUN	10.3 ± 1.5	8 ± 4.7	7.2 ± 4.5	NS	NS
Creatinine	0.6 ± 0.1	0.5 ± 0.2	0.4 ± 0.1	NS	NS
Calcium	8.8 ± 0.3	9 ± 0.2	9.1 ± 0.2	NS	NS
Phosphorus	3.5 ± 0.4	3.8 ± 0.4	4.1 ± 0.5	NS	NS
Alkaline Phosphatase	143.8 ± 83.6	131.6 ± 48	147.7 ± 26.7	NS	NS

Table 2: Sex steroids and bone mineral density of male patients

Parameter and normal values	*Normal (Group 1) Mean ± SD*	*Osteopenia (Group 2) Mean ± SD*	*Osteoporosis (Group 3) Mean ± SD*	*P value Group 1 and 2*	*P value Group 1 and 3*
Number of patients	17 (37.7%)	13 (28.8%)	15(33.4%)		
Total Testosterone >50 ng/dl	420.3 ± 220.9	389.7 ± 205.9	390.1 ± 91.1	0.5	0.5
Total Estradiol					
11-44 pg/ml	30.1 ± 11.7	24.5 ± 4.5	22.5 ± 13	0.01	0.01
LH 1.26-10 (MIU/ml)	2.6 ± 1.2	6.2 ± 2.9	5.6 ± 1.2	0.01	0.01
FSH 1.37-13.58 (MIU/ml)	1.5 ± 0.73	3.8 ± 2.6	4.2 ± 0.8	0.01	0.01
TSH	1.5 ± 0.7	1.8 ± 1	1.9 ± 0.8	0.1	0.1
Total Hip BMD g/cm^2	1.084 ± 0.13	0.868 ± 0.10	0.592 ± 0.05	0.01	0.01
T Score	-0.03 ± 0.67	-1.525 ± 0.20	-2.65 ± 0.05		
Z Score	0.06 ± 0.7	-1.325 ± 0.44	-2.2 ± 0.39		
L1-L4 Spine BMD g/cm^2	1.115 ± 0.14	0.868 ± 0.13	0.651 ± 0.09	0.01	0.01
T Score	0.19 ± 1.48	-2.08 ± 0.67	-3.9 ± 0.09		
Z Score	-1-1.0 ± 0.61	-2.08 ± 0.67	-3.2 ± 0.62		

Table 3: Demographic data of female patients

Parameter	*Normal (Group 1) Mean ± SD*	*Osteopenia (Group 2) Mean ± SD*	*Osteoporosis (Group 3) Mean ± SD*	*P value Group 1 and 2*	*P value Group 1 and 3*
Number	19 (32.7%)	18 (31.03%)	21 (36.3%)		
Age (Years)	28.9 (25-40)	26 (24-29)	29.1 (22-41)	NS	NS
BMI kg/M^2	20.1 ± 4.9	15.5 ± 5.1	16.6 ± 4.9	0.01	0.05
Hemoglobin 'S' (%)	89.5 ± 4.2	85.2 ± 3.9	86.7 ± 3.7	NS	NS
Hemoglobin Concentration (g/l)	9.5 ± 1.17	9.7 ± 0.97	9.4 ± 0.97	NS	NS
BUN	6.2 ± 2.45	7.1 ± 1.72	7.1 ± 2.4	NS	NS
Creatinine	0.54 ± 0.18	0.51 ± 0.13	0.41 ± 0.09	NS	NS
Calcium	9 ± 0.26	8.8 ± 0.37	8.2 ± 1.1	0.01	0.01
Phosphorus	3.6 ± 0.37	3.7 ± 0.67	3 ± 0.83	NS	NS
Alkaline Phosphatase	93.7 ± 32.4	110.1 ± 47.9	125 ± 58	0.3	0.1

the rest had normal bone mass. Table 4 shows that total testosterone levels were significantly lower in osteopenic and osteoporotic females [*P* = 0.05 and = 0.001 (95% CI, 2.3-198.5 and 84.4-257.6) respectively]; whereas there was no difference between the estradiol levels of normal and osteopenic patients. The total estradiol levels in the osteoporotic patients were much lower when compared with the non-osteoporotic patients [43.5 *vs.* 61 pg/mL; *P* = 0.05 (95% CI, 4-38.9)].

DISCUSSION

Secondary osteoporosis is common, and young people suffer from steroid-induced osteoporosis;[18] SCD is emerging as the most common cause of secondary osteoporosis in the younger population. Studies have reported the incidence of osteoporosis to be 69% to 79%,[7,9,19] even though 5% of the world's population carries sickle cell gene.[20] In Saudi Arabia, the gene is prevalent in 5.7% of the population.[21] It appears there is complacency among physicians to diagnose and properly manage patients with secondary osteoporosis.

The exact cause or causes of osteoporosis in SCD are yet to be established. It was suggested that hyperplasia of the marrow may cause trabecular destruction. Faber *et al.*[22] showed that chronic anemia causes

Table 4: Sex steroids and bone mineral density of female patients

Parameter	*Normal (Group 1) Mean ± SD*	*Osteopenia (Group 2) Mean ± SD*	*Osteoporosis (Group 3) Mean ± SD*	*P value Group 1 and 2*	*P value Group 1 and 3*
Number of patients	19 (32.7%)	18 (31.03%)	21 (36.3%)		
Total testosterone >50 ng/dl	190.4 ± 192	90 ± 100.9	19.4 ± 13.9	0.05	0.001
Total estradiol 11-44 pg/ml	61 ± 40.25	51.1 ± 33.5	43.5 ± 26.9	0.4	0.05
LH 1.26-10.05 (MIU/ml)	9.3 ± 19.19	3.28 ± 1.08	10.99 ± 18	0.05	0.1
FSH 1.37-13.58 (MIU/ml)	4.90 ± 2.53	4.16 ± 1.23	13.04 ± 24.1	0.1	0.001
TSH	1.9 ± 0.66	1.3 ± 0.6	1.09 ± 0.3	0.1	0.1
Total Hip BMD g/cm^2	0.995 ± 0.15	0.772 ± 0.09	0.536 ± 0.08	0.03	0.001
T Score	0.062 ± 0.71	-1.5 ± 0.37	-3.1 ± 0.56		
Z Score	0.231 ± 0.77	-1.6 ± 0.31	-2.65 ± 0.58		
BMD L1-L4 Spine	0.995 ± 0.15	0.770 ± 0.06	0.617 ± 0.08	0.03	0.001
T Score	-0.47 ± 1.31	-2.50 ± 0.52	-4.2 ± 1.06		
Z Score	-0.28 ± 1.34	-2.41 ± 0.55	-3.76 ± 1.15		

increase in trabecular spacing, which leads to trabecular destruction, which in turn causes osteopenia or osteoporosis. It was reported that in patients with Hbβ-thalassemia, osteopenia and osteoporosis occur due to marrow expansion.[23] Gurevitch and Slavin[24] put forward a hypothesis of hematological cause of osteoporosis. In our patients, we did not encounter any significant differences regarding the hematological parameters between normal, osteopenic, and osteoporotic patients.

Seeman[25] found that in 20% to 30% of elderly men, osteoporosis occurred due to lack of testosterone. In our study, only one male patient had testosterone level below the normal range, and none of the other patients had normal estradiol levels. Our male osteoporotic patients had the lowest estradiol levels. Recently Karim and his associates[26] raised another issue, that of FSH being one of the gonadotropins which could be implicated in the bone loss independent of estrogen. Our results concur with those of the said study.

The limitations of this study are few. All efforts were made to rule out other causes of secondary osteoporosis on the basis of clinical and laboratory tests, but still we could have missed some patients. Secondly, we did not perform test for determining vitamin D level in these patients, which may play a minor role in osteopenia and osteoporosis. In conclusion, this study suggests that sex steroids play an important role in causing low bone mass in young patients with SCD. Hence measurement of estrogen levels is essential in the evaluation of male osteoporosis; and in females, both testosterone and estradiol levels should be determined in the evaluation of osteoporosis.

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