ANNALS OF HUMAN BIOLOGY, 1993, VOL. 20, NO. 1, 39–46

Serum alkaline phosphatase activity and skeletal maturation in Guatemalan adolescents

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Received 12 September 1991; revised 3 March 1992

Summary. Serum alkaline phosphatase activity (AP), stature and Tanner-Whitehouse-2 RUS skeletal age (SA) were determined for 873 rural Guatemalan youth and young adults 11–25 years of age. Mean AP decreases systematically with chronological age (CA) in girls, while an adolescent increase in mean AP occurs at 14 years in boys. When mean AP is calculated within SA groups, clear adolescent increases are apparent in girls, peaking at 11 years SA, and at 14 years SA in boys. Correlations between AP and relative skeletal age (SA-CA) decrease systematically from moderately positive at the youngest CA groups to moderately negative at the older ages, crossing zero at the chronological ages of maximum adolescent AP values. Analyses suggest the patterns of mean AP in adolescence follow closely the timing and patterns of growth velocity in stature in each sex, and are only indirectly related to SA as it is a proxy for the maturational timing of the adolescent spurt in stature.

1. Introduction

Alkaline phosphatases (AP) are a group of enzymes with low substrate specificity that are capable of hydrolysing a wide variety of phosphate esters at an alkaline pH (Kaplan 1972). They originate mainly from the osteoblasts of the bone, from the liver and intestine (Afonja and Ademiluyi 1983). During adolescence, a rapid increase in growth velocity, particularly in stature, occurs in all normal children. The osteoblastic activity attending this increase in skeletal mass is accordingly increased, so a great amount of AP is released and total serum AP rises markedly (Round 1973).

Although studies have demonstrated that serum AP changes systematically with chronological age and stages of secondary sex characteristics during adolescent growth and development (Cherian and Hill 1978, Krabbe, Christiansen, Rodbro and Transbol 1980), the relationships between serum AP and skeletal maturation have rarely been studied during this period. The associations with skeletal maturation are important because of the origins of AP related to skeletal development. Furthermore, because the metric of skeletal maturation is continuous, examining serum AP relative to skeletal maturation offers opportunities to describe maturational patterns and associations of AP better in some ways than the categorical stages of sexual maturation.

The purpose of this study is to describe the patterns of serum AP during adolescence as they relate to age and skeletal maturation in a group of Guatemalan youth and young adults. This sample comprises individuals who are typical of many Guatemalans and have been reared in areas where poverty and mild-to-moderate protein-energy malnutrition are endemic. We know of no other studies of adolescent changes in AP in similar populations.

2. Materials and methods

The study was carried out in Guatemala in 1988 and comprises 873 individuals aged from 11 to 25 years. All subjects were chosen from seven rural villages and were participants in the Longitudinal Study of Nutritional Supplementation, Growth and Development, conducted in collaboration with the Institute of Nutrition of Central America and Panama (INCAP). All subjects were clinically normal but living in poverty. Chronological age (CA) was verified, when necessary, by village records; most subjects were born into the study and had date of birth recorded.

For subjects less than 18·5 years of chronological age, standardized radiographs of left hand-wrist were taken with a tube-film distance of 91·4 cm, and the central ray focused on the distal end of the third metacarpal. All the radiographs were assessed by a single observer according to the Tanner-Whitehouse-2 (TW2) method (Tanner, Whitehouse, Cameron, Marshall, Healy and Goldstein 1983). RUS (radius, ulna, short bone) maturity scores and RUS skeletal ages were used for analyses because the carpals have largely completed maturation at these ages (Roche 1989). Relative skeletal age was calculated as RUS age minus CA (years) as a measure of delay or advancement in skeletal age relative to the TW2 referent population.

Blood samples were drawn by venipuncture and total serum alkaline phosphatase activity was measured by the method of Tietz and Schiele. Precisions for this method are 0·7 to 2·6% (Tietz, Burtis, Duncan, Ervin, Petitclerc, Rinker, Shuey and Zygowicz 1983, Schiele, Henny, Hitz, Petitclerc, Gueguen and Siest 1983). Because of differences in various laboratory standards, exact levels of AP are often difficult to compare across studies, but are adequate to describe patterns and relationships within studies.

Stature was measured according to recommended protocols (Lohman, Roche and Martorell 1988). Pseudovelocities of statural growth were calculated as the differences between stature means for adjacent groups defined by RUS age or CA. Correlation coefficients (r) between relative skeletal age and serum AP were calculated within age and sex groups and were smoothed across ages using a resistant non-linear smoother '4253H, twice' (Velleman 1980). All data protocols were approved by institutional review boards at INCAP and at University of Minnesota.

3. Results

Stature of the Guatemalan adolescents approximates the 5th percentile of the NCHS reference data (Martorell, Rivera and Kaplowitz 1990). Mean serum AP

Table 1. Mean and SD of serum alkaline phosphatase (U/L).

	Males			Females		
Midpoint age (years)	*n*	Mean	SD	*n*	Mean	SD
11	16	73·23	25·55	12	89·08	31·68
12	44	72·72	27·21	32	77·66	20·85
13	46	74·64	32·14	35	73·44	30·18
14	36	91·69	33·65	43	64·96	29·64
15	39	74·22	32·27	41	56·60	26·01
16	48	79·99	33·13	34	49·89	19·60
17	31	61·53	24·29	31	42·20	18·98
18	36	60·07	23·35	26	44·59	26·06
19	21	46·17	16·21	31	39·17	14·11
20	27	47·53	14·56	24	41·73	20·69
22	56	43·34	16·56	68	41·89	19·18
25	38	37·55	16·39	58	38·54	10·96

Table 2. Relative RUS age for individuals who are not skeletally mature (RUS score < 1000) in each chronological age group.

	Males				Females			
Midpoint age (years)	*n*	Not mature (%)	Mean	SD	*n*	Not mature (%)	Mean	SD
11	15	100	−1·74***	1·47	12	100	−0·32	1·35
12	47	100	−1·47***	1·59	36	100	0·07	1·46
13	47	100	−1·08***	1·72	36	97·3	0·32	1·12
14	39	100	−0·77*	1·91	36	87·8	0·25	1·03
15	39	97·5	−0·26	1·25	23	59·0	−0·14	0·68
16	44	91·7	−0·61***	1·12	10	29·4	−0·65**	0·64
17	29	85·3	−0·87***	0·91	5	15·2	−1·70***	0·42
18	14	51·8	−1·07***	0·60	2	0·09	−2·79	0·62

*Mean significantly different from zero, $p<0·05$; **$p<0·01$; ***$p<0·001$.

activity is presented in table 1 according to sex and chronological age groups. In males, serum AP increases markedly at 14 years of age and decreases sharply until 19 years, with a less rapid decline until 25 years of age. In females, mean serum AP declines rapidly from 11 years onwards, with a marked deceleration beginning at 17 and 18 years of age. It is difficult to determine from these cross-sectional data at what approximate ages adult AP levels are attained. For males, means at all younger ages are greater than two standard errors above mean AP at 25 years. For females, serum AP at 19 years approximates the mean level (40·35 ± 15·96 U/L) of 22–25 years.

Means for relative skeletal age (RUS age − CA) are presented for individuals in each chronological age group who had RUS scores less than 1000 (table 2). In males, RUS skeletal ages are significantly delayed at almost all chronological ages, with a pattern of decreasing delay until 15 years of age. Mean relative RUS ages are generally not significantly different from zero in females except at the oldest ages, where only the slowest maturing girls are still not skeletally mature. The TW2 RUS referent ages are mature (RUS score = 1000) at 16·0 years in girls, and at 18·2 years in boys. The portion of the age group which still has RUS scores less than 1000 as these terminal ages are approached and passed are, by definition, relatively delayed skeletally.

Mean serum AP is presented relative to corresponding chronological and skeletal age groups in figures 1 and 2, for males and females, respectively. For these comparisons, individuals whose hand-wrist is skeletally mature are presented separately. The pubescent spurt in serum AP is especially well defined when skeletally immature boys are grouped by skeletal age (figure 1), with the apex of the spurt at 14 years.

For girls, mean serum AP according to chronological age groups provides only a descending pattern (figure 2). When viewed according to skeletal age groups, a spurt peaking at 11 years is clearly defined in mean serum AP.

Especially in boys, those who are skeletally mature have considerably lower mean AP than their corresponding chronological age peers who are skeletally immature. In girls, mean AP clearly continues to decrease after the hand-wrist is skeletally mature.

The pattern of correlation coefficients between relative skeletal age and serum AP, smoothed across the age groups, are presented in figure 3 for boys and girls. In each sex, the correlation coefficients decrease systematically with age from positive to negative, crossing zero at the approximate ages of the peak levels of mean serum AP in each sex. At the early ages, children who are more advanced skeletally are also those

Figure 1. Mean serum alkaline phosphatase by age in males. RUS, by RUS age; CA-I, by chronological age, RUS score < 1000; CA-M, by chronological age, RUS score = 1000.

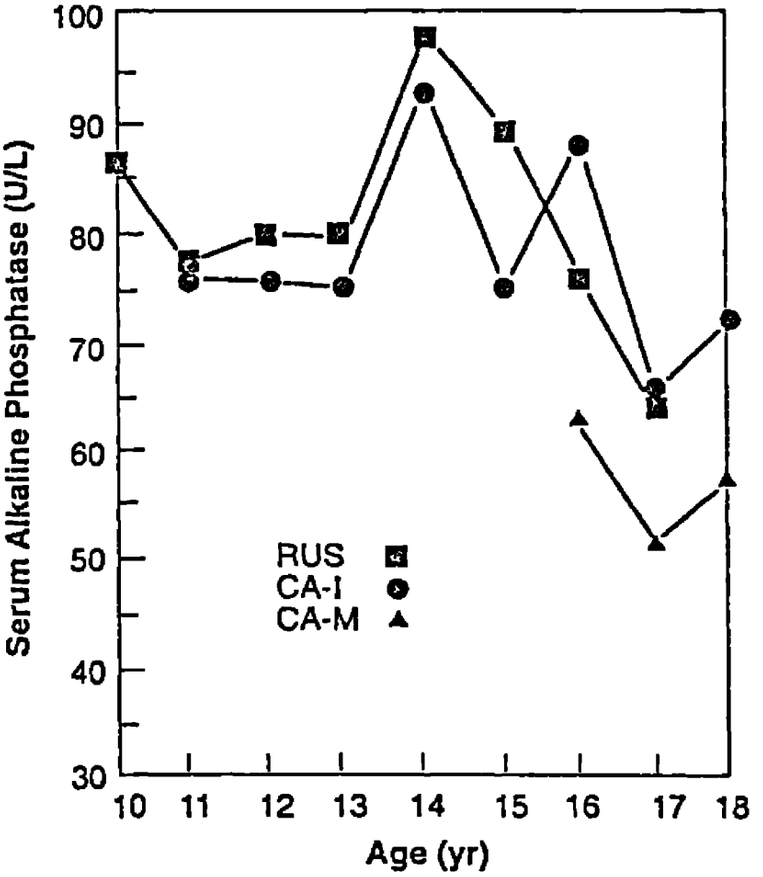


Figure 2. Mean serum alkaline phosphatase by age in females. RUS, by RUS age; CA-I, by chronological age, RUS score < 1000; CA-M, by chronological age, RUS score = 1000.

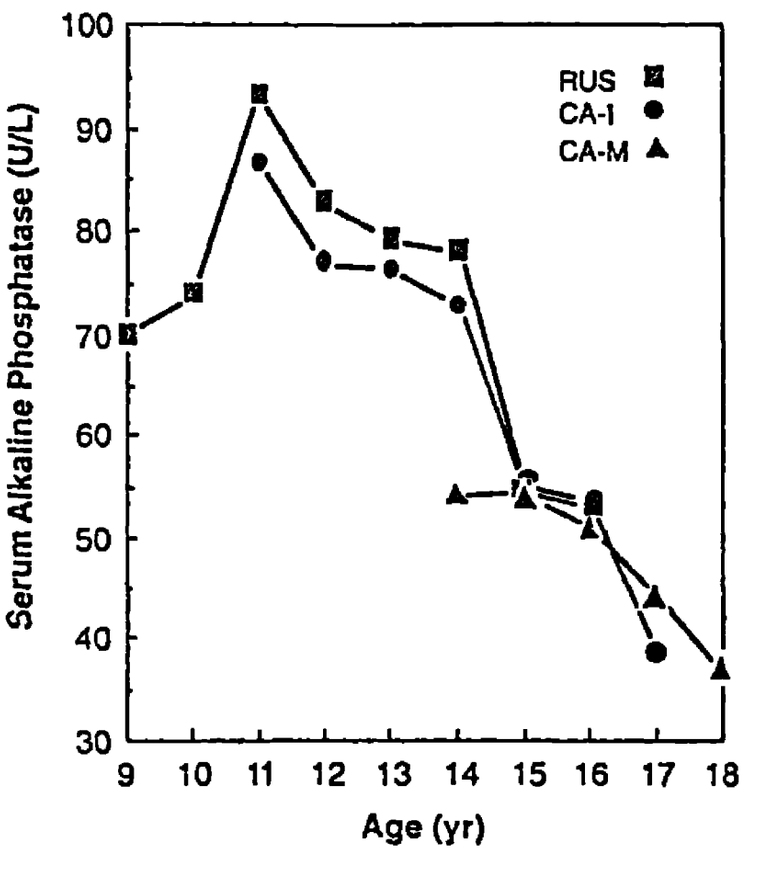


Figure 3. Correlation coefficients between relative RUS age (RUS score < 1000) and serum alkaline phosphatase smoothed across chronological ages.

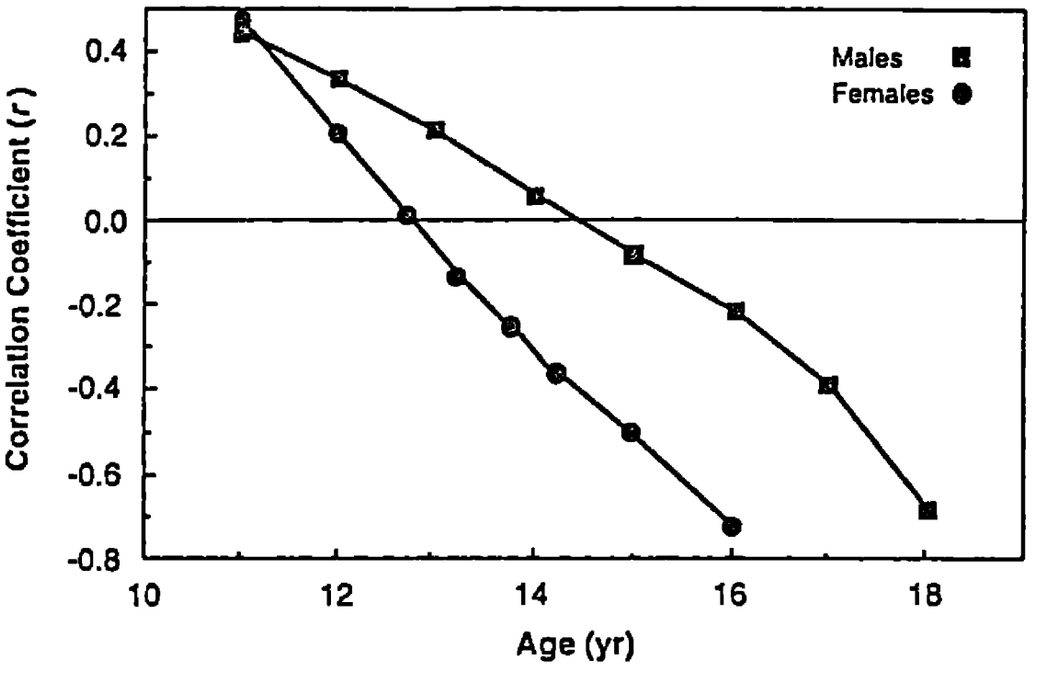
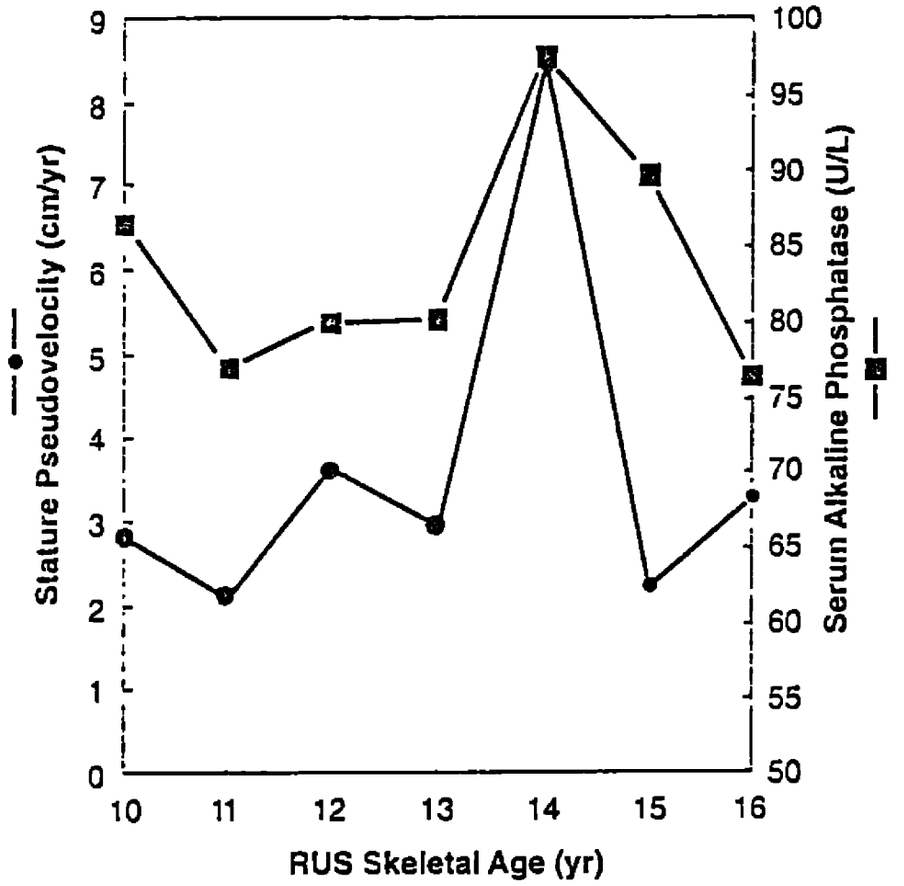


Figure 4. Stature pseudovelocity and mean serum alkaline phosphatase according to RUS skeletal age in males.



who are growing faster, hence the correlations are positive. At the later ages, the skeletally more advanced children are those who are growing relatively slower because peak velocity has passed, hence the correlations are negative. The correlation coefficients are lower for girls than boys at most ages because the velocity of girls' growth is decelerating more rapidly than that of boys at these ages.

The foregoing results suggest that serum AP follows closely the patterns of association expected for a proxy measure of stature velocity in these Guatemalan children. Because these data are cross-sectional, no true stature velocities could be calculated. Pseudovelocities, however, are generally descriptive of the expected pattern in mean increments in stature. As an example of the probable associations between serum AP and stature velocity, the pseudovelocities in stature and mean serum AP are presented for boys according to RUS skeletal age groups in figure 4. The qualitative similarity between the two curves are obvious, with coincident timing in peak levels at 14 years. Similar parallels are seen when stature pseudovelocities and mean serum AP are compared in girls (not shown).

4. Discussion

The pattern of changes in mean AP associated with chronological age are similar to those reported previously for other cross-sectional samples of well nourished youth (Posen and Doherty 1981, Widhalm and Holzl 1985). When mean AP is calculated within skeletal age groups, however, the adolescent spurt in AP is more clearly defined and more intense, i.e. higher peak values, than when expressed according to chronological age. A similar phenomenon occurs when adolescent stature or weight increments are grouped according to maturational or growth tempo groups rather than by chronological age (Tanner 1962, Roche and Himes 1980). Because chronological age groups include a mixture of early and late maturing children, patterns related to maturation considered across these groups are less apparent. Because stages of secondary sex characteristics are usually limited to four or five categories, adolescent spurts in AP expressed relative to these stages tend also to be dampened (Kantero, Wide and Widholm 1975).

The adolescent changes in AP are best studied longitudinally as done by Round *et al.* (Round, Butcher and Steele 1979). By aligning individual peaks in spurts in AP during adolescence, they have described the expected patterns for individuals, controlling for maturation-associated differences in timing directly.

Because osteoblastic activity is a chief source of AP, one might presume a close and causal association between skeletal maturation and AP. The magnitude and pattern of associations between skeletal age and serum AP in Guatemalan children, however, suggest the significant associations are only due to skeletal maturation being a fair proxy measure for somatic growth velocity during the adolescent years. In this regard, skeletal age is a better proxy than chronological age. The continued declines in mean AP after the hand-wrist is skeletally mature (figures 1 and 2) are consistent with the fact that appreciable growth remains elsewhere in the body and appreciable growth velocities still occur after this point (Roche and Davila 1972).

It is unclear whether living in chronic poverty has affected the associations between skeletal maturation and serum AP in the Guatemalan children. These children are short and light relative to international reference data (Martorell, Rivera and Kaplowitz 1990) and the boys are somewhat delayed in skeletal age (table 2; Chapman, Haas, Rivera and Martorell 1990). Some limited data from Brazil suggest skeletal age relationships with AP are similar in well nourished and poorly nourished adolescents (Linhares, Round and Jones 1986). Differing presentations of adolescent changes in AP from cross-sectional studies of well nourished youth make it difficult to determine if the adolescent patterns of the Guatemalan youth differ in any substantial way that might be attributed to poverty or malnutrition.

It is clear that adolescent changes in serum AP in these Guatemalan children are

better discerned relative to skeletal age (RUS) than relative to chronological age. Nevertheless, associations with skeletal age are probably indirect via more direct associations with adolescent velocities in somatic growth.

Acknowledgements

Data collection and analyses were supported by grants HD-22440 (to Stanford University) and HD-24684 (to University of Minnesota) from the National Institutes of Health, Bethesda, Maryland, USA.

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Zusammenfassung. Für 873 Jugendliche und junge Erwachsene im Alter von 11–25 Jahren aus ländlichen Regionen Guatemalas wurden die Aktivität der alkalischen Phosphatase (AP), die Körperhöhe und das Skelettalter (SA) nach der Tanner-Whitehouse-2 RUS Methode bestimmt. Bei Mädchen nimmt die durchschnittliche AP-Aktivität mit fortschreitendem chronologischen Alter (CA) systematisch ab, während bei Jungen im Alter von 14 Jahren ein adoleszenter Anstieg in der mittleren AP-Aktivität zu beobachten ist. Wenn die durchschnittliche AP-Aktivität nach SA-Gruppen ausgewertet wird, zeigt sich ein deutlicher adoleszenter Anstieg, bei Mädchen mit einem Peak im SA-Alter von 11 Jahren und bei Jungen im SA-Alter von 14 Jahren. Die Korrelationen zwischen der AP-Aktivität und dem relativen Skelettalter SA-CA) nehmen systematisch ab, von moderat positiven Werten in den unteren CA-Gruppen bis zu moderat negativen Werten in den höheren chronologischen Altersklassen, wobei Korrelationen um Null in den chronologischen Altersstufen erreicht werden, in denen eine maximale adoleszente AP-Aktivität beobachtet werden konnte. Die Ergebnisse legen nahe, daß die Muster der durchschnittlichen AP-Aktivität während der Pubertät in beiden Geschlechtern stark dem Timing und dem Muster der Wachstumsgeschwindigkeit der Körperhöhe ähneln. Insofern stehen sie nur indirekt mit dem SA im Zusammenhang, da letzteres ein Indikator für das Timing des adoleszenten Wachstumsspurts in der Körperhöhe ist.

Résumé. L'activité de la sérum alcaline phosphatase (AP), la structure et l'âge squelettique selon Tanner-Whitehouse-2 RUS (AS), ont été déterminés pour 873 jeunes guatemaltèques ruraux de 11 à 25 ans. L'AP moyenne décroit systématiquement avec l'âge chronologique (AC) chez les filles, tandis qu'elle augmente à l'adolescence chez les garçons de 14 ans. Quand l'AP moyenne est calculée à l'intérieur des groupes d'AS, des augmentations liées à l'adolescence sont apparentes, chez les filles avec pic à l'AS de 11 ans et chez les garçons avec pic à AS de 14 ans. Les corrélations entre AP et âge squelettique relatif (AS–AC) diminuent systématiquement, de modérément positives aux groupes d'AC les plus jeunes, à modérément négatives aux âges plus avancés, en passant par la valuer zéro à l'âge chronologique des valuers d'AP maximum de l'adolescence. Les analyses suggèrent que l'évolution des moyennes d'AP au cours de l'adolescence, suit étroitement le rythme et les formes de la vitesse de croissance staturale dans chaque sexe et sont seulement indirectement reliés à l'AS, comme il en va pour le rythme de maturation de la poussée de croissance staturale pubertaire.