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ORIGINAL ARTICLE

Insulin resistance and bone health in adolescents

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Abstract

Summary Insulin resistance may be linked to bone health in young people. This study is the first on adolescents that jointly examined the association of bone health with insulin resistance and body composition. Our results revealed significant negative association between bone parameters and insulin resistance, even after adjustment for confounding factors.

Purpose Previous studies are suggestive of the protective role of insulin on bone in adults. Whether this association exists in younger individuals is not clear, yet. This investigation aimed to evaluate the association between insulin resistance, bone parameters, and body composition amongst Iranian adolescents' population.

Methods A cross-sectional study was conducted on 423 participants (224 girls and 199 boys) aged 9–19 years old. Insulin resistance was assessed, using a homeostatic model assessment of insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI). Bone mineral density (BMD), bone mineral content (BMC), total body fat mass (TBFM), and total body lean mass (TBLM) were measured, using dual energy X-ray absorptiometry (DXA), and bone mineral apparent density (BMAD) was calculated.

Results In multiple regression analyses adjusted for potential confounders, the HOMA-IR showed statistically significant negative association with most of the bone parameters ($\beta = -1.1$ to -0.002, $P = 0.004$ to 0.036). On the subject of QUICKI index, this relationship was detected only for lumbar spine (LS) parameters ($\beta = 0.062$ to 37.21, $P = 0.0001$ to 0.026) and femoral neck bone mineral content (FNBMC) ($\beta = 1.297$, $P = 0.013$).

Conclusion Our results suggest that insulin resistance may be inversely and independently associated with the bone indices in younger individuals. Whether high insulin levels have detrimental effects on growing bone is still unclear and has to be answered.

Keywords Adolescent · Bone mineral content · Bone mineral density · Insulin resistance · Total body fat mass · Total body lean mass

Introduction

Adolescence is a critical period for reaching peak bone mass, and 90% of bone mass is gained by the age of 18. Hence, to prevent future bone loss, it is imperative to identify the factors that affect bone acquisition in adolescents as well as adults [1]. In the last few years, bone has been recognized as an endocrine organ that modulates the glucose and lipid metabolism [2]. It is suggested that physiological levels of insulin exert anabolic effects on the bone [3, 4]. Also, insulin might have synergistic influence on other anabolic hormones, such as insulin-like growth factor I (IGF-I) and parathyroid hormone (PTH) [5, 6]. In this regard, the increased bone mass in patients with type 2 diabetes mellitus (T2DM) and obese individuals is attributed to insulin resistance and hyperinsulinemia [7]. On the other hand, recent studies reported an inverse association between insulin resistance and bone density, and hyperinsulinemia was related to the inhibition of cortical bone development in adolescents [8]. Furthermore, other studies have demonstrated that the positive relationship between insulin resistance and bone density was not observed after adjustment for confounding factors such as BMI and lean mass. Hence, it was suggested that insulin resistance may affect the bone density indirectly [7, 9].

However, the skeletal impacts of high circulating insulin concentrations are not clear, and previous studies reached contradictory results. Meanwhile, there are only few reports with respect to younger individuals. Therefore, the present study was designed to investigate the association between bone

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indices and insulin resistance amongst Iranian children and adolescents. We hypothesized that (1) insulin resistance would be inversely associated with bone density and that (2) this association would be independent of the components of body composition.

Materials and methods

This cross-sectional study was conducted in Kawar, a community with an urban structure located 50 km south of Shiraz, Iran, 2010–2011. The data used in this analysis were from the baseline phase of the study with the aim to provide the first reference values for BMC and BMD amongst Iranian children and adolescents [10].

Subjects

The baseline phase of the study included 478 participants, and ultimately the data from 423 individuals (224 girls and 199 boys) aged 9–19 years were used in this research. Exclusion criteria were having any disease or using medications which could have affected bone density or serum insulin level, such as renal failure, endocrine, rheumatologic and musculoskeletal disorders, or consumption of glucocorticoids, anticonvulsant drugs, and contraceptives. The study protocol was approved by the local Ethics Committee of Shiraz University of Medical Sciences. After explaining the research objectives, written informed consents were obtained from the participants' parents/guardians.

Anthropometric measurements and Tanner stage

Body weight was measured, using a standard scale (Seca, Germany), while the participants wore light clothes and no shoes. Height was measured while standing in the upright position and barefooted, using a wall-mounted meter. The weight and height values were rounded to the nearest 0.1 kg and 0.5 cm, respectively. Body mass index (BMI) was calculated for each person as body weight in kilogram divided by height in squared meter. Our subjects were divided into two groups based on their calculated BMI centile values, which were determined based on their own BMI cut-off points [11] and also age- and sex-specific cut-off points, as defined by the IOTF [12]. Group 1 was considered as normal (BMI ≤ 85th percentile), and group 2 consisted of overweight or obese individuals (BMI > 85th percentile). We also stratified the participants according to the recommendation of the American College of Sports Medicine into those with fewer and those with more than three times physical activity per week [13]. The 5-stage puberty classification of Tanner was determined by an endocrinologist, also, in order to determine the effect of pubertal status on bone parameters, we divided the participants at stages I and II as pre-early puberty and those at stages III to V as post-puberty.

Bone densitometry

The Hologic system (Discovery QDR, USA) was used to measure bone mineral density (g/cm^2) and bone mineral content (g) in the whole body (with head), lumbar spine (LS), and left femoral neck (FN). Also, we measured total body lean mass (TBLM) and total body fat mass (TBFM) in grams. Coefficients of variation based on preliminary measurements in 10 participants were 2.4% for bone mineral density (BMD) of the FN, 0.51% for the LS, and 1% for the whole body. The measurements were in accordance with international standards. In order to overcome the effect of bone size on BMD and bone mineral content (BMC) interpretation, bone mineral apparent density (BMAD) for the LS and the FN was calculated to estimate the bone density per unit volume according to the following equations [14]:

$$\mathrm{LSBMAD}\left(\mathrm{g/cm^3}\right) = \mathrm{BMC\ of\ L2{-}L4/area^{1.5}}$$
$$\mathrm{FNBMAD}\left(\mathrm{g/cm^3}\right) = \mathrm{BMC\ of\ femoral\ neck/area^2}$$

Laboratory data

Blood samples were collected in the early morning after an overnight fast. Serum separation was performed immediately and kept frozen at − 70 °C until assayed. All the tests were performed at Endocrinology and Metabolism Research Center of Shiraz University of Medical Sciences. Serum glucose was measured enzymatically using a Dirui autoanalyzer (Dirui, CS-T240, China). Serum insulin concentration was determined by immunoradiometric assay (RK-400CT, Hungary). Insulin resistance was evaluated, using the homeostasis model assessment–estimated insulin resistance index (HOMA-IR) according to the following formula: HOMA-IR = [fasting plasma glucose (mg/dL) × fasting plasma insulin (μU/mL)/405. Also, quantitative insulin sensitivity check index (QUICKI) was calculated, using the formula: 1 / (log (fasting insulin) + log (fasting glucose)). Serum level of 25-hydroxy vitamin D was measured, using high performance liquid chromatography (Young Lee 9100, South Korea).

Statistical analysis

For statistical analysis, Student's *t*-test was used to compare the mean levels of anthropometric, body composition, and bone density parameters. In addition, if the desired variable did not have normal distribution, the Mann-Whitney test was used. A Chi-square test was used to compare categorical variables. Pearson's linear correlations were used for the analysis of correlation. Multiple stepwise linear regression analysis

was used to evaluate the influence of different factors on bone parameters at different sites. Data were analyzed using SPSS v. 18 software (Chicago, IL, USA). A P value of < 0.05 was considered to be statistically significant. The corresponding unstandardized regression coefficient (β), standard error, and adjusted coefficient of determination (R^2) were determined.

Results

This cross-sectional study included 423 participants, 199 (47%) boys, and 224 (53%) girls, aged 9–19 years with a mean age of 13.93 ± 2.64 years. Baseline characteristics of all the subjects, including their anthropometric measurements, serum insulin, glucose, vitamin D, TBFM, TBLM, and bone parameters, are presented in Table 1.

Our results showed that HOMA-IR and QUICKI index were well correlated (r = − 1; P = 0.0001).

There was no significant difference between girls and boys regarding their age, BMI, LSBMC, and LSZ-score. Males had higher levels of fasting insulin and glucose concentrations, and females had higher LS BMD, TBFM, and lower TBLM compared to males (Table 1). In total, 84.2% of the subjects had normal BMI (≤ 85th percentile), and 15.8% were overweight or obese (> 85th percentile). Severe vitamin D deficiency (< 8 ng/mL) was observed in 5.6% of the individuals, while insufficient and sufficient levels were detected in 78.2 and 16.2%, respectively. We found no correlation between vitamin D and insulin concentrations (P = 0.1) or insulin resistance indices (P = 0.3).

Pubertal status was appropriate for age in all subjects; all girls over 14 years of age had experienced menarche, and all boys over 14 years had Tanner Stage of 3 or more. None of the participants had diabetes or was a smoker.

The Pearson's correlation test showed a significant correlation between HOMA-IR and bone parameters at all sites, except for LSBMAD, FNBMAD, and Z -scores. On univariate analysis, a significant relationship between bone parameters and gender, age, BMI, puberty category, TBFM, TBLM, and exercise status of the participants was identified. However, serum vitamin D levels had no significant association with the bone parameters in either skeletal site. In

Table 1 Baseline characteristics of all of the participants and in two genders

Sex	F: 224 M: 199	Girls (n = 224)	Boys (n = 199)	P value
Age (year)	13.93 ± 2.64	13.78 ± 2.76	14.11 ± 2.5	0.2
Weight (kg)	43.85 ± 13.41	41.54 ± 11.85	46.45 ± 14.57	0.001
Height (cm)	154.92 ± 14.04	150.9 ± 11.5	159.45 ± 15.24	0.0001
BMI (kg/m^2)	17.87 ± 3.28	17.92 ± 3.30	17.81 ± 3.27	0.7
WCF (cm)	69.17 ± 10.4	69.67 ± 10.19	68.61 ± 10.74	0.3
Vitamin D (ng/mL)	15.3 ± 5.66	14.73 ± 5.35	15.95 ± 5.95	0.03
Insulin (μU/mL)	8.68 ± 5.13	8.02 ± 3.6	9.41 ± 6.36	0.005
Glucose (mg/dL)	78.5 ± 12.33	75.96 ± 10.88	81.3 ± 13.24	0.0001
Exercise	Yes: 142 No: 281	Yes: 24 No: 200	Yes: 118 No: 81	0.0001
Total BFM (g)	10297.4±5528.81	12051.1±5459.36	8323.37±4917.9	0.0001
Total BLM (g)	32612.67 ± 9922.07	28924.14 ± 6648.56	36746.05 ± 11281.4	0.0001
Total BMD (g/cm^2)	0.88 ± 0.12	0.87 ± 0.12	0.90 ± 0.11	0.016
LS BMD(g/cm^2)	0.85 ± 0.17	0.87 ± 0.17	0.83 ± 0.16	0.013
FN BMD (g/cm^2)	0.72 ± 0.13	0.67 ± 0.11	0.77 ± 0.13	0.0001
Total BMC (g)	1479.9 7 ± 444.95	1384.57 ± 371.41	1587.35 ± 494.68	0.0001
LS BMC (g)	41.77 ± 16.39	41.39 ± 15.43	42.2 ± 17.43	0.6
FN BMC (g)	3.46 ± 0.88	3.1 ± 0.64	3.86 ± 0.95	0.0001
Total Z-score	− 0.82 ± 0.93	− 0.98 ± 0.9	− 0.63 ± 0.93	0.0001
LS Z-score	− 1.00±1.04	− 1.02 ± 1.1	− 0.97 ± 0.97	0.6
FN Z-score	− 1.13±1.1	− 1.4 ± 1.18	− 0.85 ± 0.93	0.0001
Total BMAD (g/cm^3)	0.88 ± 0.12	0.87 ± 0.12	0.89 ± 0.12	0.022
LS BMAD (g/cm^3)	0.21 ± 0.03	0.21 ± 0.03	0.20 ± 0.03	0.0001
FN BMAD (g/cm^3)	0.15 ± 0.02	0.14 ± 0.02	0.15 ± 0.02	0.004

Data are given as mean ± SD

F female, *M* male, *BMI* body mass index, *WCF* waist circumference, *LS* lumbar spine, *FN* femoral neck

multiple stepwise linear regression analysis after adjustment for gender, age, BMI, puberty category, exercise status, TBFM, and TBLM of the subjects (model 1), HOMA-IR revealed significant negative correlation with skeletal parameters at all sites, except for total BMC, FN Z-score, total BMAD, and FNBMAD (Tables 2, 3, 4). Moreover, multiple regression analysis using the same confounding factors as those for HOMA-IR (model 2), showed significant positive association between QUICKI index and lumbar spine related parameters (i.e. LSBMD, LSBMC, and LSBMAD) and FNBMC (Tables 2, 3, 4).

Discussion

This is the first cross-sectional study amongst adolescents that jointly examined the relationship between bone parameters with insulin resistance and body composition. Insulin resistance was evaluated by HOMA-IR and QUICKI indices, while TBFM and TBLM were considered as the two major components of body composition. Our results revealed inverse relationship between bone parameters and insulin resistance, even after adjustment for TBFM and TBLM. These associations were significant for HOMA-IR at most skeletal sites, but QUICKI index showed significant association with lumbar spine indices and FNBMC.

The impact of insulin resistance on bone turnover was recently investigated, and bone was recognized as a target organ for insulin [7, 15]. Hyperinsulinemia may account for a part of the observed association of both diabetes and obesity with BMD [5, 16]. Studies in this regard reported inconsistent results [17, 18]. Several studies have reported that insulin exerts anabolic effects on the bone, and this positive association has been used to explain the higher BMD seen in patients with T2DM [4, 7]. The idea that obesity-related metabolic alterations might adversely influence bone health in young individuals was introduced by Afghani et al. In a cohort study of overweight children and adolescents with family history of T2DM, it was shown that there was a negative relationship between the total BMC and markers of insulin resistance [19].

Table 2 Multiple stepwise linear regression analysis for the association between HOMA-IR and QUICKI index (independent variables) and LS bone parameters (dependent variables) in two models, adjusted for age, gender, BMI, TBLM, TBFM, exercise, and puberty category

	Model 1				Model 2			
Dependent variable	Independent variables	β[a]	Std. error	*P*	Independent variables	β[a]	Std. error	*P*
LSBMC	Age	2.21	0.25	0.0001	Age	1.68	0.35	0.0001
	Sex	− 7.2	1.05	0.0001	Sex	− 6.7	0.12	0.0001
	TBLM	0.001	0.000	0.0001	TBLM	0.001	0.000	0.0001
	HOMA-IR	− 1.1	0.41	0.008	Puberty	2.47	1.23	0.046
					QUICKI	37.21	10.37	0.0001
	$R^2 = 0.68$				$R^2 = 0.69$			
LSBMD	Age	0.026	0.003	0.0001	Age	0.025	0.003	0.0001
	Sex	− 0.083	0.012	0.0001	Sex	− 0.086	0.012	0.0001
	BMI	0.007	0.002	0.0001	BMI	0.007	0.002	0.0001
	TBLM	6.1	0.000	0.0001	TBLM	6.12	0.000	0.0001
	Puberty	0.026	0.012	0.035	Puberty	0.027	0.012	0.026
	HOMA-IR	− 0.01	0.004	0.011	QUICKI	0.277	0.102	0.007
	$R^2 = 0.72$				$R^2 = 0.72$			
LSBMAD	Age	0.007	0.001	0.0001	Age	0.007	0.001	0.0001
	Sex	− 0.02	0.003	0.0001	Sex	− 0.021	0.003	0.0001
	BMI	0.003	0.000	0.0001	BMI	0.003	0.000	0.0001
	HOMA-IR	− 0.002	0.001	0.029	QUICKI	0.062	0.028	0.026
	$R^2 = 0.53$				$R^2 = 0.53$			
LS Z-score	Age	− 0.082	0.024	0.001	Age	− 0.10	0.025	0.0001
	BMI	0.106	0.018	0.0001	Sex	− 0.24	0.11	0.029
	TBLM	3.12	0.000	0.0001	BMI	0.09	0.02	0.0001
	HOMA-IR	− 0.105	0.040	0.009	TBLM	4.1	0.000	0.0001
					QUICKI	2.63	1.01	0.009
	$R^2 = 0.20$				$R^2 = 0.21$			

Model 1 included age, sex, body mass index (BMI), TBLM, TBFM, exercise, puberty category, HOMA-IR

Model 2 included age, sex, BMI, TBLM, TBFM, exercise, puberty category, QUICKI index

Std. error standard error, *LS*, lumbar spine

[a] Unstandardized β coefficient

Table 3 Multiple stepwise linear regression analysis for the association between HOMA-IR and QUICKI index (independent variables) and FN bone parameters (dependent variables) in two models, adjusted for age, gender, BMI, TBLM, TBFM, exercise, and puberty category

	Model 1				Model 2			
Dependent variable	Independent variables	β[a]	Std. error	*P*	Independent variables	β[a]	Std. error	*P*
FNBMC	Age	0.045	0.013	0.0001	Age	0.044	0.013	0.001
	Sex	0.309	0.057	0.0001	Sex	0.292	0.057	0.0001
	BMI	0.024	0.010	0.018	BMI	0.024	0.010	0.020
	TBLM	5.72	0.000	0.0001	TBLM	5.7	0.000	0.0001
	HOMA-IR	− 0.060	0.021	0.004	QUICKI	1.297	0.520	0.013
	$R^2 = 0.73$				$R^2 = 0.73$			
FNBMD	Age	0.010	0.002	0.0001	Age	0.010	0.002	0.0001
	Sex	0.047	0.010	0.0001	Sex	0.045	0.010	0.0001
	BMI	0.008	0.002	0.0001	BMI	0.008	0.002	0.0001
	TBLM	5.89	0.000	0.0000	TBLM	5.5	0.000	0.0001
	HOMA-IR	− 0.010	0.004	0.010				
	$R^2 = 0.60$				$R^2 = 0.59$			
FNBMAD	Age	0.002	0.001	0.0001	Age	0.002	0.001	0.0001
	Sex	0.006	0.002	0.008	Sex	0.006	0.002	0.008
	BMI	0.002	0.000	0.0001	BMI	0.002	0.000	0.0001
	$R^2 = 0.20$				$R^2 = 0.20$			
FN Z-score	Age	− 0.076	0.028	0.006	Age	− 0.07	0.028	0.006
	Sex	0.316	0.123	0.011	Sex	0.316	0.123	0.011
	BMI	0.098	0.022	0.0001	BMI	0.1	0.022	0.0001
	TBLM	2.82	0.000	0.004	TBLM	2.82	0.000	0.004
	$R^2 = 0.20$				$R^2 = 0.20$			

Model 1 included age, sex, body mass index (BMI), TBLM, TBFM, exercise, puberty category, HOMA-IR

Model 2 included age, sex, BMI, TBLM, TBFM, exercise, puberty category, QUICKI index

Std. error standard Error, *FN* femoral neck

[a] Unstandardized β coefficient

Thereafter, Pollock et al. reported similar results in overweight pre-pubertal children who had prediabetes [20]. Our findings, also, did not support the hypothesized protective role of insulin for bone health in young people.

However, the inverse association of insulin resistance and bone can be explained by several mechanisms. For example, it is possible that insulin has direct effects on the bone. Indeed, insulin through its receptors in osteoblasts is important for survival of osteoblasts and stimulates osteocalcin production [21]. Also, it was shown that osteocalcin is essential in bone remodeling [22] and deletion of the osteoblast insulin receptors in animals leads to lower bone mass [15]. In this regard, previous studies reported lower levels of bone formation markers in children with prediabetes and in a murine model of early onset T2DM [23, 24]. Besides, in recent years, lipocalin-2 as another osteokine secreted from osteoblasts has shown to influence energy metabolism and insulin sensitivity [25]. Nevertheless, it should be noted that most of the information about the metabolic role of bone-derived osteokines was derived from studies on mice models and the experimental evidence has been only in part confirmed in humans and the results remain conflicting.

Furthermore, the contradictory results of prior studies about the effect of insulin resistance on the bone may suggest a threshold for insulin resistance in promoting healthy bone. Consistent with this hypothesis, Shin et al. showed that the association between fasting insulin level and whole body BMD differed by the degree of insulin resistance. They observed a positive association between fasting insulin level and BMD in the lowest quartile of HOMA-IR. However, in the higher quartiles of HOMA-IR, the fasting insulin level was inversely associated with the bone mass, and this relationship became more significant as the degree of insulin resistance increased [26].

Additionally, it has been suggested that the effect of insulin resistance on the bone acquisition is age dependent. Consistent with this idea, Kindler et al. observed age-dependent differences in BMD in youth-onset T2DM and concluded that T2DM might be detrimental to growing skeleton [27]. Recent studies also suggested that conditions related to insulin resistance, such as metabolic syndrome and prediabetes, could be possible disadvantages to childhood bone health [18].

Indirect factors might also contribute to the effects of insulin resistance on the bone mass. In fact, recent investigations

Table 4 Multiple stepwise linear regression analysis for the association between HOMA-IR and QUICKI index (independent variables) and whole body bone parameters (dependent variables) in two models, adjusted for age, gender, BMI, TBLM, TBFM, exercise, and puberty category

	Model 1				Model 2			
Dependent variable	Independent variables	β[a]	Std. error	*P*	Independent variables	β[a]	Std. error	*P*
Total BMC	Age	49.36	4.22	0.0001	Age	49.36	4.22	0.0001
	Sex	− 43.4	18.88	0.022	Sex	− 43.4	18.88	0.022
	BMI	14.78	3.38	0.0001	BMI	14.78	3.38	0.0001
	TBLM	0.029	0.001	0.0001	TBLM	0.029	0.001	0.0001
	$R^2 = 0.88$				$R^2 = 0.88$			
Total BMD	Age	0.021	0.001	0.0001	Age	0.021	0.001	0.0001
	BMI	0.008	0.001	0.0001	BMI	0.008	0.001	0.0001
	TBLM	4.14	0.000	0.0001	TBLM	3.88	0.000	0.0001
	HOMA-IR	− 0.005	0.002	0.029				
	$R^2 = 0.77$				$R^2 = 0.77$			
Total BMAD	Age	0.021	0.002	0.0001	Age	0.021	0.002	0.0001
	BMI	0.008	0.001	0.0001	BMI	0.008	0.001	0.0001
	TBLM	3.64	0.000	0.0001	TBLM	3.64	0.000	0.0001
	$R^2 = 0.69$				R^2=0.69			
Total Z-score	Age	− 0.16	0.022	0.0001	Age	− 0.16	0.022	0.0001
	Sex	0.21	0.10	0.033	Sex	0.20	0.10	0.047
	BMI	0.112	0.018	0.0001	BMI	0.111	0.018	0.0001
	TBLM	2.48	0.000	0.002	TBLM	2.16	0.000	0.006
	HOMA-IR	− 0.076	0.036	0.036				
	$R^2 = 0.23$				$R^2 = 0.23$			

Model 1 included age, sex, body mass index (BMI), TBLM, TBFM, exercise, puberty category, HOMA-IR

Model 2 included age, sex, BMI, TBLM, TBFM, exercise, puberty category, QUICKI index

Std. error standard error

[a] Unstandardized β coefficient

have identified an increasing number of conditions, which might potentially affect bone density in young people [15]. For instance, increased proinflammatory cytokines such as IL-6 and TNF-alpha was defined in insulin-resistant individuals, which may induce bone loss by stimulating osteoclast activity [28, 29]. Furthermore, increased fat mass (FM) as a major component of body weight was reported to stimulate the bone acquisition in children [30]. It should be noted that visceral fat was also considered as an endocrine organ by releasing adipokines and proinflammatory cytokines [31]. Conversely, it was suggested that osteocalcin, a bone-derived hormone, might induce insulin sensitivity through stimulating the secretion of adiponectin by the adipose tissue [22]. However, the influence of obesity on the bone density is still inconclusive. Although some reports showed a protective role of obesity against osteoporosis, other reports indicated a reverse relationship between adiposity and bone metabolism [30, 32]. For example, Mosca et al. showed a negative association between the percentage of FM and BMD or BMC in overweight, obese, and morbidly obese adolescents [33]. In the current study, to evaluate the possible role of FM in the relationship between insulin level and bone density, we compared the obtained results before and after adjustment for TBFM in the participants. Our data revealed a significant inverse association between insulin resistance and bone parameters, even after adjustment for TBFM. Therefore, it seems that increased FM in insulin resistant subjects could not completely explain the relation between the bone health and insulin resistance. However, the relationship between bone parameters and insulin resistance has been shown in both obese and non-obese subjects [34].

Along with the possible indirect mechanisms, we examined the correlation of TBLM as another major component of body composition with bone density. In fact, lean mass (LM) is suggested as the best predictor of BMC and BMD in adolescents, and its changes seems to be highly associated with the bone health [35]. In this regard, El Hage et al. reported LM as a strong positive determinant of BMD in boys and FM in girls [36]. Soininen et al. also showed both FM and LM as independent positive correlates for BMD in both genders [37].

Although the relationship between LM and insulin has been investigated extensively, only a few studies have examined the effects of insulin and LM on the bone health simultaneously [34, 37]. For example, Costoso et al. reported a positive influence by LM on the bone but an inverse relationship between LM and insulin levels [38].

Our study, in contrast, revealed a direct relationship between insulin concentrations and TBLM. Nevertheless, the

importance of LM as a mediator or confounder in the relationship between insulin and bone is uncertain. Insulin through stimulation of protein synthesis and inhibition of proteolysis in the skeletal muscle is linked to LM [39]. On the other hand, skeletal muscle has recently been considered as a secretory organ able to release myokines [40]. In this regard, irisin, a newly discovered myokine, has been shown to improve insulin sensitivity [41]. Moreover, dynamic loading resulting from physical activity and muscle contraction promotes bone mineralization and improves bone strength [42]. In the present study, the significant negative association between insulin resistance and bone parameters was remained almost unchanged after further adjustment for TBLM and physical activity.

Furthermore, another reason for the observed diversity in the results of the published studies might be the differences in the adjustment for confounding factors. In line with this idea, several studies revealed a loss of positive association between BMD and insulin after adjustment for BMI [7, 17]. Lawlor et al. also found no significant association between fasting insulin and BMD after adjustment for confounding factors, such as age and pubertal status [3]. However, in the current study, the negative association between the insulin resistance indices and bone parameters was observed even after adjustment for multiple confounding factors.

Finally, previous studies suggested that the rate and magnitude of bone mass accrual during pubertal years might differ amongst skeletal sites and individuals [43]. On the other hand, sex hormones might also be related to differences in bone mass gain between genders [43]. Therefore, other potential causes for the discrepancies in previous studies might be attributed to differences in age, race, and ethnicity of the participants or differences in bone mass gain between genders [43–45]. Genetic factors also play an important role in the peak bone mass achievement and account for about 60–80% of its variance [1, 44]. However, further studies in a variety of populations are warranted to confirm the insulin-bone association and reveal the underlying mechanisms before reaching a conclusive result.

The strength of this study is adjustment for several possible confounding factors, such as age, gender, BMI, TBFM, TBLM, puberty category, and exercise status in multivariate regression analyses. These adjustments helped to reduce biases in the obtained results. Also, due to lack of standardized levels for insulin and HOMA-IR in children and adolescents, we also used QUICKI as another index of insulin sensitivity for better evaluation of the relation between bone health and insulin resistance. Our study had some limitations including its cross-sectional design, which limits the inferences regarding causation and temporality. We also did not measure the biochemical markers of bone resorption and formation or pro-inflammatory cytokines.

Conclusion

This research showed significant inverse association between insulin resistance and bone parameters. Moreover, the associations remained significant even after adjustment for whole body fat mass and lean mass. Nonetheless, there are many unanswered questions regarding the relationship between glucose metabolism and bone homeostasis. For example, it is not yet clear whether the bone is another site for peripheral insulin resistance or insulin resistance might be detrimental for bone growth during puberty. Therefore, further basic and clinical studies should be performed to elucidate this issue by not only evaluating the biochemical markers of the bone formation and resorption but also by measuring insulin signaling in osteoblasts.

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Declarations

Ethics approval This study involving humans have been approved by the local Ethics Committee of Shiraz University of Medical Sciences. All procedures have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Conflict of interest None.

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