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INTERNIPPLE DISTANCE AND INTERNIPPLE INDEX IN PREPUBERTAL TURKISH GIRLS

Short Tittle: Internipple index in turkish girls

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What is already known on this topic?
Increased internipple distance is a clinical feature in some dysmorphic syndromes which is subjectively evaluated by the physician during examination. Some studies produced normative data for objective comparison of this parameter with "normal" after measurement and usually proportioning to chest circumference.

What does this study adds?
The above mentioned studies are scarce and just a few are evaluating subjects beyond the neonatal period. In Turkey no reference values were published. Our study provides the first references in the country and will serve internationally for the school aged girls. A short overview of the literature is given as well to depict the present status.

ABSTRACT
Objective: To determine internipple distance and internipple index in prepubertal Turkish girls.
Methods: The internipple distance and chest circumference of 667 healthy prepubertal Turkish girls aged 6 to 11 years were measured in a school screening program in Duzce. Measurements were performed at the end of expiration with a standard non-stretch tape measure graduated in millimeters with the arms hanging in a relaxed position on the sides of the body. The internipple distance was measured between the centers of both nipples, and chest circumference was measured across the internipple line. The internipple index was calculated by dividing the internipple distance (cm) x100 by the chest circumference (cm). The age specific internipple index reference curves were constructed and smoothed with the LMS method. Mean and standard deviations of internipple distance and internipple index were calculated according to decimal ages.
Results: Age was found to be positively correlated with internipple distance and chest circumference, while it was negatively correlated with internipple index. The reference values of internipple index, including 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles, and standard deviations were calculated for prepubertal girls.
Conclusions: The reference ranges provided by this study might be helpful for the evaluation of syndromic cases by serving as normative data for internipple index in prepubertal girls aged 6-11 years in Turkey and although ethnic differences may affect results even across countries.
Keywords: Internipple distance, Internipple index, Turkey

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INTRODUCTION
Anthropometric evaluation of nipple placement may be helpful diagnosing some syndromes. For instance, increased internipple distance is seen especially in Turner syndrome (TS), Noonan syndrome, fetal hydantoin syndrome, deletion 9p syndrome, Trisomy 8, Trisomy 18 and bilateral renal hypoplasia, while it may also be found in cerebro-oculo-facio-skeletal syndrome, Fraser syndrome, Bartsocas-Papas syndrome, Juberg-Hayward syndrome and Langer-Giedion syndrome (1). On the other hand, decreased internipple distance is generally reported in Jeune syndrome (asphyxic thoracic dystrophy) and cerebro-costo-mandibular syndrome (2).
TS is rather common with its frequency of one case per 2500 live female births. However, diagnosis may be delayed due to the subtlety of dysmorphic features; in fact, it is not a rare occasion that patients may only be recognized in the prepubertal or pubertal period (3,4). Turner syndrome should be considered in girls with short stature or primary amenorrhea; however, it is often overlooked in short stature as shown in a study that found up to 4% of girls underwent genetic analysis due to short stature were found to have TS (5,6). Early diagnosis and prompt treatment are crucial in TS to prevent delayed intervention, growth disturbance, cognitive limitations, osteoporosis and severe cardiac malformations (mostly aorta coarctation and bicuspid aortic valve) (7,8,9).

It was claimed that widened internipple distance is "illusionary" in TS, but the study supporting this idea was conducted in 36 syndromic and 247 normal children in both sexes which are small numbers (10). Moreover, though the contribution to the diagnosis is not well known, subjective evaluation about internipple distance is almost always accomplishing the clinical records of such cases. Thus an objective comparison of this stigma may increase the quality of the clinical examination in several syndromes. The evaluation of TS is part of the daily practice of pediatric endocrinologists. Not just that considering internipple distance may contribute to diagnosis, it is important as well for research purposes. Therefore to attempt to accurately measure internipple distance in girls and compare with normative data might be a reasonable tool. On the other hand, data regarding internipple index and internipple distance are very limited in the literature. Considering that racial differences significantly affects internipple distance and internipple index, our aim with this study was to determine reference values for internipple distance and internipple index in prepubertal Turkish girls.

MATERIALS AND METHODS

The study was conducted between March–May 2009 in the context of a large school survey on 9177 children at 1-8. grade from 14 schools. The aim of this survey was to determine local height, weight and pubertal development data and finally to extract cases with short stature and puberty precox who then were invited to the hospital for a complete endocrine work-up (11). The schools were selected by stratified sampling method among 29 schools located in the city center of Duzce, Turkey, a small city located in North-West Anatolia, in close vicinity to the most wooded cities of the country. **The stratification was made according to the socioeconomic level of the districts and the schools with highest student numbers were selected.** A sample of 667 girls aged between 6-11 years randomly selected from the schools and distributed as evenly as possible by number and age were included in the present study. **In every school the students came in an order starting from the first to the 6th level and each level was divided in four subgroups (classes). Approximately 50 girls in each school and 9 in each level were targeted to screen and the first coming class was fulfilled the target number in most of the occasions.** Birth date, date of physical examination, measured height, weight, internipple distance, chest circumference and pubertal scores according to Tanner were recorded and decimal age was calculated. Internipple distance and chest circumference were measured with a non-flexible tape at the end of expiration and with the arms hanging on the sides, by the same experienced pediatric endocrinologist who evaluated puberty as well, whereas height and weight was measured by a pediatrician. All measurements were made with light clothing, barefoot; internipple-chest measurements were made with naked upper body in a separate room. Internipple index was calculated using the following formula: Internipple distance (cm) x 100 / chest circumference. Subjects with body mass index (BMI) above the 95th percentile, children with congenital anomalies or with a chronic disease were excluded from the study. Girls with thelarche were observed, then excluded from the study (Tanner stage ≥ 2). The study protocol was approved by the Ethics Committee of Duzce University and permission was obtained. Parents' written consent was obtained prior to the study and the procedures were in accordance with those outlined by the Declaration of Helsinki.

Statistical analysis

The SPSS version 22 and the LMS Chart Maker Pro version 2.54 software (12) were used for analyses. Descriptive statistics of the variables in the study were calculated. The normality assumption of continuous quantitative variables was checked with the Kolmogorov-Smirnov test. Mean, standard deviation, minimum and maximum values were given as descriptive statistics of the variables in tables since all quantitative variables provided the normal distribution assumption. The relationships between quantitative variables were analyzed with the Pearson Correlation test. The age-specific internipple index reference curves were constructed and smoothed with the LMS method in which the final curves of percentiles were produced by three smooth curves represented as L (Lambda, skewness), M (Mu, median) and S (Sigma, coefficient of variation)(13). Reference values of internipple index, including 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles were determined. p values of <0.05 were considered statistically significant.

RESULTS

The mean age of the 667 individuals included in the study was 8.2 ± 1.2 (6.3-11.5) years. Descriptive statistics for weight, height, BMI, internipple distance, chest circumference and internipple index for each decimal age are given in Table 1 and Table 2. Numbers in increasing age groups are decreasing related to the increasing proportion of pubertal cases.

The internipple index values were estimated with LMS method according to age are presented in Table 3 along with L (lambda-skewness), M (median) and S (coefficient of variation) values for each age group. The graphical presentation of results is shown in Figure **1. These latter analyses were made among 657 subjects after removing the 11 age group.**

Age was found to be positively correlated with weight (r=0.491 p<0.001), height (r=0.660 p<0.001), internipple distance (r=0.158 p<0.001) and chest circumference (r=0.412 p=0.001); whereas it was negatively correlated with internipple index (r=-0.176 p<0.001). There was no relationship between age and BMI values (r=0.041 p=0.295).

BMI values were found to be positively correlated with internipple distance (r=0.404 p<0.001) and chest circumference (r=0.628 p<0.001), while they were negatively correlated with internipple index (r=-0.084 p=0.030).

Internipple index values were negatively correlated with weight (r=-0.187 p<0.001), height (r=-0.190 p<0.001), BMI (r=-0.084 p=0.030) and age (r=-0.176 p<0.001).

DISCUSSION

The majority of studies assessing internipple index are comprised of patients in the newborn period (Table 4). (1,14,15,16,17,18,19,20). Newborn period is an important occasion for recognizing dysmorphic syndromes, therefore, these studies are valuable references. But performing end-expiratory measurements in newborns and infants is almost impossible, while it is difficult in little children. Measurements performed with these limitations may cause erroneously high chest circumference, decreasing internipple index values. Therefore, studies with larger subject numbers are more reliable as measurement errors are balanced by the number of subjects.

On the other hand, there are very few studies in older age groups (10,18,19,21). We summarized all studies we could find in the literature. Chest measurement is easier in school aged girls since they cooperate quite well with instructions. But when puberty starts, the contribution of breast tissue to this parameter changes individually. Therefore, the measurement is the

easiest to standardize in prepubertal girls. We chose Tanner stage 1 girls which gives rise to the present age distribution of our study. This age group is well representative of the age interval in which a great majority of TS patients attend to clinics. Feingold and Bossert (21) screened 2403 children (2006 Caucasian, 206 Black and 43 Asian) between newborn period and 14 years of age for many anthropometric indices, and they reported that internipple index was the highest in the newborn period, with the lowest values between 15 months and 7 years of age. This finding was partly supported by a study by Chen et al. (1) who also found that internipple index was maximum at birth and decreased until 2 years of age. Furthermore, in a study by Leung et al. (18) internipple index decreased steadily from 1 to 18 years of age. Pelz et.al. (19) claimed that intermammillary index (same as internipple index) does not change with age prior to puberty.

In our study, we also observed this gradual decrease of internipple index. Especially the difference between 3rd and 97th percentiles is the biggest in the age 6 group, it decreases somehow in the age 7 group, but is stabilized completely in the 8-10 groups. These groups show minor differences in percentiles between 5 and 95, which is perhaps ignorable. The correlation analyses depict the internipple index-age relationship as well, there was a negative correlation between these two parameters. Weight and height show this negative relationship with internipple index as well. BMI is also negatively correlated with internipple index but this relationship is much weaker than the formers. Weight and height are more affected by increasing age than BMI, which could explain this. In the study of Leung et al. (18) the decrease of internipple index with age relatively stabilized between the ages of 6 to 11 years. When we compared our 6–11 age results with their corresponding results, we found that internipple index values in our study group were considerably higher.

There are different views on the influence of ethnicity on internipple index measurements (1,15,18,19,20,21). In addition to ethnicity, methodologies and measurement devices may also contribute to these differences in internipple distance. When we reviewed the literature, we observed that Chinese neonates had higher internipple indexes than those reported in US, Nigerian and Hungarian (1,16,17).

The contribution of increased internipple distance to the diagnoses of Turner and Noonan patients was questioned in some of the former studies (1,10). Chen et. al. (1) found that internipple distance in patients with TS (n 40) was significantly different (p (0.001) from normal after adjusting for height but not for age; but the difference was less striking when compared to chest width or circumference (0.01). Collins et. al. (10) suggested that the increased internipple distance is a subjective clinical impression owing to the illusion created by the body shape and short stature. These two studies are quite small studies and their argument should be tested in a larger group of Turner and Noonan patients in comparison to normal subjects. Since height is effective on both the objectively measured internipple index as shown in our study and on perceived internipple distance as claimed in Collin's study, it might be reasonable to compare Turner subject's height age with normative data, rather than chronological age.

Limitations

Numbers in increasing age groups are decreasing related to the increasing proportion of pubertal cases.

Conclusion

Although the internipple index provides a method of assessment that is objective in comparison to physical examination alone, and could increase the chances of early diagnosis in many syndromes, especially in Turner syndrome; it is apparent that racial and ethnic differences may cause variations in assessment. Therefore, appropriate reference intervals should be used. In this study, normal values of internipple distance and internipple index were obtained for the Turkish population in prepubertal girls aged between 6-11 years. Despite the possibility of contribution of ethnic differences to a variation in internipple index, our data might be used as reference values for other countries as well, until their local normative values are produced. Regarding our country, the missing neonatal reference standards might be helpful when studies would be performed about this index.

Ethics

Ethics Committee Approval: 2008.211/2189

Informed Consent:2008.211/2190

Authorship Contributions

Surgical and Medical Practices: Seda Erişen Karaca, İlknur Arslanoğlu

Concept: İlknur Arslanoğlu

Design: İlknur Arslanoğlu

Data Collection or Processing: Seda Erişen Karaca, İlknur Arslanoğlu

Analysis or Interpretation: Şengül Cangür

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TABLES

Table 1: Mean anthropometric values of age groups.

Age (years)	Weight (kg)			Height (cm)		BMI	
	N	Mean±SD	Min-Max	Mean±SD	Min-Max	Mean±SD	Min-Max
6 (6-6.99)	122	22.3±3.2	15.6-33.2	119.8±4.9	106.1-133.4	15.5±1.6	10.5-19.6
7 (7-7.99)	201	24.1±3.3	17.2-36.8	123.6±5.5	109.5-140.5	15.7±1.5	11.9-19.5
8 (8-8.99)	190	26.0±3.6	16.8-37.8	128.4±5.7	116.1-154.4	15.8±1.6	12.1-19.4
9 (9-9.99)	114	27.4±4.3	12.0-39.0	132.4±5.3	119.0-145.5	15.6±2.0	12.9-19.4
10 (10-10.99)	30	29.3±3.6	24.0-37.2	136.0±6.3	122.9-150.0	15.8±1.5	13.4-19.2
11 (11-11.99)	10	29.7±2.5	25.8-33.8	136.5±5.8	128.7-145.5	15.9±1.3	14.4-19.1
Total	667	25.2±4.1	12.0-39.0	126.5±7.3	106.1-154.4	15.7±1.6	10.5-19.6

Mean±SD: Mean ± Standard Deviation, Min-Max: Minimum-Maximum

Table 2: Internipple distance and internipple indices with regard to age groups.

Age (years)	N	Internipple Distance (cm)		Chest Circumference (cm)		Internipple index	
		Mean±SD	Min-Max	Mean±SD	Min-Max	Mean±SD	Min-Max
6 (6-6.99)	122	14.0±1.3	11.1-20.0	57.5±3.4	49.5-68.5	24.3±2.1	19.7-33.1
7 (7-7.99)	201	14.4±1.2	11.2-18.2	58.8±3.3	51.0-67.5	24.4±1.7	19.6-28.9
8 (8-8.99)	190	14.3±1.2	11.5-18.4	60.3±3.7	50.2-71.6	23.8±1.7	18.9-28.8
9 (9-9.99)	114	14.6±1.2	11.6-17.1	61.7±3.9	51.7-75.5	23.7±1.7	18.9-28.1
10 (10-10.99)	30	14.8±1.2	12.8-17.3	62.9±3.8	57.0-72.6	23.5±1.7	20.7-28.2
11 (11-11.99)	10	14.6±1.4	12.4-16.5	63.4±3.1	59.7-69.1	23.0±1.7	20.6-25.3

Total	667	14.3±1.2	11.1-20.0	59.7±3.9	49.5-75.5	24.0±1.8	18.9-33.1

Mean±SD: Mean ± Standard Deviation, Min-Max: Minimum-Maximum

Table 3: Smoothed age-specific internipple index percentile values of prepubertal girls aged 6 to 10 years.

				Percentiles								
Age	**L**	**M**	**S**	**3rd**	**5th**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**	**97th**
6 (6-6.99)	-0.733	24.181	0.079	21.0	21.4	21.9	22.9	24.2	25.5	26.9	27.7	28.3
7 (7-7.99)	0.315	24.368	0.072	21.2	21.6	22.2	23.2	24.4	25.6	26.7	27.4	27.8
8 (8-8.99)	1.193	23.796	0.070	20.6	21.0	21.6	22.7	23.8	24.9	25.9	26.5	26.9
9 (9-9.99)	1.037	23.729	0.070	20.6	21.0	21.6	22.6	23.7	24.9	25.9	26.5	26.9
10 (10-10.99)	-0.354	23.427	0.071	20.6	20.9	21.4	22.3	23.4	24.6	25.7	26.4	26.9

L: Lambda-Skewness, M: Median, S: Coefficient of variation

Table 4. Internipple distances and internipple indices in other studies.

Study authors (years)	**Place**	**Subjects N**	**Internipple index (%) mean±SD**
Pelz[19] (1972)	Germany	390 (newborn - 18 years)	23.09±4.1 M 23.41±1.9 F
Collins[10] (1973)	Australia	247 (2-10 years)	Internipple distance: 11.2±1.8 M 11.6±2
Feringold and Bossert[21] (1974)	United States	2403 (0-14 years)	26.4 ± 1.6
Mehes and Kitzveger.[17](1974)	Hungary	600 (0-5 days)	25.1±2.9
Chen et al.[1] (1974)	Michigan, USA	472 (0-3 days)	25±0.018
Sivan et al.[14] (1983)	Israel	198 (term-preterm)	23.2 (27 weeks) 24.5 (41 weeks)
Ejiwumni et al[16] (1984)	Nigeria	278 (term eonates)	22.88±1.94
Leung et al.[18] (2004)	China	3290 (0-18 yrs.)	Neonates: 26.4 ± 1.6 M 26.3 ± 2 F Child: 23.8 ± 1.2 M 23.8 ± 1.4 F),

Fok et al.[54] (2005)	Hong Kong	10.339 (24-42 weeks)	Internipple distance: 8.4 (41 weeks) M 8.2 (41 weeks) F
Faridi et al.[20] *(2013)*	India	1 077 (term neonates)	27.1±3.5 F 27.0±3.5 M

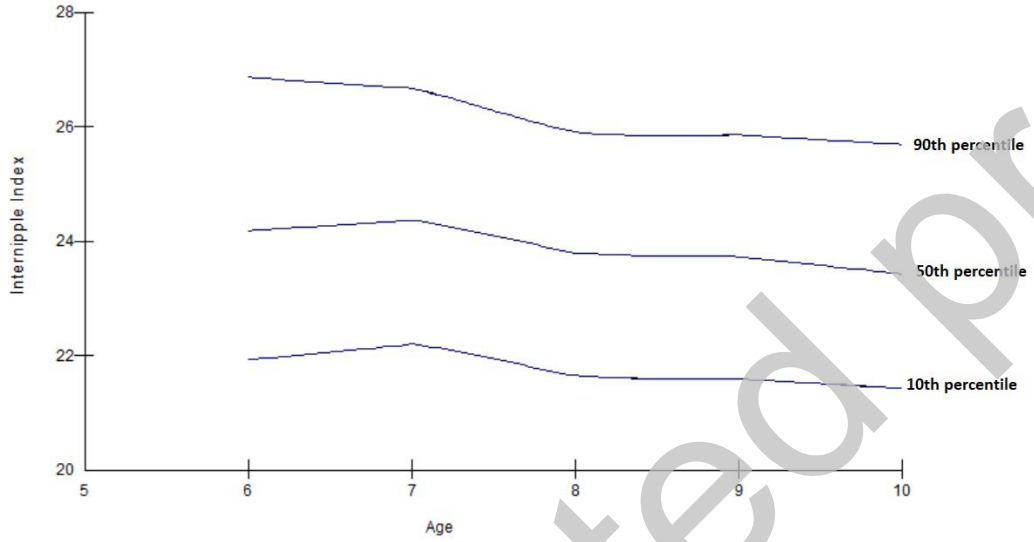

Figure 1. Graph showing the internipple index values (10th, 50th and 90th percentile) with the LMS method according to age.