Clin. Lab. 2025;71:XXX-XXX

ORIGINAL ARTICLE

Correlation between Insulin Resistance and Bone Turnover Markers in Girls with Idiopathic Central Precocious Puberty

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SUMMARY

Background: **This study was performed to investigate the influence of insulin resistance (IR) on bone turnover markers in girls with idiopathic central precocious puberty (ICPP).**
Methods: **One hundred and sixteen ICPP girls and 91 healthy girls were enrolled in this study. The levels of total procollagen type I N-terminal propeptide (P1NP), N-terminal midfragment of osteocalcin (N-MID), β-C-terminal telopeptide of type 1 collagen (β-CTX), insulin, and other biochemical parameters were detected.**
Results: **The serum P1NP and β-CTX levels were significantly different between the non-IR and IR groups and the control group ($p < 0.05$). Serum N-MID was not significantly different among the groups ($p > 0.05$). The serum P1NP level was negatively correlated with vitamin D ($r = -0.162$, $p < 0.05$) and positively correlated with homeostatic model assessment for IR ($r = 0.160$, $p < 0.05$).**
Conclusions: **The influence of ICPP on bone turnover markers may be associated with IR for girls with ICPP. Strict blood glucose control and insulin regulation appear to play an extremely important role in restoring bone metabolism status in ICPP girls.**
(Clin. Lab. 2025;71:xx-xx. DOI: 10.7754/Clin.Lab.2024.240901)

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Manuscript accepted November 6, 2024

KEYWORDS

bone turnover markers, insulin resistance, idiopathic central precocious puberty, obesity, P1NP

INTRODUCTION

The development of puberty is affected by many factors, including the environment and nutritional supplementation [1]. Puberty is a period of positive bone remodeling activity, and bone development during puberty has a crucial influence on peak bone mass and bone strength in adults [2]. Idiopathic central precocious puberty (ICPP) is defined as activation of the hypothalamic-pituitary-gonadal axis before the age of 8 years in girls and 9 years in boys [3]. Girls with ICPP show premature secretion of estradiol, which accelerates the progression of bone age and increases the risks of osteoporosis and fractures in adulthood [4]. Bone turnover markers (BTMs) are widely used to predict bone metabolism dysfunction and monitor the treatment effect of

osteoporosis, because these markers provide valuable information on the rate of bone turnover [5,6]. In our previous study, we found that girls with ICPP had obviously abnormal bone metabolism compared with healthy girls of the same age. The level of serum procollagen type I N-terminal propeptide (P1NP) was increased and the level of serum β-C-terminal telopeptide of type 1 collagen (β-CTX) was decreased in girls with ICPP [7]. However, the reason for the abnormal bone development in girls with ICPP remains unclear.

In recent years, the mechanism underlying the interaction between glucose metabolism and bone metabolism has been gradually revealed. Multiple endocrine functions of bones, other than those related to mineral metabolism, such as regulation of insulin sensitivity, glucose homeostasis, and energy metabolism, have been discovered [8]. Various bone-derived factors such as osteocalcin, osteoprotegerin, receptor activator of nuclear factor-κB ligand (RANKL), fibroblast growth factor 23, sclerostin, and lipocalin 2 have been found to be related to glucose metabolism [9]. Accumulating evidence suggests that bone is an insulin target tissue and may be a determinant of glucose and energy homeostasis [10]. Diabetes or impaired glucose metabolism can affect bone health, leading to reduced bone formation, increased bone marrow fat, and increased fracture risk [11,12]. The results of a recent cross-sectional study of female patients near the age of peak bone mass (18 – 19 years) suggest that insulin resistance (IR) might mediate the link between adiposity and bone [13]. Another study showed that IR was associated with deficits in cortical bone size and estimated bending strength in boys and girls aged 9 to 13 years in the early stages of sexual maturation [14].

In addition, evidence indicates that girls with CPP have lower insulin sensitivity, increased compensatory insulin secretion, and adverse lipid profiles at diagnosis [15]. Research on the relationship between IR, glucose metabolism, and BTMs in girls with ICPP remains scarce and inconclusive, clearly warranting further study. Therefore, to further observe whether bone metabolism in girls with ICPP is related to IR, we selected girls with ICPP as the subjects of the present preliminary study and examined the correlation between BTMs and IR indicators.

MATERIALS AND METHODS

Patients

The study was performed at our hospital from January 2021 through June 2022. We initially enrolled 285 girls aged 5 to 9 years with precocious puberty. Out of these, we excluded girls who did not satisfy the diagnostic criteria for CPP (n = 128) and those who had other diseases or treatments with exogenous sex hormone drugs (n = 41). Ultimately, 116 girls with ICPP were included in the study (Figure 1). Another 91 healthy girls identified in the central health examination database with a matched age distribution were included as the control group (Figure 1). The 116 girls with ICPP were divided into the non-IR (NIR) group (n = 48) and the IR group (n = 68) according to a homeostatic model assessment for IR (HOMA-IR) of ≥ 2.69 [16]. Trained staff collected all data, including gender, age, medical history, weight, height, body mass index (BMI), and bone age. The study protocol was approved by the Clinical Trial Ethics Committee of our hospital (no. 2020040). Informed consent was obtained from the parents of all girls before enrollment. All clinical investigations were conducted in accordance with the principles outlined in the Declaration of Helsinki.

All patients in this study were confirmed to have ICPP. According to the 2015 guidelines of the Chinese Medical Association [17], a diagnosis of ICPP requires children to meet all the following conditions simultaneously: (1) development of secondary sex characteristics before the age of 8 years in girls and 9 years in boys, with the same sequence of sexual development as in normal children; (2) higher annual growth rate than children of the same age and gender; (3) higher bone age relative to chronological age by at least 1 year; (4) increased size of uterus and ovaries and more than one ovarian follicle with a diameter of ≥ 4 mm on pelvic ultrasound in girls; and (5) hypothalamic-pituitary-gonadal axis activation. To confirm hypothalamic-pituitary-gonadal axis function activation, a gonadotropin hormone-releasing hormone excitation test must show a luteinizing hormone peak level of ≥ 5.0 U/L and luteinizing hormone/follicle-stimulating hormone peak ratio of > 0.6.

The exclusion criteria were: evaluation by head magnetic resonance imaging and evaluation of thyroid function, adrenal function, and other conditions, except for secondary CPP. Height and weight were measured by the same staff at the same location. Bone mineral density was assessed by dual X-ray absorptiometry.

Biochemical parameters

After an overnight fast, a 4-mL sample of venous blood was obtained from the patients. The serum was separated by centrifugation and stored at −80°C for subsequent analysis. The serum P1NP, N-MID, and β-CTX levels were measured with an electrochemical luminescence immunity analyzer (Cobas E411; Roche, Mannheim, Germany). The serum levels of fasting blood glucose (FBG), total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were measured using a clinical chemistry system (ADVIA 2400; Siemens AG, Munich, Germany). Serum vitamin D (VitD) was measured by an immunoluminescence detector (Abbott i2000SR; Abbott Laboratories, Chicago, IL, USA). Fasting insulin (FINS) was measured by an immunoassay system (ADVIA Centaur XP; Siemens AG). HOMA-IR was calculated using the following simplified equation: HOMA-IR = FBG × FINS/22.5 [18]. HOMA-IR of ≥ 2.69 was defined as IR, and that of < 2.69 was defined as non-IR (NIR). Sample collection, transportation, sep-

Table 1. Patients' baseline clinical characteristics.

Items	Control group (n = 91)	NIR group (n = 48)	IR group (n = 68)
CA (years)	8.00 (7.00 - 8.00)	8.00 (7.00 - 8.00)	8.00 (7.00 - 8.00)
Height (cm)	124.50 (122.50 - 126.50)	131.40 (127.33 - 136.28) [a]	133.00 (128.51 - 137.38) [a]
Weight (kg)	25.00 (23.00 - 26.50)	30.50 (25.00 - 35.63) [a]	29.00 (25.63 - 34.60) [a]
BMI (kg/m^2)	15.94 (15.00 - 16.91)	16.85 (15.71 - 19.40) [a]	16.42 (15.30 - 19.87) [a]

[a] - Significantly different from the control group, [b] - significantly different from the NIR group.
IR - insulin resistance, NIR - no insulin resistance, CA - chronological age, BMI - body mass index.

Table 2. Blood biochemical characteristics.

Items	Control group (n = 91)	NIR group (n = 48)	IR group (n = 68)
HDLC (mmol/L)	1.34 (1.27 - 1.62)	1.50 (1.25 - 1.85)	1.53 (1.27 - 1.77) [a]
LDLC (mmol/L)	2.28 (2.12 - 2.72)	2.19 (1.90 - 2.71)	2.19 (1.93 - 2.61)
TC (mmol/L)	3.79 (3.34 - 4.22)	3.88 (3.60 - 4.26)	3.80 (3.55 - 4.43)
TG (mmol/L)	0.85 (0.67 - 1.16)	0.78 (0.67 - 1.07)	0.79 (0.68 - 1.08)
VitD (ng/mL)	26.50 (22.60 - 30.60)	20.00 (17.35 - 23.30) [a]	21.00 (16.93 - 24.15) [a]
FINS (μIU/mL)	7.37 (5.36 - 8.86)	8.04 (6.50 - 10.01)	20.86 (15.32 - 24.18) [ab]
FBG (mmol/L)	5.03 (4.64 - 5.24)	4.64 (4.30 - 4.89) [a]	4.92 (4.69 - 5.12) [b]
HOMA-IR	1.59 (1.18 - 2.08)	1.64 (1.30 - 2.00)	4.53 (3.47 - 5.44) [ab]

[a] - Significantly different from the control group, [b] - significantly different from the NIR group.
IR - insulin resistance, NIR - no insulin resistance, HDLC - high-density lipoprotein cholesterol, LDLC - low-density lipoprotein cholesterol, TC - total cholesterol, TG - triglycerides, VitD - vitamin D, FINS - fasting insulin, FBG - fasting blood glucose, HOMA-IR - homeostatic model assessment for insulin resistance.

Table 3. Levels of BTMs.

BTMs	Control group (n = 91)	NIR group (n = 48)	IR group (n = 68)
P1NP (ng/mL)	772.90 (602.60 - 1,022.00)	1,046.50 (817.20 - 1,196.35) [a]	944.35 (714.75 - 1,065.5) [ab]
N-MID (pg/mL)	74.57 (57.49 - 90.45)	77.65 (62.64 - 87.36)	75.90 (63.06 - 88.49)
β-CTX (ng/mL)	1,620.00 (1,400.00 - 1,940.00)	1,463.50 (1,058.50 -1,796.50) [a]	1,485.00 (1,200.00 - 1,850.00) [a]

[a] - Significantly different from the control group, [b] - significantly different from the NIR group.
BTM - bone turnover markers, IR - insulin resistance, NIR - no insulin resistance, P1NP - procollagen type I N-terminal propeptide, N-MID - N-terminal midfragment of osteocalcin, β-CTX - β-C-terminal telopeptide of type 1 collagen.

aration, and storage were performed according to standard laboratory operating procedures.

Statistical analysis

Data were analyzed using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA). Data are presented as median (interquartile range). The Mann–Whitney U test was performed to test differences in BTMs and biochemical parameters. Spearman's correlation analysis was used to determine the associations between the variables. A value of $p < 0.05$ was considered significant for all statistical analyses.

Table 4. Correlation analysis between bone turnover markers and insulin resistance.

Items	P1NP		N-MID		β-CTX	
	r	p	r	p	r	p
CA	0.021	0.793	0.034	0.672	-0.008	0.925
Height	0.163 *	0.040	0.096	0.230	-0.055	0.488
Weight	0.083	0.297	0.065	0.413	-0.047	0.557
BMI	-0.052	0.516	0.004	0.963	-0.010	0.902
HDLC	0.006	0.936	0.128	0.107	0.057	0.473
VitD	-0.162 *	0.041	-0.048	0.551	0.041	0.604
FINS	0.155	0.051	-0.013	0.872	-0.231 **	0.003
FBG	0.013	0.866	0.028	0.731	0.011	0.886
HOMA-IR	0.160 *	0.044	-0.005	0.947	-0.219 **	0.005

*** - p < 0.05 was considered statistically significant.**
P1NP - procollagen type I N-terminal propeptide, N-MID - N-terminal midfragment of osteocalcin, β-CTX - β-C-terminal telopeptide of type 1 collagen, CA - chronological age, BMI - body mass index, HDLC - high-density lipoprotein cholesterol, VitD - vitamin D, FINS - fasting insulin, FBG - fasting blood glucose, HOMA-IR - homeostatic model assessment for insulin resistance.

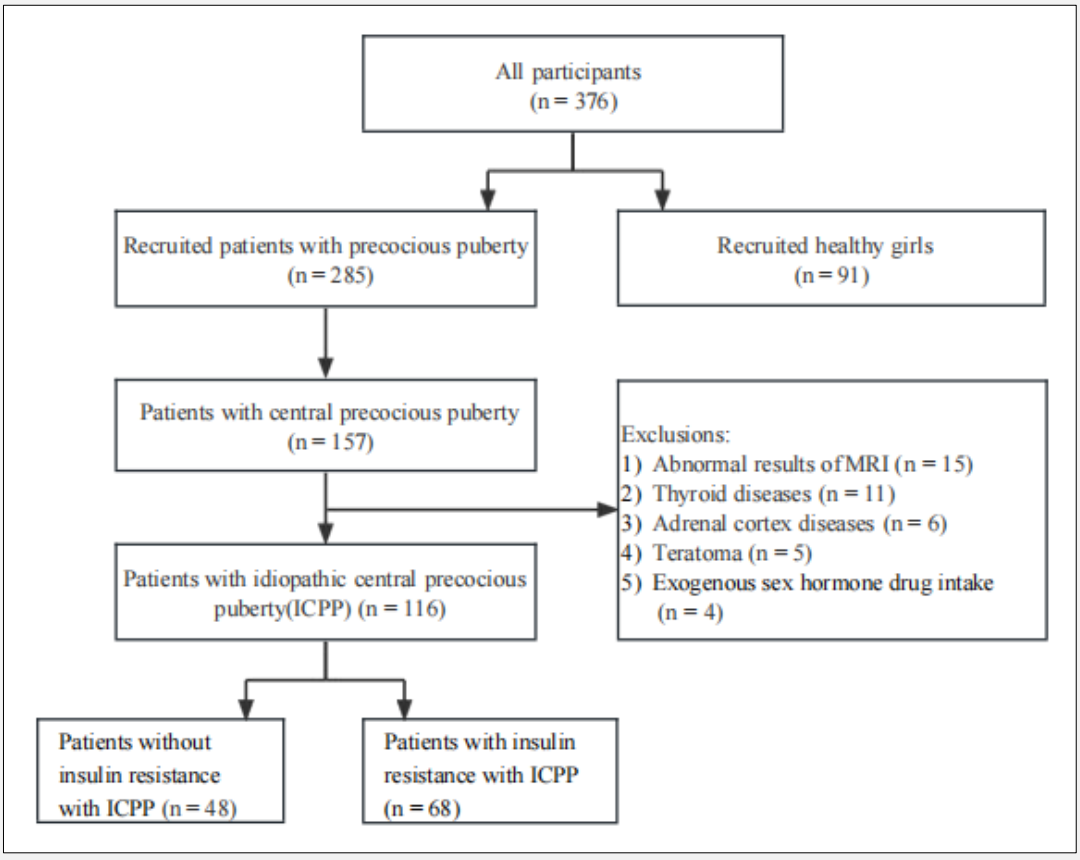

Figure 1. Flow chart of the study participants.

MRI - magnetic resonance imaging, ICPP - idiopathic central precocious puberty.

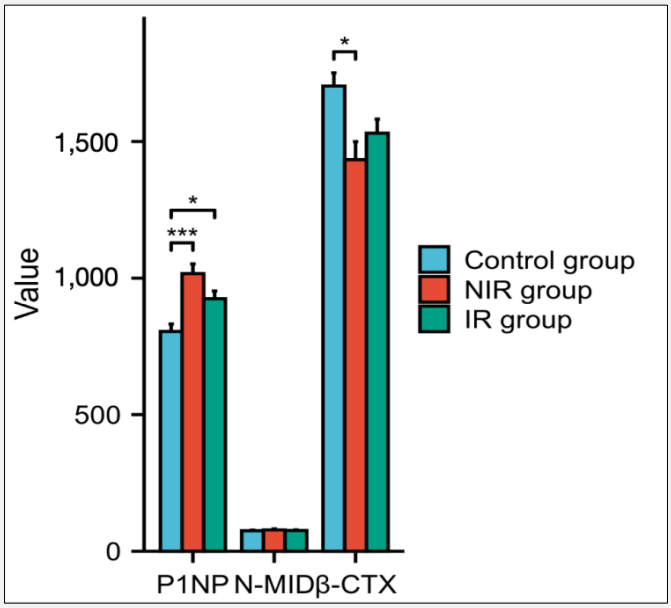

Figure 2. Differences in bone turnover markers between the groups.
IR - insulin resistance, NIR - no insulin resistance, P1NP - procollagen type I N-terminal propeptide, N-MID - N-terminal mid-fragment of osteocalcin, β-CTX - β-C-terminal telopeptide of type 1 collagen.

RESULTS

Clinical characteristics of IR and NIR groups

The patients' baseline clinical characteristics are shown in Table 1. There was no difference in chronological age among the groups ($p > 0.05$). The comparisons of weight, height, and BMI are shown in Table 1.

Biochemical characteristics

The serum VitD and FBG levels were significantly lower in the NIR than in the control group ($p < 0.05$). The serum levels of high-density lipoprotein cholesterol, VitD, and FINS were significantly different between the IR and control group ($p < 0.05$) (Table 2).

Serum BTM levels

Table 3 shows the BTM levels among the groups. The serum P1NP and β-CTX levels were significantly different between the NIR and IR groups and the control group ($p < 0.05$). The serum P1NP level was significantly different between the IR and NIR groups ($p < 0.05$). The serum N-MID level was not significantly different among the groups ($p > 0.05$). The differences in BTMs are compared in Figure 2.

Correlation analysis between bone metabolism and IR

As shown in Table 4, the serum P1NP level was negatively correlated with VitD ($r = -0.162$, $p < 0.05$) and positively correlated with HOMA-IR ($r = 0.160$, $p < 0.05$). N-MID had no significant correlation with HOMA-IR ($p > 0.05$). The serum β-CTX level was negatively correlated with FINS level ($r = -0.231$, $p < 0.05$) and HOMA-IR ($r = -0.219$, $p < 0.05$).

DISCUSSION

IR can lead to a variety of chronic metabolic diseases, the most important of which are type 2 diabetes mellitus (T2DM) and metabolic syndrome. IR is also associated with several other diseases, including non-alcoholic liver disease, dyslipidemia, atherosclerosis, and certain cancers [19,20]. It is nowadays clear that IR is not inherited or a condition of unclear origin. IR is metabolically induced by the hormonal activity of the visceral lipid tissue, which is part of the development process of obesity. Basically, all of the so far identified > 200 adipokines secreted in the lipid cell growth process act against insulin in glucose metabolism and induce other damage in parallel, such as e.g. angiotensin II (→ hypertension) or proinflammatory cytokines, TNF-alpha, etc. (→ chronic systemic inflammation and atheroscle-

rosis) [21,22]. Studies have already shown that there is a correlation between cardiopulmonary health and bone turnover markers with inflammatory markers in adults with metabolic syndrome. However, there is currently almost no research on the correlation between cardiopulmonary health and bone turnover markers with inflammatory markers in children with precocious puberty, which will be one of our future research directions. Although the mechanism of IR is unclear, research has shown that the severity of IR varies with increases in the BMI, waist circumference, and especially waist–hip ratio [23]. In the present study, weight, height, and BMI were significantly higher in the NIR and IR groups than in the control group ($p < 0.05$). The reason for this may be that lipotoxicity caused by obesity impairs insulin post-receptor signaling. Other factors involved in the development of IR include inflammatory factors, insulin antagonist hormones, advanced glycation end products, adipokines, and by-products of nutrient overload accumulating in insulin target organs [19,24,25]. Studies have shown that in the development of IR, poor glycemic control is correlated with excessive urinary calcium loss, with subsequent stimulation of chronic parathyroid hormone secretion and deleterious effects on the skeletal system [26].

Bone metabolism is a continuous remodeling or turnover process that depends on a tightly coupled balance between bone formation by osteoblasts and bone resorption by osteoclasts. BTMs are collagenous and non-collagenous components released by osteoblasts or osteoclasts during the bone remodeling process. P1NP and N-MID secreted by osteoblasts are markers of bone formation. β-CTX is regarded as a marker of bone resorption and osteoclast activity. These markers may provide a dynamic picture of changes in bone formation and resorption, thus helping to identify changes in bone remodeling within a relatively short time interval [27]. P1NP is a specific indicator of bone formation, and the amount of P1NP in the blood is proportional to the ability of osteoblasts to synthesize collagen [28]. In the current study, the serum level of P1NP was significantly different between the NIR and IR groups and the control group ($p < 0.05$). The serum P1NP level was negatively correlated with the VitD ($r = -0.162$, $p < 0.05$) and positively correlated with HOMA-IR ($r = 0.160$, $p < 0.05$). A recent study suggested that HOMA-IR was negatively correlated with P1NP in patients with T2DM [29]. Arikan Senay et al. [30] showed that among patients with T2DM, the bone mineral density was lower in those with more severe IR. The mechanism underlying this difference may be that IR affects the anabolic response of bone tissue, leading to impairment of bone renewal, which adversely affects bone strength [31]. Studies have also shown a bidirectional relationship between insulin resistance and bone health. Bone turnover in the insulin resistant state may be affected by multiple factors, including local and systemic metabolic changes. For example, it has been shown that there is a complex relationship between insulin resistance and bone mineral density, and this relationship may be influenced by various factors such as age, gender, obesity, and diabetes [32-35]. More research is needed in this area to fully understand these complex interactions and to explore potential therapeutic targets.

β-CTX is the most widely used marker of bone resorption, serving as a sensitive indicator in situations where osteoblasts are apoptotic and type I collagen degradation occurs. This process leads to the generation of type I collagen crosslinks, providing a responsive measure of osteoclast activity [36,37]. Several studies have revealed lower β-CTX levels in individuals with T2DM than in individuals without T2DM [38,39]. The present study showed that the serum level of β-CTX was significantly lower in the NIR and IR groups than in the control group ($p < 0.05$). The serum β-CTX level was negatively correlated with FINS level ($r = -0.231$, $p < 0.05$) and HOMA-IR ($r = -0.219$, $p < 0.05$). A study involving a mouse model of impaired hepatic insulin clearance showed that peripheral tissue IR and hyperinsulinemia can lead to bone resorption disorders. The mechanism may involve impairment of the RANKL pathway by IR, thereby affecting the recruitment and differentiation of osteoclasts [40].

N-MID is a proteolytic product of osteocalcin, which is more stable in peripheral blood than intact osteocalcin. Osteocalcin is derived from osteoblasts and reflects the rate of bone formation [41]. Compared with the first two markers, the relationship between N-MID and IR is much more complex. Studies have shown that the skeletal system regulates glucose metabolism through N-MID [42]. N-MID can increase the proliferation of pancreatic cells and insulin expression *in vitro*, but the specific mechanism is not clear [43]. Hyperglycemia and IR can negatively affect the gene expression of osteocalcin [44]. In our study, we found no difference in N-MID between the NIR and IR groups and the control group. We may need more in-depth studies to explore the relationship between N-MID IR.

The two main strengths of our study are that, first, we used detailed inclusion and exclusion criteria to ensure a more precise sample population, and second, to the best of our knowledge, this is the first study to analyze the correlation between BTMs and IR in girls with ICPP. However, it also has some limitations, namely its small sample size and lack of Turner staging of the patients. Therefore, we will continue to expand the sample size for a follow-up study to more deeply explore the relationship between BTMs and IR in a larger population. In addition, the definition of IR through HOMA index alone is not sufficient. HOMA assumes that insulin is the only hormone that is capable of lowering glucose. However, when subjects have stage III ß-cell dysfunction, i.e. are also secreting proinsulin in addition to insulin, the HOMA score is not correct [45]. Limitations of the HOMA-B score for assessment of beta-cell functionality in interventional trials results from the PIOglim study [45]. Proinsulin can also lower glucose and is not measured by the insulin assays; hence, the

HOMA-score is always wrongly too low under these circumstances, and proinsulin should have been measured to obtain a clean NIR population. In any case, the HOMA score is insufficient to describe an IR population. In future studies, in order to obtain more accurate research results, the minimal model assessment or hyperglycemic clamp can be added for evaluation. The association between IR and obesity is well known. Studies have shown that obesity has an impact on children with precocious puberty, and we can further investigate the relationship between bone metabolism and obesity in girls with ICPP. Although the present results did not confirm a direct effect of IR on prediction of bone metabolism or risk of fracture in girls with ICPP, strict blood glucose control and insulin regulation appear to play an extremely important role in restoring the bone metabolism status in girls with ICPP.

CONCLUSION

The bone formation level of P1NP was lower in the IR than in the NIR group among girls with ICPP but was higher than that in the control group. The serum β-CTX level was significantly different between the NIR and IR groups and the control group. No obvious difference in the N-MID level was found among the groups. The serum P1NP level, however, was found to be positively correlated with HOMA-IR. Large-scale clinical studies are required to clarify the specific mechanisms underlying the present observations.

Source of Funds:
This research was supported by the Sichuan Province Science and Technology Support Program (2023YFS0 218).

Ethical Approval Statement:
This case-control study complied with the ethics of the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee of West China Second University Hospital (ethical approval No. 2020 040).

Data Availability Statement:
The data used to support the findings of this study are included in the article. Due to the sensitivity of the data and the restrictions from the informed consent, the data will not be stored at a public repository but are available from the corresponding author upon reasonable request.

Declaration of Interest:
The authors declare that they have no conflicts of interest.

References:

1. Dunger DB, Ahmed ML, Ong KK. Effects of obesity on growth and puberty. Best Pract Res Clin Endocrinol Metab 2005;19(3): 375-90. (PMID: 16150381)

2. Seibel MJ. Clinical application of biochemical markers of bone turnover. Arq Bras Endocrinol Metabol 2006;50(4):603-20. (PMID: 17117286)

3. Carel J-C, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009;123(4):e752-62. (PMID: 19332438)

4. Latronico AC, Brito VN, Carel J-C. Causes, diagnosis, and treatment of central precocious puberty. Lancet Diabetes Endocrinol 2016;4(3):265-74. (PMID: 26852255)

5. Massera D, Biggs ML, Walker MD. Biochemical Markers of Bone Turnover and Risk of Incident Diabetes in Older Women: The Cardiovascular Health Study. Diabetes Care 2018;41(9): 1901-8. (PMID: 30002202)

6. van Bommel EJM, de Jongh TR, Brands M. The osteoblast: Linking glucocorticoid-induced osteoporosis and hyperglycaemia? A post-hoc analysis of a randomised clinical trial. Bone 2018;112:173-6. (PMID: 29729427)

7. Zhang J, Gao R, Jiang Y, et al. Novel serological biomarker models composed of bone turnover markers, vitamin D, and estradiol and their auxiliary diagnostic value in girls with idiopathic central precocious puberty. Bone 2022;154:116221. (PMID: 34600161)

8. Weivoda MM, Chew CK, Monroe DG, et al. Identification of osteoclast-osteoblast coupling factors in humans reveals links between bone and energy metabolism. Nat Commun 2020;11(1):87. (PMID: 31911667)

9. Cipriani C, Colangelo L, Santori R, et al. The Interplay Between Bone and Glucose Metabolism. Front Endocrinol (Lausanne) 2020;11:122. (PMID: 32265831)

10. Ferron M, Wei J, Yoshizawa T, et al. Insulin signaling in osteoblasts integrates bone remodeling and energy metabolism. Cell 2010;142(2):296-308. (PMID: 20655470)

11. Khan MP, Singh AK, Joharapurkar AA, et al. Pathophysiological mechanism of bone loss in type 2 diabetes involves inverse regulation of osteoblast function by PGC-1a and skeletal muscle atrogenes: AdipoR1 as a potential target for reversing diabetes-induced osteopenia. Diabetes 2015;64(7):2609-23. (PMID: 25633418)

12. Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. Am J Epidemiol 2007;166(5):495-505. (PMID: 17575306)

13. Kindler JM, Pollock NK, Ross HL, et al. Obese Versus Normal-Weight Late-Adolescent Females have Inferior Trabecular Bone Microarchitecture: A Pilot Case-Control Study. Calcif Tissue Int 2017;101(5):479-88. (PMID: 28710506)

14. Kindler JM, Pollock NK, Laing EM, et al. Insulin Resistance and the IGF-I-Cortical Bone Relationship in Children Ages 9 to 13 Years. J Bone Miner Res 2017;32(7):1537-45. (PMID: 28300329)

15. Sørensen K, Andersson AM, Skakkebaek NE, Juul A. Serum sex hormone-binding globulin levels in healthy children and girls with precocious puberty before and during gonadotropin-releasing hormone agonist treatment. J Clin Endocrinol Metab 2007; 92(8):3189-96. (PMID: 17519314)

16. Yin J, Li M, Xu L, et al. Insulin resistance determined by Homeostasis Model Assessment (HOMA) and associations with metabolic syndrome among Chinese children and teenagers. Diabetol Metab Syndr 2013;5(1):71. (PMID: 24228769)

17. Subspecialty Group of Endocrinologic, Hereditary and Metabolic Diseases, the Society of Pediatrics, Chinese Medical Association; Ethical Board, Chinese Journal of Pediatrics. [Consensus statement for the diagnosis and treatment of central precocious puberty (2015)]. Zhonghua Er Ke Za Zhi 2015;53(6):412-8. (PMID: 26310550)

18. Wallace TM, Levy JC, Matthews DR. Use and Abuse of HOMA Modeling. Diabetes Care 2004;27(6):1487-95. (PMID: 15161807)

19. Muntoni S, Muntoni S. Insulin resistance: pathophysiology and rationale for treatment. Ann Nutr Metab 2011;58(1):25-36. (PMID: 21304221)

20. Mastrototaro L, Roden M. Insulin resistance and insulin sensitizing agents. Metabolism 2021;125:154892. (PMID: 34563556)

21. Gustafson B. Adipose tissue, inflammation and atherosclerosis. J Atheroscler Thromb 2010;17(4):332-41. (PMID: 20124732)

22. Gil-Cosano JJ, Gracia-Marco L, Courteix D, et al. Cardiorespiratory Fitness and Bone Turnover Markers in Adults With Metabolic Syndrome: The Mediator Role of Inflammation. Int J Sport Nutr Exerc Metab 2022;33(1):23-9. (PMID: 36270626)

23. Aronne LJ, Segal KR. Adiposity and fat distribution outcome measures: assessment and clinical implications. Obes Res 2002; 10(Suppl 1):14S-21S. (PMID: 12446853)

24. Tong Y, Xu S, Huang L, Chen C. Obesity and insulin resistance: Pathophysiology and treatment. Drug Discov Today 2022;27(3): 822-30. (PMID: 34767960)

25. James DE, Stöckli J, Birnbaum MJ. The aetiology and molecular landscape of insulin resistance. Nat Rev Mol Cell Biol 2021; 22(11):751-71. (PMID: 34285405)

26. Schwartz AV. Diabetes mellitus: does it affect bone? Calcified Tissue Int 2003;73(6):515-9. (PMID: 14517715)

27. Wei X, Zhang Y, Xiang X, et al. Exploring the Relationship of Bone Turnover Markers and Bone Mineral Density in Community-Dwelling Postmenopausal Women. Dis Markers 2021;2021: 6690095. (PMID: 33968284)

28. Koivula M-K, Risteli L, Risteli J. Measurement of aminoterminal propeptide of type I procollagen (PINP) in serum. Clin Biochem 2012;45(12):920-7. (PMID: 22480789)

29. Li W, Liu X, Liu L, et al. Relationships of Serum Bone Turnover Markers With Metabolic Syndrome Components and Carotid Atherosclerosis in Patients With Type 2 Diabetes Mellitus. Front Cardiovasc Med 2022;9:824561. (PMID: 35548441)

30. Yang L, Hu X, Zhang H, Pan W, Yu W, Gu X. Association of bone mineral density with a first-degree family history of diabetes in normoglycemic postmenopausal women. Menopause 2019; 26(11):1284-8. (PMID: 31688576)

31. Arikan S, Tuzcu A, Bahceci M, Ozmen S, Gokalp D. Insulin resistance in type 2 diabetes mellitus may be related to bone mineral density. J Clin Densitom 2012;15(2):186-90. (PMID: 22321655)

32. Li M, Chi X, Wang Y, Setrerrahmane S, Xie W, Xu H. Trends in insulin resistance: insights into mechanisms and therapeutic strategy. Signal Transduct Target Ther 2022;7(1):216. (PMID: 35794109)

33. Xourafa G, Korbmacher M, Roden M. Inter-organ crosstalk during development and progression of type 2 diabetes mellitus. Nat Rev Endocrinol 2024;20(1):27-49. (PMID: 37845351)

34. Zhuo M, Chen Z, Zhong M-L, et al. Association of insulin resistance with bone mineral density in a nationwide health check-up population in China. Bone 2023;170:116703. (PMID: 36781092)

35. Armutcu F, McCloskey E. Insulin resistance, bone health, and fracture risk. Osteoporos Int 2024;35(11):1909-17. (PMID: 39264439)

36. Jain S, Camacho P. Use of bone turnover markers in the management of osteoporosis. Curr Opin Endocrinol Diabetes Obes 2018; 25(6):366-72. (PMID: 30299435)

37. Vervloet MG, Brandenburg VM; CKD-MBD Working Group of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA). Circulating markers of bone turnover. J Nephrol 2017;30(5):663-70. (PMID: 28502032)

38. Hannon TS, Kahn SE, Utzschneider KM, et al. Review of methods for measuring beta-cell function: Design considerations from the Restoring Insulin Secretion (RISE) Consortium. Diabetes Obes Metab 2018;20(1):14-24. (PMID: 28493515)

39. Vilaca T, Schini M, Harnan S, et al. The risk of hip and non-vertebral fractures in type 1 and type 2 diabetes: A systematic review and meta-analysis update. Bone 2020;137:115457. (PMID: 32480023)

40. Liang J, Lian S, Qian X, et al. Association Between Bone Mineral Density and Pancreatic beta-Cell Function in Elderly Men and Postmenopausal Women. J Endocr Soc 2017;1(8):1085-94. (PMID: 29264561)

41. Yang Y, Zhong W, Huang J, Geng L, Feng Q. Association of serum osteocalcin levels with glucose metabolism in trauma patients. Medicine (Baltimore) 2020;99(36):e21901. (PMID:32899020)

42. Booth SL, Centi A, Smith SR, Gundberg C. The role of osteocalcin in human glucose metabolism: marker or mediator? Nat Rev Endocrinol 2013;9(1):43-55. (PMID: 23147574)

43. Ferron M, McKee MD, Levine RL, Ducy P, Karsenty G. Intermittent injections of osteocalcin improve glucose metabolism and prevent type 2 diabetes in mice. Bone 2012;50(2):568-75. (PMID: 21550430)

44. Komori T. Functions of Osteocalcin in Bone, Pancreas, Testis, and Muscle. Int J Mol Sci 2020;21(20):7513. (PMID: 33053789)

45. Pfützner A, Derwahl M, Jacob S, et al. Limitations of the HOMA-B score for assessment of beta-cell functionality in interventional trials-results from the PIOglim study. Diabetes Technol Ther 2010;12(8):599-604. (PMID: 20615100)