Original Article

Bull Emerg Trauma 2017;5(1):29-35.

Bulletin of Emergency And Trauma

Prevalence of Fracture in Healthy Iranian Children Aged 9–18 Years and Associated Risk Factors; A Population Based Study

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Received: October 24, 2016
Revised: December 5, 2016
Accepted: December 16, 2016

ABSTRACT

Objective: To determine the prevalence of fractures and associated risk factors in healthy Iranian children and adolescents.
Methods: In this cross sectional population based study, 478 healthy Iranian children and adolescents aged 9–18 years old participated. Baseline data and bone mineral content and density have been determined. One questionnaire was completed for all individuals including previous history of fracture, its location, and level of trauma. Albumin, calcium, phosphorus, alkaline phosphatase, and vitamin D levels were measured.
Results: We found a prevalence of 12.9% for fracture. (34.5% for girls and 65.5% for boys); about 71% suffered long bone fracture with distal forearm as the most common site. Totally 58% of the boys and 54% of the girls had fracture with low-energy trauma. The fracture group had lower bone mineral apparent density in the lumbar spine (0.19±0.04 vs. 0.20±0.03, p=0.04), lower serum albumin (4.6±0.5 vs 4.8±0.4, p=0.02), and higher serum alkaline phosphatase level (446±174 vs. 361±188, p=0.02) compared with non-fracture subjects. By logistic regression analysis, we found a significant association for sex, and bone mineral content of the lumbar spine with fracture (p=0.003, p=0.039).
Conclusion: Compared to other studies, our subjects had lower rate of fracture. We found an association between low bone density and fracture in children and adolescents. This finding has important implications for public health. Further research may contribute to recognition of preventive measures.

Keywords: Fracture; Children; Trauma; Long bone; Risk Factors.

Please cite this paper as:
Jeddi M, Dabbaghmanesh MH, Kharmandar AR, Ranjbar Omrani G, Bakhshayeshkaram M. Prevalence of Fracture in Healthy Iranian Children Aged 9–18 Years and Associated Risk Factors; A Population Based Study. *Bull Emerg Trauma*. 2017;5(1):29-35.

Introduction

Multiple genetic, hormonal, and environmental factors determine bone growth and development in children and adolescents [1]. Some of these factors are also associated with fracture during childhood and adolescence; as a general rule, fracture during this period is dependent on the underlying bone problems (impaired bone structure, low bone density) and precipitating factors (obesity, falls) [2].

Approximately, one out of three healthy children is involved with fracture, and the most common site is the distal forearm. There are some differences in the incidence of fracture over time and in different geographic regions [3]. Although some studies determined that the relationship between fracture and bone mineral density was related to the level of trauma [4], there is some evidence that fracture in childhood may be related to skeletal fragility and low bone density [5]. In spite of a decline in global fracture incidence in recent years [6], the incidence of distal forearm fractures in children and adolescents has a continuous rise [7]. Explanations for this increase are not fully implicated; thus, inquiry of the potential risk factors is necessary as children and adolescents who sustain forearm fractures are at risk for succeeding fractures not only during the growth but also later in lifetime [8, 9]. Therefore, in this population-based study we aimed to report the prevalence of fracture in the children and adolescents in the south of Iran for the first time and also investigate the relationship between fracture and other risk factors in Iranian children.

Materials and Methods

Recruitment and Baseline Assessment of the Study Population

The patient population in this study has been described previously [1]. In brief, subjects of this cross-sectional study were 478 9-18-year-old boys and girls in Kawar, an urban community located about 50Km east of Shiraz, the capital of Fars Province in southern Iran. They were selected by systematic random sampling in the elementary, guidance, and secondary schools of this community according to student numbers. Participants were excluded from the study if they had a history of precocious or delayed puberty, known systemic disease such as hypo- or hyperthyroidism, diabetes, renal failure, adrenal insufficiency, or chronic musculoskeletal diseases, recurrent fractures, or prolonged immobility, or if they used anticonvulsants or steroids (sex steroids or glucocorticoid). Baseline anthropometric parameters, puberty status, level of physical activity, calcium, and vitamin D status were reported previously in this population [1, 10]. Bone mineral density was measured by Dual Energy X-ray Absorptiometry as a basic method for assessment of bone health and their result reported previously [1]. The study was approved by the ethics committee of Shiraz University of Medical Sciences.

Fracture History

We collected data on the history of fractures. A questionnaire was completed for all individuals including previous history of fracture, its location, and level of trauma severity according to Descriptive Categories of Landin's Modified Trauma Levels [4]. Further than detailed questioning, effort was made to verify self-reported fractures using radiology reports (where possible). The time of data gathering, blood sampling and densitometry was after the acute phase of fracture and all fractured patients clinically were well and improved. The expectation of long bone fracture in our study was fracture in the bones of the extremities with greater length than the width and considered the fracture of radius, ulna, humerus, clavicle, tibia, fibula, or femur as long bone fracture [11].

Statistical Analysis

We reported mean and SD for anthropometric, body composition and bone parameters. Statistical analysis included t-test, Kruskal-Wallis and Mann-Whitney test. We used t-test and Chi-square for comparing anthropometric, body composition, bone variables, Tanner stage, and level of exercise between the two groups with and without fracture. To evaluate the association between fracture and its risk factors, we used Binary Logistic Regression analysis. All analyses were done using statistical package for social sciences (SPSS Inc., Chicago, Illinois, USA) version 22. A 2-sided P value of less than 0.05 was considered significant.

Results

Prevalence and Site of Fracture

The study population consisted of 241 boys and 237 girls with a mean age of 13.7±2.6 and 13.7±2.7 years old. (p=0.9) Anthropometric and bone parameters have been published in a previous article [1]. We found 55 individuals (12.9%) with the history of fracture (34.5% in the girls and 65.5% in the boys). Totally, 8.9% of the girls and 17.1% of the boys had a history of fracture. About 36% of all fractures were between ages of 13-15 years old. Table 1 shows different sites of fracture in the boys and girls (Table 1). We detected 39 cases (71% of all fractures) with long bone fracture

Table 1. Number of fracture in Iranian children and adolescents in different sites

Site of Fracture	Boys	Girls
Facial bone	1 (2.4%)	2 (10.5%)
Skull	3 (7.3%)	1 (5.3%)
Clavicle	1 (2.4%)	1 (5.3%)
Humerus shaft	0 (0%)	1 (5.3%)
Proximal forearm	7 (17.0%)	0 (0%)
Forearm shaft	5 (12.3%)	2 (10.5%)
Distal forearm	11 (26.9%)	4 (21.0%)
Hand fingers	4 (9.7%)	4 (21.0%)
Vertebra	0 (0%)	0 (0%)
Pelvic	0 (0%)	0 (0%)
Femur neck	0 (0%)	0 (0%)
Femur shaft	2 (4.9%)	2 (10.5%)
Distal femur	1 (2.4%)	0 (0%)
Tibia/Fibula shaft	5 (12.3%)	0 (0%)
Distal Tibia	1 (2.4%)	0 (0%)
Tarsal	0 (0%)	1 (5.3%)
Foot fingers	0 (0%)	1 (5.3%)

with a mean age of 13.2±2.5 years old. The most common site of fracture was the distal forearm (15 cases, 27.3%) and we didn't find any fracture in the femoral neck or vertebra. Of all these cases, 48 had one fracture, 6 had two fractures and 1 had three fractures.

Fracture and Bone Parameters

Table 2 shows anthropometric, body composition and bone parameters in subjects with and without fracture. We found that in subjects with the history of fracture only lumbar spine BMAD was significantly lower than that in the subjects without the history of fracture; other bone and body parameters didn't show a significant difference. In comparing these parameters between subjects with long bone fracture and those without fracture, again we found a significant difference only in the lumbar spine BMAD (0.19±0.04 and 0.20±0.03) (p=0. 04). Using ANOVA analysis, we found a significant difference in BMI, subtotal area, neck area, neck BMC, subtotal BMC, and total lean mass in the subjects with one or more fracture (Table 3).

Biochemical Parameters

We compared the level of albumin, calcium, phosphate, alkaline phosphatase, and vitamin D level in subjects with and without fracture. Table 4 shows these data. We detected a significant difference in the serum albumin and alkaline phosphatase level between the two groups.

Fracture and Trauma

We recorded a history of trauma based on Descriptive Categories of Landin's Modified Trauma Levels [4] and divided them into three levels of trauma: mild, moderate and severe. We found that 57.5% of the individuals with the history of fracture had mild trauma, 26% moderate trauma, and 16.5% severe trauma. Of the subjects with long bone fracture, 45% had mild trauma, 42% moderate trauma, and 13% had severe trauma. Totally, 58% of the boys and 54% of the girls had fracture with low-energy trauma. We reported previously level of physical activity in

Table 2. Anthropometric, Body Composition and Bone Parameters in Iranian children and adolescents with and without fracture

	Subjects with Fracture	Subjects Without Fracture	*p* value
Age (years old)	13.8±2.6	13.7±2.6	0.11
Weight (Kg)	45.5±14.9	42.9±13.3	0.69
Height (cm)	156.7±14.9	153.6±14.2	0.78
BMI (Kg/m^2)	18.0±3.5	17.7±3.2	0.84
Waist Circumference (cm)	69.0±10.1	68.6±10.5	0.22
Left Arm BMC (g)	86.9±47.5	85.8±40.7	0.82
Right Arm BMC (g)	89.7±46.4	89.6±41.4	0.98
Lumbar Spine BMC (g)	39.6±16.2	47.5±13.0	0.42
Femoral Neck BMC (g)	3.5±0.9	3.4±0.8	0.72
Total Body BMC (g)	1496.0±473.0	1454.7±441.2	0.78
Left Arm BMD (g/cm^2)	0.61±0.22	0.59±0.10	0.18
Right Arm BMD (g/cm^2)	0.61±0.12	0.61±0.11	0.86
Lumbar Spine BMD (g/cm^2)	0.83±0.17	0.84±0.17	0.62
Femoral Neck BMD (g/ cm^2)	0.71±0.13	0.71±0.13	0.93
Total BMD (g/ cm^2)	0.87±0.12	0.87±0.11	0.61
Lumbar Spine BMAD (g/cm^3)	0.19±0.04	0.20±0.03	0.04
Femoral Neck BMAD (g/cm^3)	0.14±0.02	0.15±0.02	0.60
Lumbar Spine Z Score	-0.98±1.07	-1.04±1.07	0.68
Femoral Neck Z Score	-1.00±0.97	-1.15±1.13	0.37

Table 3. ANOVA analysis showing difference in some parameters in subjects with one or more than one fracture

	BMI[a]	Femoral Neck Area	Sub Total Area	Femoral Neck BMC[b]	Sub Total BMC	Total Lean Mass
F (between groups)	15.2	4.6	8.8	9.3	10.4	7.3
p	<0.001	0.036	0.004	0.003	0.002	0.009

[a]Body Mass Index; [b]Bone Mineral Content

Table 4. Biochemical parameters in subjects with and without fracture

	Subjects with fracture	Subjects without fracture	*p* value
Albumin (mg/dl)	4.6±0.5	4.8±0.4	0.02
Calcium (mg/dl)	9.9±0.5	9.8±0.5	0.88
Phosphate (mg/dl)	4.0±0.5	4.0±0.7	0.96
Alkaline phosphatase (mg/dl)	446±174	361±188	0.02
Vitamin D (ng/ml)	14.7±4.7	15.4±5.6	0.37

these subjects [1]. We found that 40 % of individuals with all fracture and 46% with long bone fracture participated in physical activities three times per week or more. We didn't show significant difference in the level of physical activity between fracture and non-fracture group.

Low Bone Mass for Chronological Age

Of all the subjects, 16.9% had low bone mass in the lumbar spine and 18.8% had it in the femoral neck (Z score≤-2) according to their chronological age. The result of Chi-Square analysis revealed that there was no significant difference in the lumbar spine (p=0.53) and neck (p=0.51) low bone mass between groups with or without fracture. In cases of long bone fracture, again we didn't show any significant difference with the control group in the lumbar spine (p=0.47) and neck of the femur (p=0.61).

Binary Logistic Regression Analysis

We found the association between anthropometric and bone parameters with fracture in our subjects by binary logistic regression analysis and found a significant association only for sex with fracture after adjusting for age, BMI, Tanner stage of puberty, vitamin D level and bone parameters of the left and right arm, lumbar spine, femoral neck and total body (B=0.168, 95%CI: 0.058-0.49, p=0.001).

After adding the level of trauma to this model, this significant association was faded. We repeated this analysis for girls and boys separately and found a significant association between the fracture and lumbar spine BMD in the boys (p=0.005) and with vitamin D in the girls (p=0.047).

Discussion

Prevalence of Fracture

The most common injuries during growing years are fractures; it constitutes about third of all pediatric injuries. In developing countries, fracture is the most common category of unintentional injuries in children requiring hospital admission [3]. To date, to the best of our knowledge, there is no published study on the prevalence of fractures in childhood in Iran. In this article, for the first time, we collected and presented the prevalence of fracture in children and adolescents in southern Iran in a population-based study.

There are some studies on fractures in adolescents containing details of their epidemiology. Ruda¨ng *et al*., [12] reported that 38.4% of males (ages 23 to 25 years) had at least one prior fracture. Cooper *et al*., [13] reported that approximately 33% of the girls sustain at least one fracture before 17 years of age. However, Farr *et al*., [14] showed that fracture prevalence in their young sample (465 girls aged 8 to 13 years) was lower (19%). Fracture prevalence in our young sample also was lower (12.9%) (8.9% of the girls and 17.1% of the boys). Nonetheless compared to other studies in this age, we have to acknowledge that our rate of fracture is rather lower than the other results in this age range.

Common risk factors associated with sustained fractures in children and adolescents include age, sex, season, risk-taking behavior, bone mineral density (BMD), sports, violence and race/ethnicity, and socioeconomic status [15]. Advances in understanding the common risk factors of the Iranian children skeleton development help and could explain different epidemiology of fracture. The overall distribution of fractures in our study by anatomic regions was similar to other reported studies [3, 6, 13, 15] with fractures of the distal forearm being the most common specific fracture and fractures of the upper extremity far exceeding fractures of the lower extremity (67.2% vs. 23.6%, respectively). The remaining 9.2% were fractures of the skull, face and clavicle. Distal radius fractures are the most common fractures in the pediatric population, with an incidence of 21–31% of all fractures [16]. The etiology of forearm fracture seems to be sex-specific. In girls, insufficiencies in bone strength are associated with the forearm fractures. In boys, a combination of poor balance, excess body fat, and low physical activity might lead to fractures [16].

In our study, male to female ratio of fracture was 1.89 and about a third of fractures occurred in those between 13-15 years of age. The overall predominance of fractures sustained by boys over girls was consistent with the current knowledge. In one study done in Sweden, the male to female incidence ratio of fracture was 1.5 and the peak incidence of fracture in the girls occurred at 12-15 years of age and in the boys in 13-14 year old ones [17]. There is some evidence to support the assumption that high incidence of fractures in adolescence is related to a period of relative skeletal weakness resulting from dissociation between bone expansion and bone mineralization through the period of rapid growth [18].

In our study, boys suffered a higher number of fractures compared with girls. Biological and behavioral differences associated to sex and ages are supposed to predominantly explain the male predominance in the adolescent patient group [19]. Although explanations for this sex difference are not entirely clear, it may partly be due to the boys' higher bone turnover rate [17]. Bone mineral density decreases towards the age of pubertal peak height velocity and girls enter this peak earlier than boys. On the other hand, in comparison to girls, the boys have a growth spurt of longer duration and a greater peak height velocity [10]. This biological consequence might contribute to the male predominance in adolescents in this study. Also, this gender difference may be explained by behavioral changes. Boys usually participate in physical activities with more physical risks [20]. Another study reported that the same physical activity increases the rate of upper limb fracture in boys and decreases it in the girls, suggesting high potential of boys for trauma during physical activity [21].

Relationship between Fracture and Bone Parameters

Pediatric osteoporosis has been defined as a disease of children and adolescents with low bone density for their age, gender, race, and body size, in addition to a history of clinically significant fragility fracture [22]. Clark and his colleagues in a systematic review showed that evidence for association between fracture and bone mineral density in children is limited [5]. Children and adolescents with forearm fractures had significantly lower bone mineral content (BMC) and/or a real BMD compared with the same sex children without fractures [23, 24]. This deficit in bone mineral density is obvious not only at the radius but also at other skeletal regions, suggestive of potential systemic skeletal scarcities [23, 25].

In this study, we showed that fracture was associated with lumbar spine BMC and lumbar spine BMAD. In children and adolescents, there is not site specificity of BMD measurement for predicting the upper limb fracture [26] and generalized bone deficit can predict the fracture in the forearm or each other bone site [8]. It is important to adjust bone mass for body size in DXA method. This adjustment is difficult [5]. Crabtree NJ and his coworkers found that all size-adjusted bone measurements were more accurate than non-size-adjusted values for predicting the fracture and showed that lumbar spine BMAD had the greatest odds ratio for lumbar fracture [27].

In this study, we also used BMAD to adjust the bone mineral mass for body size and found that subjects with fracture had lower lumbar spine BMAD than others without fracture. Some other studies also found the strongest association between BMAD and risk of fracture [26]. Gould *et al*., [8] found that lumbar spine BMAD predicts not only the forearm but also all fractures in children.

Growing of weight, height and bone mass in children and adolescents is not synchronous. Usually, they achieve adult height earlier than peak bone mass. In other words, bone size and bone area grows up before maximal increment in bone mineral content [25]. Lower BMAD in subjects with fracture can be explained by this rule.

Fracture and Trauma

In this study, we reported trauma according to descriptive categories of Landin's modified trauma levels and found that more fractures were consequence of low-energy trauma, especially falling down. These results are in agreement with those of some previous studies. Rennie et al. reported that falls accounted for 57% of all fractures in British children, especially at a younger age and in males [28]. Similarly, Valerio *et al*., [20] showed that low-energy trauma (mainly falls) caused 77% of fractures that occurred more frequently in males in school children and adolescents.

Some previous studies found that reduced BMD is a major risk factor for low-energy distal radius fracture in middle-aged and elderly men [29] and women [30]. The other retrospective case control study reported a history of previous fracture as the only independent risk factor for low-energy fracture [31]. Olney *et al*., [32] found a significant hypercalciuria and lower BMD Z score in children with low energy fracture. In the subjects of our study, we didn't find a significant difference in BMD in children with fracture compared to those without it. Low energy trauma fracture (especially in the distal forearm) in these subjects can be explained by low bone strength, higher fall load-to-strength ratio, and more severe cortical thinning in the distal forearm [2].

Fracture and Biochemical Markers

In this population-based study, we found a significant difference in the serum level of albumin and alkaline phosphatase between subjects with and without fracture. We didn't find any significant difference between vitamin D level in the fracture and non-fracture groups. Also, we didn't find a significant difference in the rate of vitamin D deficiency between the two groups (p=0.26 by Chi-Square test). It seems that the difference in alkaline phosphatase is independent of vitamin D level. We didn't find this difference in subjects with long bone fracture. Alkaline phosphatase is a marker of bone turnover and is used for monitoring of metabolic bone disorders [33]. There is some evidence that women with osteoporotic fracture have a high serum level of alkaline phosphatase compared with those without fracture [34], and also it is shown that higher serum alkaline phosphatase level in Japanese hemodialysis adult patients is independently associated with the incidence of the hip fracture [35].

To the best of our knowledge, this study is the first population- based study that reported high alkaline phosphatase level in children and adolescents with fracture. In this study, we assigned children and adolescents with previous history of fracture. Higher alkaline phosphatase level in subjects with fracture may be explained by higher bone turnover. In one study [36], in a group of maintenance hemodialysis adult patients, negative association of serum alkaline phosphatase level and bone mineral density assessed by DXA has been found.

We found lower serum albumin level in subjects with fracture. Recently, Formosa et al. also found that serum albumin level could be indicative of fracture risk in Maltese Postmenopausal Women [37]. Another study also reported the association of serum albumin level with osteoporosis in all bone sites independent of other variables [38]. The mechanism of this association is not well known. There are some theories that may explain this association. First, for proper bone health, suitable protein intake is important and low serum albumin level indicated protein malnutrition [39] that may affect bone remodeling through the level of IGF-I. Second, hypoalbuminemia may directly be linked to nuclear factor-κB (NF-κB) or indirectly as an acute phase reactant through inflammatory cytokines and activate osteoclasts and suppress osteogenesis [38]. More fractures of all types have been observed in children who did exercise less than 3 times a week although there was no significant difference. It is noteworthy to mention that only one third of all the children did exercise more than 3 times a week.

Limitations

Our study was a population-based research on the prevalence of fracture in Iranian children and adolescents. This study has some limitations. First, fracture history was verbally obtained rather than medically or X-Ray based in many individuals; although, the accuracy of this method has been shown and the majority of parents precisely reported their child's previous fractures in other studies [11, 40]. Second, due to the retrospective and cross-sectional nature of the study, we cannot evaluate the actual risk factors of fracture. Third, there are some other factors that contribute to fracture risk and have not been included in this study, such as race, nutritional status and biomechanics of the bone. Future prospective studies are needed to validate our observations.

In conclusion, compared to other studies, our subjects had lower rate of fracture. We found an association between low bone density and fracture in children and adolescents. This finding has important implications for public health. Further research may contribute to recognition of preventive measures.

Acknowledgements

The authors would like to thank Shiraz University of Medical Sciences, Shiraz, Iran and also Center for Development of Clinical Research of Nemazee Hospital and Dr. Nasrin Shokrpour for editorial assistance.

Conflict of Interest: None declared.

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