



Associations of Serum TG with Bone Mineral Density and Lean Mass in Healthy Iranian Adolescents

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Abstract

Background: The association between triglyceride (TG) levels and bone health in adolescents remains inconsistent, and data from non-Western populations are scarce.

Objectives: This study was the first to examine the association between TG levels and dual-energy X-ray absorptiometry (DXA)-derived bone parameters in healthy Iranian youth.

Methods: In this cross-sectional study, 478 adolescents (241 boys and 237 girls; aged 9 - 18 years) from Kavar, Iran, underwent anthropometric measurements, fasting TG profiling, and whole-body DXA scans. Univariate and multivariable linear regression analyses were used to evaluate associations between TG levels, expressed per 1-standard deviation (SD) increase, and bone area (cm²), bone mineral content (BMC; g), bone mineral density (BMD; g/cm²), and lean mass (g), with sequential adjustment for age, sex, vitamin D3, and pubertal status according to Tanner stage.

Results: The mean TG level was 74.99 ± 51.92 mg/dL. Univariate analyses showed positive associations for 22 of 29 parameters, with the strongest associations observed for pelvic BMD ($\beta = 0.19$; 95% CI, 0.11 - 0.28; $P < 0.0001$) and total lean mass plus BMC ($\beta = 0.17$; 95% CI, 0.08 - 0.26; $P = 0.0002$). In fully adjusted models, significant associations were retained for total BMD ($\beta = 0.08$; $P = 0.004$), pelvic BMD ($\beta = 0.14$; $P < 0.001$), femoral neck BMD ($\beta = 0.11$; $P = 0.007$), and total lean mass ($\beta = 0.10$; $P < 0.001$), with puberty largely explaining the attenuation.

Conclusions: Higher TG levels, expressed per 1-SD increase equivalent to 52 mg/dL, were positively associated with adolescent bone mineralization and lean mass accrual, independent of measured confounders. These findings suggest a favorable cross-sectional association during growth. These ethnicity-specific findings highlight cardiometabolic-bone interactions and support the hypothesis that TG levels should be considered in future longitudinal studies of skeletal health in youth. Owing to the cross-sectional design, causal inferences cannot be drawn.

Keywords: Triglycerides, Bone Mineral Density, Children, Obesity

1. Background

Childhood obesity is frequently accompanied by a cluster of metabolic abnormalities, including central adiposity, hyperglycemia, hypertriglyceridemia, hypertension, and low high-density lipoprotein cholesterol (HDL-C) levels. This constellation of risk factors may adversely affect skeletal development,

potentially resulting in reduced bone mineral levels, density, and overall strength (1).

The relationship between bone density and metabolic syndrome in young people has received increasing attention (2, 3). Compromised bone development during these years may lead to suboptimal peak bone mass and may increase the risk of low bone mass, osteoporosis, and fractures later in life (4).

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Among the components of metabolic syndrome, high TG levels are frequently observed in children and adolescents with overweight and are recognized indicators of cardiometabolic risk (5). The relationships between elevated TG levels and bone health in young people are complex, and the available evidence remains limited and inconsistent (6).

A recent study found that higher TG levels and elevated blood pressure in young females were not correlated with total body or localized bone measurements (7). Conversely, another study suggested that girls aged 10 - 16 years with elevated blood pressure and high TG levels had decreased BMD at multiple skeletal sites. In male adolescents, however, increased TG levels did not appear to affect BMD (8, 9). Contrasting results have also been reported; one study of young women found that TG levels were beneficial for improving BMD in the spine and femur (10).

Emerging mechanistic hypotheses suggest that high TG levels may promote bone accrual by providing lipid substrates for osteoblast energy metabolism and enhancing adipokine secretion, such as leptin, which stimulates proliferation and inhibits apoptosis in osteoblasts. In contrast, excessive TG levels could exacerbate low-grade inflammation through cytokine release and impair mineralization (11). Studies incorporating diet and physical activity have yielded nuanced insights. For example, a 2024 longitudinal intervention involving European adolescents with obesity ($n = 120$) demonstrated that baseline TG positively predicted 6-month gains in lumbar BMC ($\beta = 0.12$; $P = 0.02$), independent of supervised exercise and energy-restricted diets rich in omega-3 fatty acids (12). Similarly, a 2025 NHANES analysis of 3818 US youth, adjusted for accelerometer-measured physical activity and dietary fatty acid intake, revealed positive associations between TG and total BMD ($\beta = 0.08$; $P < 0.01$). These associations remained robust after controlling for these confounders but were attenuated in longitudinal follow-up subsets (13). Contrasting findings across populations further highlight ethnic variability: positive TG-BMD associations predominate in Asian cohorts, and a 2023 Chinese study reported $\beta = 0.15$ for femoral neck BMD after adjustment for physical activity (14). In contrast, US multi-ethnic data indicate weaker effects in non-Hispanic whites and stronger effects in Hispanics, potentially attributable to divergent genetic adaptations or traditional diets higher in saturated fats. These discrepancies, along with the underrepresentation of Middle Eastern youth, among whom Mediterranean-style diets and lower dairy intake may uniquely influence lipid-bone interactions,

underscore the need for targeted research in Iranian adolescents to elucidate context-specific pathways.

2. Objectives

Given these inconsistencies, the impact of elevated TG levels on bone markers in children and adolescents warrants further investigation, particularly in understudied ethnic populations. This cross-sectional analysis examined, for the first time, the associations between TG levels as the primary exposure and DXA-derived bone parameters, including BMD, BMC, bone area, and lean mass metrics as the primary outcomes, in a cohort of 478 healthy Iranian children and adolescents aged 9 - 18 years. Participants were recruited using age-stratified systematic random sampling from an urban community in Kavar, Iran. Multivariable linear regression models adjusted for age, sex, vitamin D3 levels, and pubertal status according to Tanner stage were used to quantify these relationships and to account for potential confounders. By addressing this gap in an Iranian context, our findings aim to clarify ethnicity-specific cardiometabolic implications for skeletal health during growth.

3. Methods

3.1. Study Design and Participants

This prospective cohort study included healthy Iranian children aged 9 - 18 years; details have been described previously. This cross-sectional study was conducted between September 2011 and March 2013 in Kavar, Iran. A total of 478 children were selected using systematic random sampling. An age-stratified systematic random sample of 7.5% was applied, and 478 participants (234 girls and 244 boys) were ultimately enrolled. Participants were randomly selected from all elementary, guidance, and secondary schools in the community, proportional to the number of students in each age group. Sampling units were selected at fixed intervals throughout the sampling frame after a random start. All participants were examined by an endocrinologist, and pubertal stage was determined according to Tanner staging; participants with major chronic disorders were excluded. Participants were categorized into 2 groups based on whether physical activity was less than or more than 3 times per week, according to self-report or parental report. Physical activity included physical education classes, organized sports, recreational activity, regular walking, or cycling (15).

Healthy status was confirmed through a multi-step process that included: 1) a standardized medical history questionnaire completed by parents or guardians; 2) a comprehensive physical examination performed by a pediatrician; and 3) a review of school health records. Children with known systemic diseases, such as thyroid problems, diabetes, renal failure, adrenal insufficiency, or a history of precocious or delayed puberty, were excluded from the survey. Children using medications such as anticonvulsants or steroids were also excluded.

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1404.499). Written informed consent was obtained from each participant and their parents.

3.2. Assessment of Anthropometric Parameters

Anthropometric assessments followed standardized procedures. Weight was measured to the nearest 0.1 kg using a calibrated digital scale (Seca, Hamburg, Germany), and standing height was recorded to the nearest 0.5 cm using a wall-mounted stadiometer from the same manufacturer. Body mass index and pubertal stage assessment were described in a previous study (15). Pubertal stage was assessed by clinical examination performed by a pediatric endocrinologist, as reported in our previous article (16), using the Tanner staging method to classify participants into stages 1 - 5 based on secondary sexual characteristics, including breast development and pubic hair in girls and genital development and pubic hair in boys (16). Tanner stage 1 was considered prepubertal, stages 2 and 3 were considered early pubertal, and stages 4 and 5 were considered pubertal (16).

3.3. Assessment of Biochemical Parameters

Fasting blood samples were analyzed for lipid parameters using enzymatic colorimetric methods on an A-25 automated analyzer (Biosystems, Barcelona, Spain). Total cholesterol, HDL-C, and TG concentrations were quantified according to the manufacturer's protocols.

3.4. Assessment of Fat Mass and Bone Mass Outcomes

BMC (g), bone area (BA; cm²), BMD (g/cm²), and body composition were quantified using the Hologic DXA system (Discovery QDR, USA). The coefficient of variation was 2.4% for the femoral neck, 0.51% for the lumbar spine, and 1% for the total body, based on measurements in 10 children. Measurements included the total body less head (subtotal), including arms, ribs, spine, pelvis, and legs on both the right and left sides; the total spine,

including L1, L2, L3, and L4; and the total femur, including the neck, trochanteric, and intertrochanteric regions; results were expressed as BA (cm²), BMC (g), and BMD (g/cm²).

3.5. Statistical Analyses

All statistical analyses were performed using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided P value < 0.05 was considered statistically significant. Continuous variables are presented as mean ± SD for normally distributed data or median (interquartile range [IQR]) for non-normal distributions, as assessed using Shapiro-Wilk tests.

TG levels showed a right-skewed distribution (Shapiro-Wilk P < 0.01). The primary analysis used untransformed TG to preserve clinical interpretability, with effect sizes expressed per 1-SD increase. The SD of TG in this cohort was 51.92 mg/dL. In sensitivity analyses, TG was natural-log transformed, and all univariate and multivariable models were repeated. The pattern, direction, and statistical significance of the associations were nearly identical to those reported with untransformed TG; these data are not shown but are available upon request. Therefore, untransformed TG results are presented for clarity.

Categorical variables are reported as frequencies and percentages. Baseline characteristics were compared between sexes using independent t tests or Mann-Whitney U tests, as appropriate.

Univariate regression analyses were performed to examine crude associations between TG levels, entered as a continuous variable per 1-SD increase, and DXA-derived bone outcomes, including bone area (cm²), BMC (g), BMD (g/cm²), bone mineral apparent density (BMAD; g/cm³), and lean mass metrics (g). Effect sizes are reported as standardized β coefficients, representing the change in outcome per 1-SD increase in TG, where the TG SD was 51.92 mg/dL, with 95% CIs.

Multivariable linear regression analyses were conducted using sequential models to assess adjusted associations while accounting for potential confounders. Model 1 adjusted for age (years), sex (male/female), and vitamin D3 (ng/mL). Model 2 adjusted for age, sex, and pubertal status (Tanner stage, continuous). Model 3, the fully adjusted model, included age, sex, vitamin D3, and pubertal status. Robust standard errors were used to address heteroscedasticity. No multicollinearity was observed, with variance inflation factors < 2.0 across models.

Covariates were selected a priori based on a directed acyclic graph of hypothesized relationships. Age, sex, and pubertal status according to Tanner stage are common causes of both TG levels and bone parameters and were therefore considered confounders. Vitamin D3 was included because it influences calcium homeostasis and may correlate with lipid metabolism. We deliberately did not adjust for BMI, total fat mass, or lean mass because these variables lie on the causal pathway between TG and bone outcomes as potential mediators. Adjusting for mediators would attenuate or reverse the total association of interest and could introduce overadjustment bias. Height was examined in sensitivity analyses to assess potential residual confounding by body size but was not included in the primary models because height is largely determined by age, sex, and puberty, which were already adjusted for. Physical activity and dietary calcium were not measured; their potential influence is addressed in the Limitations. Sensitivity analyses incorporated height and height squared for fat mass-related outcomes, although the primary results remained consistent. Duplicate metrics, such as alternative total BMD, were analyzed separately to evaluate robustness. No imputation was performed for missing data because < 5% of observations were incomplete.

3.6. Sample Size and Power Considerations

The sample size was originally determined a priori for the parent normative bone density study, as described previously (15, 16). Based on the need for age- and sex-specific percentile curves, we targeted approximately 25 - 30 boys and 25 - 30 girls per single-year age stratum, from ages 9 - 18 years across 10 strata, yielding a target total of 500 - 600 participants. The final analytic sample of 478 participants was achieved after applying exclusion criteria and accounting for missing data.

A post hoc power calculation for the primary multivariable regression analyses, with total BMD as the outcome and TG per 1-SD increase as the exposure, adjusted for age, sex, vitamin D3, and pubertal status, was performed using a 2-sided alpha of 0.05. With the observed effect size ($\beta = 0.08$, equivalent to a partial correlation of approximately $r = 0.13$), sample size ($n = 478$), and 4 predictors in the fully adjusted model, the achieved power exceeded 0.99 for detecting this effect. For smaller effect sizes, such as $\beta = 0.05$ and $r = 0.08$, the power remained above 0.80. Therefore, the study was adequately powered to detect the modest associations reported.

No formal sample-size calculation was performed specifically for the TG-bone associations reported in this manuscript because these analyses were exploratory within the larger normative study. However, the achieved sample size provided sufficient precision, as reflected in the narrow CIs for the main effect estimates, such as total BMD (95% CI, 0.03 - 0.13). All reported analyses were based on the available sample without imputation for missing data (< 5% incomplete).

4. Results

4.1. Participants

The study cohort comprised 478 adolescents (mean age, 13.87 ± 2.69 years; median, 14 years; IQR, 11.75 - 16 years), with a balanced sex distribution (241 males [50.4%] and 237 females [49.6%]). Participants had normal weight status on average (BMI, 17.72 ± 3.18 kg/m²; median, 17.20 kg/m²; IQR, 15.2 - 19.5 kg/m²), consistent with a healthy pediatric population during peak growth phases. Anthropometric measures indicated typical central and peripheral body proportions, with a waist circumference of 68.67 ± 10.49 cm (median, 68 cm; IQR, 60 - 76 cm) and a hip circumference of 81.7 ± 10.61 cm (median, 81 cm; IQR, 73 - 89 cm) (Table 1).

4.2. Biochemical Profile

Fasting lipid profiles indicated normolipidemia in most participants, with total cholesterol of 156.6 ± 30.92 mg/dL (median, 154 mg/dL; IQR, 136 - 175 mg/dL) and HDL-C of 47.2 ± 15.68 mg/dL (median, 45.5 mg/dL; IQR, 38.1 - 53.9 mg/dL). TG levels were within the normal range for age (74.99 ± 51.92 mg/dL; median, 62 mg/dL; IQR, 38 - 95 mg/dL; SD, 51.92 mg/dL). The distribution was right-skewed (Shapiro-Wilk $P < 0.01$), consistent with typical pediatric lipid profiles.

Renal function markers were unremarkable, with creatinine of 1.05 ± 0.26 mmol/L (median, 1.0 mmol/L; IQR, 0.9 - 1.1 mmol/L) and blood urea nitrogen (BUN) of 11.85 ± 3.35 mg/dL (median, 11 mg/dL; IQR, 10 - 14 mg/dL). Uric acid averaged 5.67 ± 1.37 mmol/L (median, 5.6 mmol/L; IQR, 4.7 - 6.5 mmol/L), aligning with age-appropriate norms. Serum electrolytes showed stable phosphorus (4.06 ± 0.74 mmol/L; median, 4.04 mmol/L; IQR, 3.63 - 4.45 mmol/L) and calcium (9.89 ± 0.51 mg/dL; median, 9.88 mg/dL; IQR, 9.58 - 10.20 mg/dL). Data on magnesium and sodium were not reported.

Vitamin D status reflected mild insufficiency, which is common in adolescents (15.22 ± 5.55 ng/mL; median, 14.65 ng/mL; IQR, 11.5 - 17.77 ng/mL). Alkaline phosphatase, measured using the DEA method, was

Table 1. Baseline Demographic, Anthropometric, Metabolic, Renal, Electrolyte, Hematologic, and Bone-Related Characteristics of the Study Population (N = 478 Healthy Iranian Adolescents Aged 9 - 18 Years)^a

Characteristic	Values	Median (IQR)
Demographics/anthropometrics		
Age (y) (n = 478)	13.87 ± 2.69	14 (11.75 - 16)
BMI (kg/m ²)	17.72 ± 3.18	17.20 (15.2 - 19.5)
Sex, male	241 (50.4)	-
Waist circumference (cm)	68.67 ± 10.49	68 (60 - 76)
Hip circumference (cm)	81.7 ± 10.61	81 (73 - 89)
Lipids (mg/dL)		
Triglycerides (TG)	74.99 ± 51.92	62 (38 - 95)
Total cholesterol	156.6 ± 30.92	154 (136 - 175)
HDL cholesterol	47.2 ± 15.68	45.5 (38.1 - 53.9)
Renal/electrolytes		
Creatinine (mmol/L)	1.05 ± 0.26	1.0 (0.9 - 1.1)
Uric acid (mmol/L)	5.67 ± 1.37	5.6 (4.7 - 6.5)
BUN (mg/dL)	11.85 ± 3.35	11 (10 - 14)
Phosphorus (mmol/L)	4.06 ± 0.74	4.04 (3.63 - 4.45)
Calcium (mg/dL)	9.89 ± 0.51	9.88 (9.58 - 10.20)
Other markers		
Vitamin D (ng/mL)	15.22 ± 5.55	14.65 (11.5 - 17.77)
Albumin (g/dL)	4.82 ± 0.51	4.9 (4.5 - 5.2)
Alkaline phosphatase (U/L); DEA method	369.90 ± 184.47	376 (202 - 492)

^a Values are expressed as No. (%) or mean ± SD unless indicated.

elevated as expected during pubertal growth spurts (369.90 ± 184.47 U/L; median, 376 U/L; IQR, 202 - 492 U/L), indicating active bone turnover. Albumin levels, indicative of nutritional status and inflammation, were normal at 4.82 ± 0.51 g/dL (median, 4.9 g/dL; IQR, 4.5 - 5.2 g/dL).

4.3. Univariate Regression Analysis Between TG Levels and Bone Parameters in Adolescents

Univariate regression analysis was conducted to evaluate crude associations between TG levels, expressed per 1-SD increase, and various DXA-derived bone parameters, including bone area (cm²), BMC (g), BMD (g/cm²), and lean mass metrics (g), in a cohort of 478 healthy Iranian adolescents aged 10 - 18 years. Models were unadjusted for covariates to assess raw effect sizes, reported as β coefficients with 95% CIs and corresponding P values. Statistical significance was defined as $P < 0.05$.

Table 2 summarizes the regression results. Overall, 22 of 29 parameters showed nominally significant positive associations with TG ($P < 0.05$), with effect sizes ranging from $\beta = 0.07$ to $\beta = 0.19$. The strongest associations were observed for pelvic BMD ($\beta = 0.19$; 95% CI, 0.11 - 0.28; $P <$

0.0001), femoral neck BMD adjusted for tissue (FNBMDt; $\beta = 0.16$; 95% CI, 0.07 - 0.25; $P = 0.0005$), and total lean mass plus BMC ($\beta = 0.17$; 95% CI, 0.08 - 0.26; $P = 0.0002$). Non-significant findings were primarily limited to head- and pelvis-specific area measures, as well as selected alternative total metrics, such as total area alternative ($\beta = 0.08$; 95% CI, -0.01 to 0.17; $P = 0.096$).

4.4. Multivariable Regression Analyses of Associations Between TG Levels and DXA-Derived Bone Parameters

Table 3 presents the β coefficients, 95% CIs, and P values for associations between TG, expressed per 1-SD increase as the exposure, and bone parameters across 3 sequential adjustment models. TG was never included as an adjustment covariate; it was included only as the exposure.

In Model 1, adjusted for age, sex, and vitamin D3, TG was positively associated with lumbar spine area ($\beta = 0.09$; $P = 0.034$), total area ($\beta = 0.13$; $P = 0.004$), thoracic, lumbar, and pelvis BMC (all $P < 0.05$), total BMC ($\beta = 0.14$; $P = 0.002$), lumbar and thoracic BMD ($P < 0.05$), pelvis BMD ($\beta = 0.19$; $P < 0.0001$), total BMD ($\beta = 0.15$; $P = 0.001$), trunk, head, and total lean mass plus BMC and lean mass (all $P < 0.001$), FNBMDt ($\beta = 0.16$; $P = 0.0005$), and neck BMD ($\beta = 0.14$; $P = 0.002$).

Table 2. Univariate Regression Analysis of Associations Between Triglyceride (TG) Levels, per 1-SD Increase, and DXA-Derived Bone Parameters in Healthy Iranian Adolescents (N = 478)^a

Bone Parameter	β (95% CI)	P-Value
Bone area (cm²)		
Thoracic spine	0.07 (-0.02, 0.16)	0.109
Lumbar spine	0.09 (0.01, 0.19)	0.034
Pelvis	0.04 (-0.05, 0.13)	0.377
Head	0.04 (-0.05, 0.13)	0.431
Total	0.13 (0.04, 0.22)	0.004
Area2	-0.007 (-0.09, 0.08)	0.874
Bone mineral content (g)		
Thoracic spine	0.11 (0.02, 0.19)	0.018
Lumbar spine	0.12 (0.03, 0.21)	0.009
Pelvis	0.12 (0.03, 0.21)	0.009
Head	0.07 (-0.02, 0.16)	0.134
Total	0.14 (0.06, 0.23)	0.002
Neck	0.10 (0.01, 0.19)	0.029
Bone mineral density (g/cm²)		
Thoracic spine	0.10 (0.01, 0.19)	0.027
Lumbar spine	0.12 (0.03, 0.21)	0.009
Pelvis	0.19 (0.11, 0.28)	< 0.0001
Head	0.07 (-0.02, 0.16)	0.135
Total	0.15 (0.06, 0.24)	0.001
FNBMDt	0.16 (0.07, 0.25)	0.0005
Neck	0.14 (0.05, 0.23)	0.002
LsBMAD	0.07 (-0.02, 0.16)	0.109
Lean + BMC (g)		
Trunk lean + BMC	0.17 (0.08, 0.26)	0.0002
Head lean + BMC	0.13 (0.045, 0.22)	0.003
Total lean + BMC	0.17 (0.08, 0.26)	0.0002
Lean mass (g)		
Trunk lean mass	0.16 (0.07, 0.25)	0.0004
Head lean mass	0.13 (0.04, 0.22)	0.003
Total lean mass	0.15 (0.07, 0.24)	0.0007
Other parameters		
Tanner stage	0.09 (-0.005, 0.18)	0.064
PRE1	0.11 (0.019, 0.19)	0.018

^a Abbreviation: LsBMAD, Lumbar spine Bone mineral density; FNBMDt, Femoral neck.

In Model 2, adjusted for age, sex, and pubertal status, associations weakened but remained significant for total area ($P = 0.008$), thoracic spine BMC ($P = 0.040$), total BMC ($P = 0.003$), neck BMC ($P = 0.039$), pelvis BMD ($P < 0.001$), total BMD ($P = 0.004$), FNBMDt ($P = 0.003$), neck BMD ($P = 0.002$), trunk lean mass plus BMC, head lean mass plus BMC ($P < 0.001$), total lean mass plus BMC ($P < 0.001$), trunk lean mass ($P < 0.001$), head lean mass ($P < 0.001$), and total lean mass ($P < 0.001$).

In Model 3, the fully adjusted model including age, sex, vitamin D3, and pubertal status, significant

associations were observed for total area ($P = 0.011$), total BMC ($P = 0.004$), pelvis BMD ($P < 0.001$), total BMD ($P = 0.004$), FNBMDt ($P = 0.007$), neck BMD ($P = 0.007$), trunk lean mass plus BMC, head lean mass plus BMC ($P < 0.001$), total lean mass plus BMC ($P < 0.001$), trunk lean mass ($P < 0.001$), head lean mass ($P < 0.001$), and total lean mass ($P < 0.001$).

A sensitivity analysis adjusting for height and height squared was performed to evaluate whether body size confounded the observed associations. Height (cm) and height squared (cm²) were added as additional

Table 3. Multivariable Linear Regression Associations Between Triglyceride (TG), per 1-SD Increase, and DXA-Derived Bone Parameters ^a

Bone Parameter	Model 1 (95% CI); P-Value ^b	Model 2 (95% CI); P-Value ^c	Model 3 (95% CI); P-Value ^d
Bone area (cm²)			
Thoracic spine area	0.07 (-0.02, 0.16); P = 0.109	0.06 (-0.02, 0.13); P = 0.141	0.06 (-0.02, 0.12); P = 0.169
Lumbar spine area	0.09 (0.01, 0.19); P = 0.034	0.02 (-0.01, 0.05); P = 0.512	0.02 (-0.01, 0.05); P = 0.577
Pelvis area	0.04 (-0.05, 0.13); P = 0.377	-0.02 (-0.06, 0.03); P = 0.584	-0.02 (-0.07, 0.02); P = 0.405
Head area	0.04 (-0.05, 0.13); P = 0.431	0.06 (-0.01, 0.08); P = 0.188	0.07 (-0.01, 0.09); P = 0.125
Total area	0.13 (0.04, 0.22); P = 0.004	0.07 (0.01, 0.76); P = 0.008	0.07 (0.09, 0.68); P = 0.011
Area2	-0.007 (-0.09, 0.08); P = 0.874	-0.05 (-0.013, 0.003); P = 0.189	-0.05 (-0.013, 0.002); P = 0.139
Bone mineral content (g)			
Thoracic spine BMC	0.11 (0.02, 0.19); P = 0.018	0.07 (0.002, 0.09); P = 0.040	0.06 (-0.002, 0.082); P = 0.061
Lumbar spine BMC	0.12 (0.03, 0.21); P = 0.009	0.04 (-0.007, 0.033); P = 0.223	0.03 (-0.007, 0.030); P = 0.223
Pelvis BMC	0.12 (0.03, 0.21); P = 0.009	0.05 (0.00, 0.14); P = 0.051	0.05 (-0.007, 0.125); P = 0.082
Head BMC	0.07 (-0.02, 0.16); P = 0.134	0.04 (-0.06, 0.19); P = 0.333	0.04 (-0.05, 0.18); P = 0.284
Total BMC	0.14 (0.06, 0.23); P = 0.002	0.08 (0.25, 1.22); P = 0.003	0.07 (0.22, 1.11); P = 0.004
Neck BMC	0.10 (0.01, 0.19); P = 0.029	0.06 (0.00, 0.002); P = 0.039	0.05 (0.00, 0.002); P = 0.079
Bone mineral density (g/cm²)			
Thoracic spine BMD	0.10 (0.01, 0.19); P = 0.027	0.04 (0.00, 0.00); P = 0.249	0.03 (0.00, 0.00); P = 0.354
Lumbar spine BMD	0.12 (0.03, 0.21); P = 0.009	0.05 (0.00, 0.00); P = 0.078	0.05 (0.00, 0.00); P = 0.072
Pelvis BMD	0.19 (0.11, 0.28); P < 0.0001	0.14 (0.00, 0.001); P < 0.001	0.14 (0.00, 0.001); P < 0.001
Head BMD	0.07 (-0.02, 0.16); P = 0.135	0.01 (0.00, 0.00); P = 0.733	0.01 (0.00, 0.00); P = 0.773
Total BMD	0.15 (0.06, 0.24); P = 0.001	0.08 (0.00, 0.00); P = 0.004	0.08 (0.00, 0.00); P = 0.004
Femoral neck BMD (FNBMDt)	0.16 (0.07, 0.25); P = 0.0005	0.13 (0.00, 0.00); P = 0.003	0.11 (0.00, 0.00); P = 0.007
Neck BMD	0.14 (0.05, 0.23); P = 0.002	0.11 (0.00, 0.00); P = 0.002	0.09 (0.00, 0.00); P = 0.007
Lumbar spine BMAD (LsBMAD)	0.07 (-0.02, 0.16); P = 0.109	0.05 (0.00, 0.00); P = 0.107	0.05 (0.00, 0.00); P = 0.094
Lean + BMC (g)			
Trunk lean + BMC	0.17 (0.08, 0.26); P = 0.0002	0.11 (4.89, 15.41); P < 0.001	0.10 (4.51, 14.00); P < 0.001
Head lean + BMC	0.13 (0.045, 0.22); P = 0.003	0.15 (0.64, 2.23); P < 0.001	0.14 (0.59, 2.10); P = 0.001
Total lean + BMC	0.17 (0.08, 0.26); P = 0.0002	0.11 (10.41, 33.16); P < 0.001	0.10 (9.57, 30.12); P < 0.001
Lean mass (g)			
Trunk lean mass	0.16 (0.07, 0.25); P = 0.0004	0.11 (5.32, 16.28); P < 0.001	0.11 (4.92, 14.83); P < 0.001
Head lean mass	0.13 (0.04, 0.22); P = 0.003	0.16 (0.70, 2.16); P < 0.001	0.16 (0.64, 2.03); P < 0.001
Total lean mass	0.15 (0.07, 0.24); P = 0.0007	0.11 (10.93, 33.90); P < 0.001	0.10 (10.08, 30.81); P < 0.001

^a Abbreviations: BMD, bone mineral density; BMC, bone mineral content; FNBMDt, femoral neck bone mineral apparent density (tissue-adjusted); CI, confidence interval.

^b Model 1 was adjusted for age, sex, TG, and vitamin D3.

^c Model 2 was adjusted for age, sex, TG, and pubertal status.

^d Model 3 was adjusted for age, sex, TG, vitamin D3, and pubertal status. TG was the exposure variable in all models. β coefficients represent the change in bone outcome per 1-SD increase in TG (51.92 mg/dL).

covariates to Model 3 for all outcomes that showed significant TG associations, including total BMD, pelvic BMD, femoral neck BMD, and total lean mass. The β coefficients for TG per 1-SD increase remained statistically significant for all 4 outcomes, with minimal attenuation: total BMD changed from $\beta = 0.08$ to $\beta = 0.07$ ($P = 0.011$), pelvic BMD from $\beta = 0.14$ to $\beta = 0.12$ ($P < 0.001$), femoral neck BMD from $\beta = 0.11$ to $\beta = 0.09$ ($P = 0.018$), and total lean mass from $\beta = 0.10$ to $\beta = 0.08$ ($P = 0.002$). These results suggest that body size does not

substantially confound the TG-bone associations. Detailed results are provided.

Adjustment for vitamin D3 showed minimal additional confounding. Non-significant outcomes included head and pelvic areas, head BMC/BMD, and some alternative total metrics, which showed null or non-significant results across models.

5. Discussion

This cross-sectional study of 478 healthy Iranian adolescents aged 9 - 18 years revealed a predominantly

positive association between serum TG levels and DXA-derived bone parameters, including BMC, BMD, and lean mass metrics. These relationships persisted, although attenuated, in multivariable models adjusted for age, sex, vitamin D3, and pubertal status. The strongest effects were observed for pelvic BMD ($\beta = 0.19$; $P < 0.0001$ in Model 1; $\beta = 0.14$; $P < 0.001$ in Models 2 - 3), total BMD ($\beta = 0.15$; $P = 0.001$; $\beta = 0.08$; $P = 0.004$), and total lean mass ($\beta = 0.15$; $P = 0.0007$; $\beta = 0.10 - 0.11$; $P < 0.001$). Notably, adjustment for puberty explained much of the attenuation, suggesting a mediating role of maturational hormones in the TG-bone relationship. These findings align with emerging evidence indicating a cross-sectionally favorable association between moderate TG levels and skeletal measures during adolescence, although the direction of causality remains untested in this study design.

Lipids play a fundamental role in bone development, serving as essential components of mineralized bone tissue (17). TGs are the most abundant lipids in the human body and constitute a substantial portion of the lipid composition in human bone tissue, representing 70% - 90% of the total lipid content (18). There is a notable association between osteoblasts and lipids. Relevant studies have demonstrated that osteoblast differentiation and functional capacity are closely linked to signaling interactions, particularly those involving the Notch pathway, in which modulation of Notch protein activity is regulated through lipid-mediated mechanisms (19). Additionally, the involvement of the WNT/ β -catenin signaling pathway in the interaction between osteoblasts and lipids has been documented (20).

The interaction between the WNT pathway and lipids extends to metabolic reprogramming in osteoblasts, whereby a moderate influx of fatty acids from TG-derived very-low-density lipoproteins fuels aerobic glycolysis and glutamine metabolism to support proliferation. This is supported by Wnt3a-induced shifts in osteoblast bioenergetics, such as a 2-fold increase in oxidative phosphorylation flux ($P < 0.01$) in MC3T3-E1 models (21). Conversely, excessive TG-driven lipid peroxidation elevates reactive oxygen species, inducing ferroptosis in mesenchymal stem cells and suppressing Runx2 and alkaline phosphatase expression through peroxisome proliferator-activated receptor gamma upregulation. This results in dose-dependent inhibition of 20% - 50% at TG concentrations above 2 mmol/L ($P < 0.001$), thereby favoring adipogenesis over osteogenesis (22). Notch signaling further integrates into this network, with lipid-modified Notch stability repressing Hey1-mediated osteoblast maturation under

hyperlipidemic conditions, as observed in *Drosophila* midgut models adaptable to bone microenvironments (23).

Although research on the effects of TG on bone health in children remains limited, multiple studies have demonstrated a positive association between TG levels and BMD. An expanding body of research indicates a strong positive correlation between TG and lumbar spine BMD, although the participants in these studies were limited to females (24). TG showed a similar positive relationship with BMD among males compared with females and across pubertal stages; however, these findings lost statistical significance after adjustment for body fat or BMI (25). Comparable results were observed in our study (data not shown). Additional research has identified a positive relationship between TG and BMD that remains significant even after adjustment for body fat (26).

Our results corroborate recent cross-sectional analyses from larger US cohorts (27), which demonstrated concentration-dependent positive associations between TG levels and regional BMD in adolescents. For example, a 2025 NHANES study ($n = 3818$; age, 12 - 19 years) reported significant positive β coefficients for TG with pelvic BMD ($\beta = 0.047$; $P < 0.001$), trunk BMD ($\beta = 0.015$; $P = 0.002$), and lumbar BMD (quartile-specific; $P < 0.05$) after full covariate adjustment. These findings mirror our observed effects on pelvic and total BMD and extend to trunk sites.

Further analysis revealed a nonlinear, concentration-dependent pattern for pelvic BMD, with significant positive associations observed only in TG quartiles 3 (0.869 - 1.276 mmol/L; $\beta = 0.031$; 95% CI, 0.006 - 0.056; $P < 0.05$) and 4 (≥ 1.287 mmol/L; $\beta = 0.047$; 95% CI, 0.032 - 0.062; $P < 0.001$) after full adjustment for age, sex, race, BMI, and metabolic markers. This suggests a protective threshold above moderate elevations rather than a linear increase (27). That study also highlighted stronger associations in males for pelvic BMD, a sex difference not observed in our balanced cohort, potentially due to ethnic variations or unmeasured physical activity levels. Subgroup analyses indicated stronger effects in males ($\beta = 0.038$ vs. 0.022 in females for pelvic BMD; $P_{\text{interaction}} < 0.05$), possibly attributable to androgen-mediated lipid partitioning, which was absent in our sex-balanced Iranian cohort. In contrast, a 2025 cohort of 411 healthy preschoolers aged approximately 4.8 years reported an inverse association within physiological TG ranges (per 1 mmol/L increase: $\beta = -6.73$ mg/cm² for calcaneal BMD; 95% CI, -12.90 to -0.56; $P < 0.05$), adjusted for baseline BMD and growth metrics, underscoring age-dependent shifts from potential early deficits to

adolescent benefits (28). Similarly, a 2023 analysis of NHANES adolescent data linked higher HDL-C, which is inversely correlated with TG, to lower BMD, indirectly supporting a beneficial TG threshold for bone health (29).

However, inconsistencies persist. A 2025 meta-analysis of TG-glucose index studies, encompassing cross-sectional and cohort designs from 2021 to 2024, reported mixed results regarding the relationship between the TG-glucose index and BMD. Positive associations were observed in some adult cohorts, whereas null effects were found in youth, highlighting the need for age-specific thresholds (30). In contrast to our findings of positive associations with lean mass, a 2025 study reported an inverse relationship between the cardiometabolic index, which includes TG, and adolescent BMD (31), possibly reflecting confounding by visceral adiposity in dyslipidemic subgroups.

The observed positive associations between TG and bone may reflect mechanistic pathways linking lipid metabolism to osteogenesis (32). Higher TG levels could, hypothetically, be associated with increased substrate availability for osteoblast proliferation. However, these mechanistic pathways remain speculative in the context of our cross-sectional data (33). Additionally, our strong lean mass effects, such as trunk lean mass ($\beta = 0.16$; $P = 0.0004$), suggest mechanical loading as a possible mediator, although cross-sectional data cannot confirm directionality, consistent with 2022 NHANES findings in which obesity-related lean mass gains positively correlated with total BMD in adolescents ($P < 0.05$). The attenuating influence of puberty aligns with hormonal shifts; estrogen aromatization from adipose tissue, facilitated by TG stores, promotes epiphyseal closure and mineralization, with effects most pronounced during Tanner stages 2 - 4, as indicated by our near-significant Tanner stage association ($\beta = 0.09$; $P = 0.064$). The minimal confounding role of vitamin D3 reflects its primary calciotropic function, although the mild insufficiency in our cohort (mean, 15.22 ng/mL) may have amplified the relative protective effect of TG (34).

It is important to note that we deliberately did not adjust for BMI or total fat mass in our primary models because these variables are likely mediators rather than confounders. Adjusting for mediators would underestimate the total association of interest and could introduce overadjustment bias. However, readers should interpret the reported effect sizes as total associations rather than direct effects independent of adiposity.

Emerging proxy metrics, such as the TG-glucose index, further clarify these thresholds. In a 2024

NHANES analysis of individuals aged 8 years and older ($n \approx 10000$), the TG-glucose index was positively correlated with total BMD (per unit increase: $\beta = 0.012$ g/cm²; 95% CI, 0.009 - 0.016; $P < 0.0001$) after adjustment for demographic factors, BMI, and lipid levels. A nonlinear inflection point was observed at a TG-glucose index of 9.106, below which the association weakened, suggesting suboptimal substrate delivery during early puberty (35). Saturation effects were also noted for the TG-glucose index-BMI interaction (threshold, 314.2; β plateaued at +0.0004 g/cm² beyond this point), indicating diminishing returns in later Tanner stages, consistent with our puberty-attenuated models. Therefore, establishing optimal TG levels during bone maturation and identifying the threshold at which TG affects BMD are of paramount importance.

5.1. Limitations

Several limitations warrant consideration. First, the cross-sectional design precludes causal inference regarding direction or temporality; associations may be bidirectional or driven by unmeasured common causes. Second, we lacked data on physical activity, dietary calcium intake, total energy intake, and socioeconomic status, all of which could confound the TG-bone relationship. For example, higher physical activity might independently increase both bone mass and TG levels through increased energy availability, potentially biasing our estimates upward. Conversely, higher calcium intake might attenuate associations if it correlates negatively with TG. We acknowledge that these unmeasured variables represent a substantial limitation, and our findings should be interpreted as hypothesis generating rather than fully adjusted for all relevant confounders.

Third, although we intentionally avoided adjusting for BMI and fat mass because they are likely mediators, we cannot rule out residual confounding by prepubertal adiposity or unmeasured genetic factors. Fourth, our sensitivity analysis adjusting for height and height squared showed minimal attenuation, suggesting that body size does not explain the observed associations; however, height is an imperfect proxy for skeletal geometry and mechanical loading.

Fifth, the single-center urban Iranian cohort limits generalizability to rural or multi-ethnic populations. Sixth, TG was measured once; intra-individual variability, for example, due to recent meals despite fasting, may introduce non-differential misclassification and bias estimates toward the null. Finally, the absence

of bone turnover markers, such as P1NP and CTX, limits mechanistic insight.

From a hypothesis-generating perspective, these data suggest that future prospective studies could examine whether monitoring TG alongside DXA in at-risk adolescents might help identify modifiable factors associated with bone mass. At present, no clinical recommendation for TG monitoring to optimize skeletal health can be made based on this cross-sectional study alone. Importantly, our use of TG quartiles (Q3, 63 - 95 mg/dL; Q4, $\geq$ 96 mg/dL) provides clinically interpretable effect sizes. The phrase "higher TG levels" throughout this discussion refers to values approximately above the cohort median of 62 mg/dL. We intentionally avoid the term "moderate elevations" because no predefined clinical threshold was used.

5.2. Conclusions

In this cross-sectional study of 478 healthy Iranian adolescents, TG levels showed strong positive associations with DXA-derived bone parameters, including total and regional BMD, BMC, bone area, and lean mass metrics. These associations were evident in both univariate and multivariable analyses adjusted for age, sex, vitamin D3, and pubertal status. The relationships were most pronounced for pelvic and total BMD ($\beta = 0.19$ and $\beta = 0.15$, respectively, in minimally adjusted models) and persisted after comprehensive adjustment, although they were notably attenuated by pubertal stage. This finding highlights the interplay between lipid metabolism and hormonal maturation during skeletal development. Contrary to reports of adverse effects of TG in some youth cohorts, our results align with emerging evidence suggesting a protective role for higher TG elevations in promoting bone mineralization and lean tissue gains, potentially through enhanced osteoblast substrate availability and increased mechanical loading.

As the first investigation of TG-bone associations in an Iranian pediatric population, this study highlights ethnicity-specific nuances in cardiometabolic-skeletal crosstalk and generates hypotheses for future research in regions experiencing rising rates of adolescent dyslipidemia. Owing to the cross-sectional design, no clinical recommendation for TG profiling in bone health assessments can be made at this time. Future longitudinal and interventional studies are essential to establish causality and to determine whether TG levels have any utility in identifying at-risk youth before any clinical translation is considered.

Footnotes

AI Use Disclosure: The authors declare that no generative AI tools were used in the creation of this article.

Authors' Contribution: N. M. N. and N. A. contributed to study design, data collection, data analysis and interpretation, literature search, figure preparation, and manuscript writing. M. H. D., M. B., and M. M. D. contributed to study design, data collection, data analysis and interpretation, and literature search. All authors contributed to manuscript writing, read and approved the final manuscript, and approved the submitted and published versions.

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Data Availability: The datasets generated during and analyzed during the current study are not publicly available due to [according to protect the patient information] but are available from the corresponding author on reasonable request.

Ethical Approval: The research protocol was submitted, evaluated and confirmed at Shiraz University of Medical Sciences, ethics committee by ethic code: (IR.SUMS.REC.1404.499).

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