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# Evaluation of visceral adipose tissue thickness in precocious puberty

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**Abstract. – OBJECTIVE: Although there is a relationship between earlier onset of puberty and increased adiposity tissue. Publications in the literature on adiposis in patients with central precocious puberty (CPP) and visceral fat thickness (VFT) have conflicting results. So, in this study, we aimed to evaluate the relationship between sexual maturation and obesity in the development of early puberty and to examine their relationship with pelvic sonographic parameters.**

**PATIENTS AND METHODS: A total of 126 girls [patients – premature thelarche (PT) and CPP – and controls] were included in this study. Anthropometric and ultrasonographic evaluations were made by the same pediatric endocrinologist and pediatric radiologist, respectively. Pubertal stages were made according to the Tanner stages. Height, weight, and body mass index were measured as anthropometric measurements, and visceral, subcutaneous, and transabdominal fat thicknesses were measured in sonographic evaluation.**

**RESULTS: The study population was divided into three groups: 44 healthy subjects to Group 1, 23 patients with PT to Group 2, and 59 patients with CPP to Group 3. When we evaluated the anthropometric and ultrasonographic parameters according to pubertal status, significant differences, especially between Group 1 and Group 3, were observed in all data. In the multiple logistic regression analysis, the endometrial thickness (OR = 7.521, $p < 0.001$) and VFT (OR = 1.530, $p < 0.001$) were found to be independent predictors of precocious puberty.**

**CONCLUSIONS: It has been found that VFT and endometrial thickness measurements, which are evaluated quickly and accurately by USG, are important predictors of prepubertal precociousness.**

*Key Words:*
Obesity, Central precocious puberty, Visceral fat thickness, Ultrasonography.

## Introduction

Obesity in childhood is becoming an important health problem with increasing frequency and is associated with many metabolic diseases[1]. It is known that obesity affects many aspects of pubertal development, such as the timing of puberty and pubertal hormonal parameters[2].

Obesity has also been associated with the risk of systemic arterial hypertension and metabolic syndrome, as well as early onset of puberty[3]. Adiposity refers to the amount of body fat, and it has been shown that higher levels of adiposity can lead to an earlier onset of puberty. There is evidence to suggest that there is a relationship between earlier onset of puberty and increased adiposity tissue[4,5]. However, the findings are inconsistent, as there are studies[6-9] documenting a higher incidence of obesity in girls with idiopathic central precocious puberty (CPP) than in those without idiopathic CPP, and other studies[6-9] that did not find this association.

Imaging methods such as ultrasonography (USG), computed tomography (CT), and magnetic resonance imaging (MRI) are used to differentiate visceral fat tissue (VFT) from subcutaneous fat tissues (SFT) and to determine the amount of these tissues[10]. USG is a less expensive and less invasive method, making it a more feasible option for routine clinical use; it is the preferred method for evaluating children since there is no exposure to ionizing radiation. Although visceral obesity was not found to be high in girls with CPP, it was associated with early breast development in CPP girls[5].

The relationship between pubertal development and visceral, subcutaneous, and transabdominal fat deposition has been little investigated in the literature. Although data on adiposity in patients with CPP is available in the literature, there are conflicting results about VFT. So, in this study, we aimed to evaluate the relationship between sexual maturation and obesity in the development of early puberty by measuring visceral, subcutaneous, and transabdominal fat tissue (TAFT) by USG and to examine their relationship with pelvic sonographic parameters.



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## Patients and Methods

### Study Population

Female patients who were diagnosed with sequential premature thelarche (PT) and CPP and applied to the pediatric endocrinology outpatient clinic in our institution between April 2019 and March 2020 were prospectively included in this study. The control group consisted of healthy subjects who were referred to the USG unit of the radiology department of our hospital for non-gynecological reasons such as urinary tract infections or acute infections.

The diagnosis of idiopathic CPP is typically made based on a combination of physical exam, laboratory tests, and imaging studies. The criteria for diagnosis of CPP were as follows: (a) onset of breast development before 8 years and/or menses before 9 years of age, (b) pubertal LH response to exogenous GnRH, (c) a ratio of stimulated LH / stimulated FSH > 1.0, (d) no clinical signs and/or history of organic CPP, and (e) no evidence of intracranial lesions on MRI[11]. The diagnosis of PT is typically made based on the following: patients with isolated breast development without any other sign of sexual maturation, (i) bone age ≤ chronological age, (ii) peak LH value < 5 IU/L in GnRH stimulation test, (iii) no progression in pubertal findings and (iv) bone age after at least one year of clinical follow-up[12]. CPP patients with organic pathological imaging findings in the central nervous system and peripheral precocious puberty patients with comorbidities affecting the onset of puberty were also excluded from the study. The control group consisted of 44 age-matched healthy prepubertal subjects. The study was conducted in accordance with the principles of the Declaration of Helsinki, and the local ethics committee approval was obtained for the study.

### Anthropometric Examination

Height-standard deviation score (height-SDS) was calculated by comparing a child's height to the mean height of a reference population of the same age and gender using Centers for Disease Control and Prevention (CDC) charts. Body mass index-standard deviation score (BMI-SDS) was calculated using CDC tables according to the LMS method. A BMI-SDS of 0 means that the child's BMI is equal to the average BMI for their age and gender. A BMI-SDS of +1 indicates that the child is heavier than average for their age and gender, while a BMI-SDS of -1 indicates that the child is lighter than average for their age and gender[13].

Pubertal stages – known as the Tanner stages, are a way of categorizing the physical changes that occur during puberty, which are also used to describe the progression of puberty in both males and females – were evaluated by the same pediatric endocrinologist (NC)[14].

### Radiological Evaluation

Before any hormonal treatment was initiated, ultrasonographic examination was performed by the same pediatric radiologist, unaware of the clinical diagnosis, using a GE LOGIQ S8 device (GE Healthcare, Chalfont St Giles, UK). Before the pelvic US examination, the procedure was performed with a full bladder to create an acoustic window. Ovarian volumes, uterine dimensions, and endometrial double-layer thickness were measured on pelvic USG. Anteroposterior, mediolateral, and infero-superior dimensions of the uterus and both ovaries and uterine endometrial thickness were also measured. Uterine and ovarian volume was calculated in cubic centimeters with ellipsoid formula as:

$$(\text{longitudinal dimension} \times \text{AP dimension} \times \text{transverse dimension} \times 0.52)$$[15].

The mean volume of both ovaries (right ovarian volume + left ovarian volume/2) was calculated. Endometrial echogenicity was checked, and the endometrial strip was measured at maximum AP thickness between the two basal layers on the anterior and posterior walls of the uterus as the uterus was scanned in the sagittal plane.

VFT, SFT, and TAFT were sonographically measured in all subjects. Measurements were made by the same pediatric radiologist using 3.5 MHz and 7.5 MHz probes. SFT is the thickness of the amount of fat that is stored between the skin-fat interface and the linea alba, measured axially using a linear probe at the widest point just below the xiphoid process. VFT is the thickness of visceral fat between the anterior surface of the peritoneum covering the anterior left lobe of the liver and the posterior surface of the linea alba measured using a linear probe just below the xiphoid process. TAFT, the distance between the posterior surface of the rectus abdominis muscle and the anterior wall of the aorta, is measured using a convex probe on the xiphoumbilical line axially 1 cm above the umbilicus (Figure 1)[16].

### Statistical Analysis

JAMOVI (version 2.3.1) and MedCalc statistical software (trial version 12.7.8, Mariakerke,

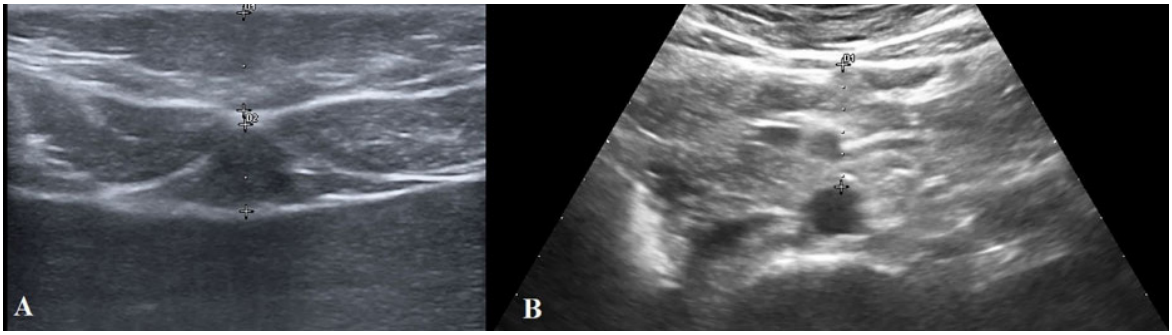


**Figure 1.** Ultrasonographic measurements of VFT, PFT and TAFT. **A**, D1 measurement shows SFT, and D2 measurement shows VFT, (**B**), D1 measurement shows TAFT.

Belgium) were used to analyze the data. The Shapiro-Wilk test was used to evaluate whether the data fit the normal distribution. A one-way ANOVA test was used in the analysis of continuous variables, and Bonferroni correction was used for post-hoc correction. Spearman correlation test was used for the correlation between prepubertal precocious and variables. Multiple logistic regression analysis was performed to find variables that could predict CPP. Parameters with $p < 0.05$ in univariate analysis were included in multiple logistic regression analysis. ROC curve analysis (AUC, z statistics) was performed to determine the optimal value that could predict CPP for the variable that was significant in the regression analysis. A $p$-value < 0.05 was considered statistically significant.

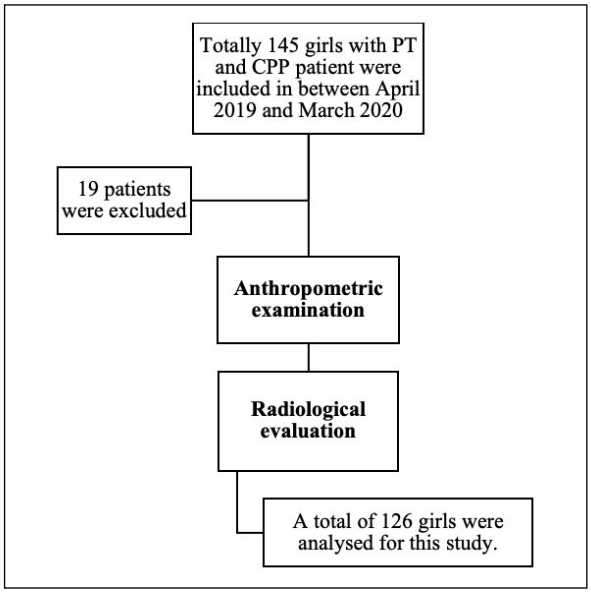


**Figure 2.** Flow chart of the study.

## Results

A total of 126 girls [44 healthy subjects (Group 1), 23 patients with PT (Group 2), and 59 patients with CPP (Group 3)] were included in this study. The flow chart of this study is shown in Figure 2. Demographic data of the study population are given in Table I. There was no statistically significant difference between the patients and control groups in terms of weight and BMI ($p > 0.05$, for both). While there was a difference between Group 2 and Group 3 in terms of decimal age, there was a statistically significant difference between Group 1 and Group 3 in terms of height z-score, and both values were higher in Group 3.

Ultrasonographic and anthropometric data of the study population are given in Table II. When we evaluated these values according to pubertal status, significant differences, especially between Group 1 and Group 3, were observed in all data. Within these parameters, uterus size, endometrial thickness, and VFT values were also found to be significantly higher in Group 3 compared to Group 2 ($p < 0.05$, for all).

Variables (age, uterine size, ovarian volume, endometrial thickness, VFT, SFT, and TAFT) that were significant in the univariate analysis performed to predict prepubertal precocious were included in the multiple logistic regression analysis. It was shown in the subsequent multiple logistic regression analysis that the endometrial thickness [OR = 7.521, 95% CI (3.702 - 15.280), ($p < 0.001$)] and VFT [(OR = 1.530, 95% CI (1.205 - 1.942), ($p < 0.001$)] were found to be independent predictors of CPP (Nagelkerke R Square = 0.702) (Table III).

In the ROC analysis performed to determine the optimal VFT value that can be used to predict prepubertal precocious, the value of VFT > 6.7 mm was determined to be the optimal value with 71.2% sensitivity (95% CI 57.9 - 82.2) and 59.7% specificity (95% CI 47.0 - 71.5) (Figure 3).

**Table I.** Demographic data of the study population.

| | Group 1 (n = 44) | Group 2 (n = 23) | Group 3 (n = 59) | ANOVA |
|---|---|---|---|---|
| Decimal age, years | 7.6 ± 0.6 | 7.4 ± 0.6 | 7.7 ± 0.5 | 0.001$^{\beta}$ |
| Height, Z-score | 1.0 ± 1.6 | 1.3 ± 1.5 | 1.5 ± 1.3 | 0.210 |
| Height, percentile | 67.3 ± 30.6 | 77.1 ± 28.5 | 81.9 ± 22.5 | 0.024$^{\alpha}$ |
| Weight, Z-score | 1.1 ± 1.1 | 1.3 ± 0.9 | 1.4 ± 1.0 | 0.401 |
| Weight, percentile | 74.6 ± 27.7 | 84.9 ± 23.9 | 82.6 ± 22.0 | 0.158 |
| BMI, Z-score | 0.8 ± 1.0 | 1.0 ± 0.8 | 0.9 ± 0.9 | 0.745 |
| BMI, percentile | 71.3 ± 25.9 | 77.4 ± 24.2 | 74.1 ±24.2 | 0.628 |

BMI = Body mass index; $^{\alpha}$ = $p < 0.05$ between group 1 *vs.* group 3, $^{\beta}$ = $p < 0.05$ between group 2 *vs.* group 3.

**Table II.** Demographic data of the study population.

| | Group 1 (n = 44) | Group 2 (n = 23) | Group 3 (n = 59) | ANOVA |
|---|---|---|---|---|
| Uterus (cm$^3$) | 1.4± 1.1 | 2.3 ± 1.9 | 4.1 ± 3.1 | < 0.001$^{\alpha, \beta}$ |
| Ovaries (cm$^3$) | 1.6 ± 0.9 | 2.4 ± 1.3 | 2.9 ± 1.7 | < 0.001$^{\alpha}$ |
| Endometrium (mm) | 1.1 ± 0.5 | 1.5 ± 0.8 | 3.4 ± 1.8 | < 0.001$^{\alpha, \beta}$ |
| VFT (mm) | 6.1 ± 2.6 | 5.8 ± 2.0 | 8.2 ± 3.1 | < 0.001$^{\alpha, \beta}$ |
| SFT (mm) | 6.4 ± 2.7 | 7.4 ± 3.4 | 8.3 ± 3.3 | 0.011$^{\alpha}$ |
| TAFT (mm) | 24.6 ± 7.3 | 28.1 ± 9.8 | 28.9 ± 8.1 | 0.030$^{\alpha}$ |

SFT = subcutaneous fat thickness, TAFT = transabdominal fat thickness, VFT = Visceral fat thickness; $^{\alpha}$ = $p < 0.05$ between group 1 *vs.* group 3, $^{\beta}$ = $p < 0.05$ between group 2 *vs.* group 3.

**Table III.** Univariate and multivariate analyses in the prediction of precocious puberty.

| | Univariate analysis | | Multivariate Analysis | | | |
|---|---|---|---|---|---|---|
| | r | *p*-value | B | OR | 95 %CI | *p*-value |
| Age | 0.225 | 0.011 | | | | 0.451 |
| BMI | 0.007 | 0.941 | | | | |
| Uterus | 0.570 | < 0.001 | | | | 0.906 |
| Ovaries | 0.366 | < 0.001 | | | | 0.899 |
| Endometrium | 0.706 | < 0.001 | 2.018 | 7.521 | 3.702 – 15.280 | < 0.001 |
| VFT | 0.311 | < 0.001 | 0.425 | 1.530 | 1.205 – 1.942 | < 0.001 |
| SFT | 0.260 | 0.003 | | | | 0.394 |
| TAFT | 0.217 | 0.015 | | | | 0.794 |

BMI = Body mass index, SFT = subcutaneous fat thickness, TAFT = transabdominal fat thickness, VFT = Visceral fat thickness.

## Discussion

The main findings of this study are (i) anthropometric data were found to be higher in patients with prepubertal precocious, (ii) endometrial thickness and VFT parameters were found to be the independent predictors of precocious puberty, and (iii) VFT value of > 6.7 mm was determined to be the optimal cut-off point in the prediction of prepubertal precocious.

BMI is moderately related to direct measurements of body composition but cannot distinguish layers of body tissues[17,18]. Central obesity assessment through waist circumference measurement is a simple and non-invasive test; however, its disadvantage is the inability to distinguish in-

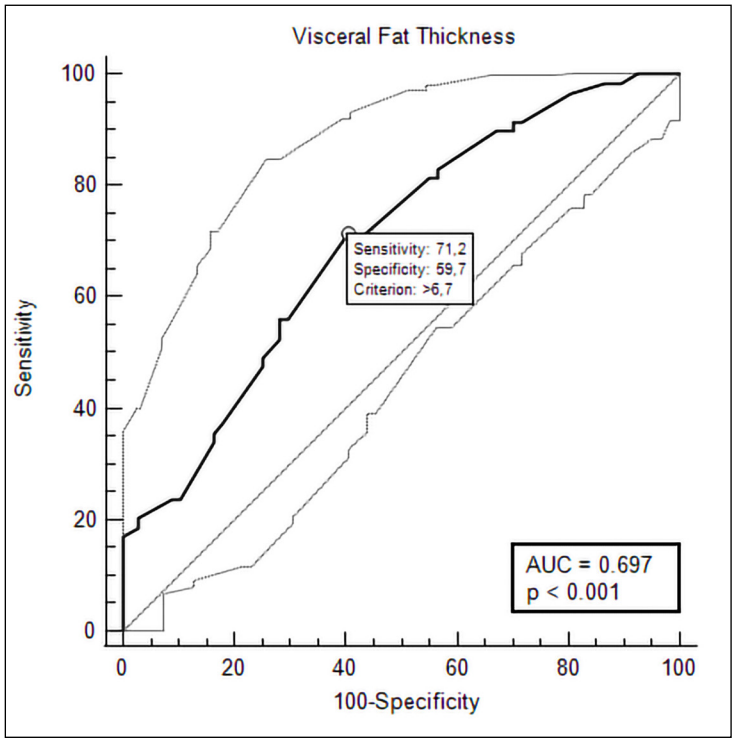


**Figure 3.** ROC analysis to determine the optimal VFT value to be used to predict prepubertal precocious.

tra-abdominal adipose tissue from subcutaneous adipose tissue, as well as variability between examiners and individuals[19]. New methods such as skinfold measurement and imaging tests have been proposed for the measurement of the adipose component[20].

For the first time in 1947, Vague[21] stated that fat distribution may be more important than total fat excess, and later studies[22] emphasized that central distribution of adipose tissue carries a higher risk for cardiovascular and metabolic outcomes. For this reason, researchers have turned to research methods that can better evaluate regional adiposity in daily practice. Radiological imaging techniques have enabled us to assess fat distribution and shifted clinicians' attention to the possibility of not only detecting a patient's total fat mass (or gyno android distribution) but also defining its distribution.

Visceral fat and subcutaneous fat are two different types of adipose tissue located in different regions of the body. Subcutaneous fat is the layer of fat located just beneath the skin and is the most visible type of fat in the body. Visceral fat, on the other hand, is the layer of fat that is located deep within the abdominal cavity, surrounding the internal organs such as the liver, pancreas, and intestines. Distinguishing between fat deposits and phenotypes at specific localizations is critical, given the evidence supporting metabolic outcomes that depend on the location of fat deposits[23]. It has been suggested that in the case of obesity and overweight, differences in fat distribution may have different effects on metabolic complications. Even in non-obese individuals, visceral fat accumulation may be associated with glucose intolerance, dyslipidemia, and hypertension[24,25].

CT, MRI, and USG imaging techniques have made it possible to distinguish between SFT and VFT. Both are generally more effective than USG in discriminating between VFT and SFT, but they are more difficult to reach and costly. In addition to its easy accessibility and low cost, pelvic evaluation with the US, which is a radiation-free imaging method, is indicated for the investigation of children with pelvic masses and puberty disorders, as well as to determine the increased risk for CPP and PT[26]. Armellini et al[27] emphasized the good relationship between USG and CT measurements of abdominal adipose tissue. Stolk et al[28] also found strong correlations between abdominal fat tissue and waist circumference measurements using USG and CT. USG is a non-invasive, safe, and common method for assessing abdominal adiposity, as well as not exposing it to the risk of ionizing radiation, making it ideal for the evaluation of children. For these reasons, in our study, we considered doing the anthropometric evalua-

tion with USG, as it was both cheap and effective.

In the literature, it was shown the relationship between BMI and pubertal status. In the PROS study[29], it was noted that 6- to 9-year-old white girls with breast development had a higher BMI-SDS score than prepubertal girls of the same age. In line with previous results, a negative association between age at menarche and BMI was found in Bogalusa Heart study[30]. However, significant associations between greater adiposity and earlier puberty development have been demonstrated in lower-percentile children. On the contrary, we did not find any relationship between age and pubertal status in our study. Although there was no difference in the BMI percentile between the groups, VFT, PFT, TAFT, and endometrial thickness values were significantly higher in the prepubertal precocious group than in the control group. Based on our data, we believe that high anthropometric parameters observed in patients with precocious puberty complaints, even when the BMI is within normal range, may be more effective in predicting precocious puberty compared to BMI alone.

Badouraki et al[31] showed that ultrasound findings of patients with premature thelarche and pubarche had a similar pattern, but CPP patients had significantly higher values for most of the measured ultrasound variables compared to controls. In our study, we found that uterine length, uterine volume, and mean ovarian volume were significantly higher in girls with CPP than in normal girls and girls with PT, consistent with previous studies[32,33]. We also found that endometrial thickness and VFT values, especially the value of > 6.7 mm of VFT, were independent predictors of CPP prediction. In light of these data, we determined that VFT is the most useful parameter to predict precocious puberty among anthropometric measurements.

### Limitations

The study's limitations include a small sample size and absence of long-term follow-up due to its cross-sectional nature. Therefore, it could not be evaluated whether these anthropometric measurements are predictive of long-term metabolic syndrome complications. Another limitation is that since our population addresses a local region, it should be considered that the VFT cut-off value may vary from region to region. Moreover, sonographic examinations were performed by a single radiologist, and therefore, both intra- and inter-observer variability could not be evaluated.

## Conclusions

In conclusion, besides allowing easy measurement of intra-abdominal fat, its inclusion in routine pelvic examinations has caused USG to be preferred in the evaluation of central obesity in children and adolescents. It has been found that VFT and endometrial thickness measurements, which are evaluated quickly and accurately by USG, are important predictors of prepubertal precocious. We think it would be beneficial to keep the VFT value in mind, especially in children presenting with early puberty complaints, in terms of predicting precocious puberty. Future large-scale studies are also needed to support our study.

### Ethics Approval

Ethics committee approval was obtained from the Ethical Committee of Inonu University (ID: 2019/422).

### Availability of Data and Materials

Not applicable.

### Conflict of Interest

None declared.

### Informed Consent

Written consent was obtained from the parents of the patients participated in the study.

### Funding

No funding was received for the study.

### Authors' Contributions

SDT, AS, NÇ, AC, GMD, AA: concepts, design, data analysis, statistical analysis, manuscript preparation, manuscript review. SDT, NÇ, AC, GMD: definition of intellectual content, literature search, experimental studies, data acquisition.

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