Original Research Article

Harris Lines Revisited: Prevalence, Comorbidities, and Possible Etiologies

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Objectives: The occurrence of transverse radiopaque lines in long bones—Harris lines (HLs)—is correlated with episodes of temporary arrest of longitudinal growth and has been used as an indicator of health and nutritional status of modern and historical populations. However, the interpretation of HLs as a stress indicator remains debatable. The aim of this article is to evaluate the perspectives and the limitations of HLs analyses and to examine their reliability as a stress indicator.

Methods: The study was conducted on 241 tibiae from a medieval Swiss skeletal material and was carried out using a standardized, semiautomated HL detection and analysis tool developed by the authors. We compared four different age-at-formation estimation methods and analyzed the correlation of HL occurrence to life expectancy, mean-age-at-death, stature, tibia length, and metabolic disorders as expressed by linear enamel hypoplasia and hypothyroidism.

Results: The evaluation of the age-at-formation estimation methods showed statistical significant differences. Therefore, a mathematical framework for the conversion between the methods has been developed. Remodeling had eliminated about half of the HLs formed during adolescence, and a further half of the remaining ones during early adulthood, whereas no association between the aforementioned conditions and HL prevalence could be determined. The peaks of high HL frequency among various populations were found to parallel normal growth spurts and growth hormone secretion.

Conclusions: We suggest a reconsideration of HLs as more of a result of normal growth and growth spurts, rather than a pure outcome of nutritional or pathologic stress. Am. J. Hum. Biol. 00:00–00, 2011.

The occurrence of transverse radiopaque lines in long bones was described early in the 20th century (Eliot et al., 1927; Harris, 1933; Ludloff, 1903). Such horizontal line densifications can occur in most bones of the skeleton, with the most frequent occurrence in the distal half of the tibia (Garn et al., 1968; Park, 1964).

Harris lines (HLs) or so-called growth arrest lines have been correlated with episodes of temporary arrest of longitudinal growth caused by the impact of stresses such as malnutrition, illness, and psychogenic stress on long bones (e.g. Acheson, 1959; Blanco et al., 1974; Dreizen et al., 1956; Harris, 1933; Marshall, 1968; McHenry, 1968; Platt et al., 1963; Sontag and Comstock, 1938).

HLs have been used as indicators of health, nutritional status, and living conditions of individuals and historical populations (Allison et al., 1974; Nowak and Piontek, 2002; Wells, 1967). However, the interpretation of HLs as stress indicators remains debatable since many studies have found no correspondence between HLs and illnesses (Alfonso et al., 2005; Clarke, 1982; Garn et al., 1968; González-Reimers et al., 2007; Mays, 1985; McHenry and Schultz, 1976; Ribot and Roberts, 1996). Furthermore, it is known that remodeling of bone tissue during growth affects the number of visible HL in an individual. Specifically, HLs formed earlier may disappear during the development of an individual (Hummert and Van Gerven, 1985). This fact makes it impossible to know with certainty the correct total number of HLs for an individual. The number of observed HLs only represents a current snapshot of the remaining stress markers of that individual. Despite the fact that researchers agree on the occurrence of remodeling, the behavior and process of remodeling are yet unknown.

A significant intraobserver and interobserver variability occurs during the manual HL detection process (Grolleau-Raoux et al., 1997; Suter et al., 2008) and adds additional constraints to the documentation of HLs. State of the art criteria for HLs were defined by Garn et al. (1968) and Gindhart (1969) and were adapted by Maat (1984) and Clarke and Mack (1988). Nevertheless, factors such as data acquisition, displaying tools and the observer's experience lead to high intraobserver and interobserver error.

The existence of various methods (Byers, 1991; Clarke, 1982; Hummert and Van Gerven, 1985; Maat, 1984) to compute the age-at-formation of HLs, creates a plurality of applied methods in different studies. Therefore, this plurality of methods increases the time required for the analysis itself as well as confounding the comparison between different studies.

In a previous article, we have described an image analysis tool that provides semiautomated detection of HLs in X-ray images and the functions needed to calculate the individual's age-at-line-formation according to the aforementioned methods (Suter et al., 2008). [The Harris lines tool by Suter et al. (2008) may be downloaded and used for research purposes from www.harrislinestool.com. The aim of the present article is to apply the new technique to a

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TABLE 1. Sex and age distribution of the investigated individuals from Tomils/Sogn Murezi (11th–15th century AD) used in the HL analysis

	Age groups						
Sex groups	Infants I: 1–6	Infants II: 7–14	Juveniles: 15–22	Young adults: 23–39	Mature adults: 40–59	Older adults: 60–80	Total
Males	0	0	11	31	44	22	108
Females	0	0	1	32	41	13	87
Unsexed subadults	31	15	0	0	0	0	46
Total	31	15	12	63	85	35	241

large skeletal series and to compare, in particular, the age-at-formation calculation methods (Byers, 1991; Clarke, 1982; Hummert and Van Gerven, 1985; Maat, 1984). Furthermore, there is a need to develop a mathematical framework in order to convert age-at-formation results of one method to another age-at-formation calculation method.

In order to examine the correlation of the occurrence of HLs relative to growth, growth-related diseases, developmental stress and longevity; we compared body measures (stature, tibia length), life expectancy, linear enamel hypoplasia (LEH), and hypothyroidism between individuals with and without HLs.

MATERIALS AND METHODS

The skeletal material originated from the site Tomils/Sogn Murezi, an alpine medieval cemetery located in the Canton Grisons, Switzerland, which is dated to the 11th to 15th century AD based on archaeological data and radiocarbon dating (by the Institute for Particle Physics Swiss Federal Institute of Technology, Zurich, Switzerland). In total, 404 well-preserved skeletons, 152 females, 123 males, 118 unsexed subadults, and 11 unsexed adults, were recovered from the cemetery. Sex was determined using standard morphological criteria (Bass, 1995; Ubelaker, 1978; Workshop of European Anthropologists, 1980) and age-at-death was estimated according to the "complex method" (Acsádi and Nemeskéri, 1970; Nemeskéri et al., 1960; Workshop of European anthropologists, 1980).

Digital radiographs (anterior–posterior view, 12-bit DICOM images) of all completely preserved tibiae (N = 241, Table 1) free of pathological conditions such as fractures, osteomyelitis or severe periostitis were taken using a conventional X-ray machine (Polydoros 80; Siemens Medical Solutions, Erlangen, Germany) at the Orthopaedic University Hospital, Zurich, Switzerland. When both tibiae were present, the left one was selected; if the left tibia was not preserved the right one was X-rayed. In order to test the representativeness of the X-rayed sample compared with the total skeletal sample, a χ^2 goodness-of-fit test was performed. A semiautomated detection tool (Suter et al., 2008) was used to carry out the HL detection and the computation of all age-at-formation (Fig. 1). For adults, the age-at-formation was computed using the methods of Clarke (1982), Maat (1984), Byers (1991) and for subadults using to the method of Hummert and Van Gerven (1985).

The three estimation methods for age-at-formation of HLs (Byers, 1991; Clarke, 1982; Maat, 1984) were compared using the method described by Altman and Bland (1983) and Bland and Altman (2010). The application of this method is appropriate in order to avoid the theoretical weakness of regression analysis. The method is based on a comparison of the difference between two estimations and their arithmetic mean. If the difference and the mean show no significant correlation, both methods are independent of each other and can be compared directly. If the difference and the mean show a significant correlation, this dependency has to be further analyzed, before a conversion is possible. In such cases, Altman and Bland (1983) recommend a transformation of the variables or further clearing of their relation by regression analysis; the last option was adopted here.

Stature was estimated using the total length of the humerus (H1), radius (R1b), femur (F1), and tibia (T1) from adult individuals. The measurements were taken on the left side using an osteometric board according to Martin's method (1928). The measured bones were free of pathologies such as fractures and osteomyelitis as these could affect the detection of HL and the normal length of the bone. The stature was calculated based on the method of Pearson (1899). Additionally, the calculated stature was used together with tibial length to compare individuals with and without HL as a marker of biological welfare (e.g. Kemkes-Grottenthaler, 2005; Komlos, 2009; Rühli et al., 2008).

The life expectancy at birth was assessed with the help of life tables (Ascádi and Nemeskéri, 1970). The probability of dying, the death rate and the life expectancy for each age group was calculated for individuals with and without HLs. For the construction of the life tables, a span of 7 years was used for subadults, a span of 6 years for juveniles, and a span of 10 years for adults and older individuals. In parallel, the mean-age-at-death between individuals with and without HLs was also calculated and compared.

LEH was recorded for all permanent teeth free of severe caries or dental wear using a three-scale system: (1) horizontal lines are slightly present, (2) horizontal lines are well-formed, or (3) intense narrow grooves are present on the crown (Papageorgopoulou, 2008). For the comparison with HLs, the three-scale system was aggregated into the terms presence or absence of LEH. The comparison with HLs was made according to the relative frequency of LEH and the number of HLs per individual.

Hypothyroidism was observed in Tomils (Papageorgopoulou, 2008). The diagnosis was based on pathological features, which are characteristic for conditions such as delayed epiphyseal fusion of both the axial skeleton and the long bones, hip and shoulder epiphyseal dysplasias, limb asymmetries, changes in the skull form and epiphyseal growth plate problems (Borg et al., 1975; de Quervain and Wegelin, 1936; Evans, 1952; König, 1965; Reilly and Smyth, 1937; Weygandt, 1904; Wieland, 1940). Macroscopic and radiological comparisons with diagnosed cases

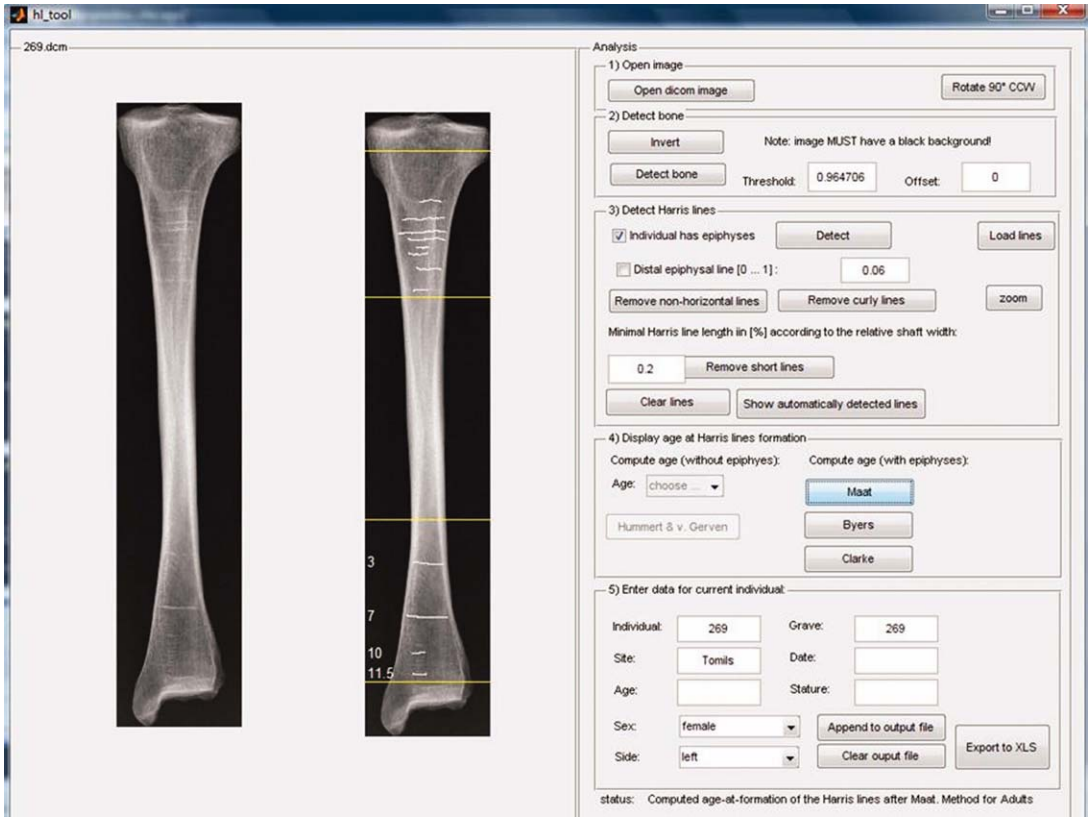

Fig. 1. Example of a work sheet from the HL-tool; left: digital X-ray of a tibia from Tomils (269) as uploaded into the HL-tool, right: HLs marked on the proximal and distal part of the tibia using age-at-formation of HLs according to the method of Maat (1984). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 2. Presence and absence of HLs by sex groups in the population of Tomils (11th–15th century AD)

	Males	Females	Total
No HL	23	17	40
HLs	85	70	155
Total	108	87	195

There was no statistically significant difference between males and females (χ^2 0.091, sig. 0.763).

TABLE 3. Presence and absence of HLs by age groups in the population of Tomils (11th–15th century AD)

	Age groups						
	1–6	7–14	15–22	23–39	40–59	60–80	Total
No HL	13	3	1	9	22	8	56
HLs	18	12	11	54	63	27	185
Total	31	15	12	63	85	35	241

There was no statistically significant difference between age groups (subadult age groups χ^2 5.561, sig. 0.062; adult age groups χ^2 2.963, sig. 0.227; all age groups χ^2 10.492, sig. 0.055).

of hyperthyroidism from 19th to 20th century Switzerland [Galler pathological reference series, Rühli et al., 2003] were also performed.

When the preconditions for parametric statistics were not fulfilled, nonparametric statistics were used. Frequencies were compared using χ^2 statistics, the correlation between metric variables was calculated by ranked values as Spearman's ρ, and the two different groups were compared by median-based Mann-Whitney U test. Results were considered as significant, when the significance was equal to or less than 0.05. All statistical analyses were made using SPSS 17.0© for Windows.

RESULTS

The χ^2 goodness-of-fit test proved that the X-rayed samples were representative for both age (χ^2 = 0.005, sig. 0.944, not sig.) and sex groups (χ^2 = 1.373, sig. 0.925, not sig.).

HLs were found in 185 of 241 (76.8%) examined individuals. Males (78.7%) and females (80.5%) did not show any statistical significant difference (Table 2). HLs were found in 41 of 58 (70.7%) subadults and 144 of 183 (75.9%) adults. The differences between the age groups were not statistically significant (Table 3). The total number of HLs, both in the proximal and distal part of the tibia, was 1,512. HLs were located mainly in the distal (n = 936) rather than in the proximal half (n = 576) of the tibia. For adults, the average distance between sequential HLs at the distal end of the tibia was 0.77 ± 0.90 cm (n = 617 distances from 147 individuals). When the measurements were restricted to two HLs formed in directly successive years e.g. 1–2, 2–3, 3–4; the average distance was 0.47 ± 0.22 cm (n = 297 distances). At the proximal end of the tibia, the average distance between sequential HLs was

TABLE 4. Age-at-formation of HLs in adult males and females as well as subadult individuals according to the four most commonly used age-at-formation estimation methods for HL calculated by the HL tool (Suter et al., 2008)

Method	Mean	SD	Median	IQR	Range
Males[a]					
Byers (1991)	9.5	3.59	10	7–12	0–15
Maat (1984)	9.9	3.34	11	7.5–12.5	1.5–15.5
Clarke (1982)	10.4	3.31	11	8–13	2–16
Females[a]					
Byers (1991)	8.3	3.02	9	6–11	0–13
Maat (1984)	8.7	2.76	9.5	7–11	1–12
Clarke (1982)	9.3	2.77	10	8–11	2–13
Hummert and Van Gerven (1985)					
All subadults	6.2	4.3	6.0	2.9–9.6	0–15.0
Infants I	2.9	1.9	3.0	1.7–3.4	0.0–7.8
Infants II	7.9	2.6	7.1	6.2–9.6	4.0–14.0
Juveniles	12.9	1.2	12.7	11.9–13.8	11.7–15.0

[a]The differences between the three methods both for males and females are statistical significant (Friedman's nonparametric test: males sig. 0.000; females sig. 0.000). The differences between males and females for each method are statistical significant (Mann-Whitney nonparametric test: Byers, $z = -5.964$, sig. 0.000; Maat, $z = -6.695$, sig. 0.000; Clark, $z = -5.789$, sig. 0.000).
SD = standard deviation; IQR = interquartile range.

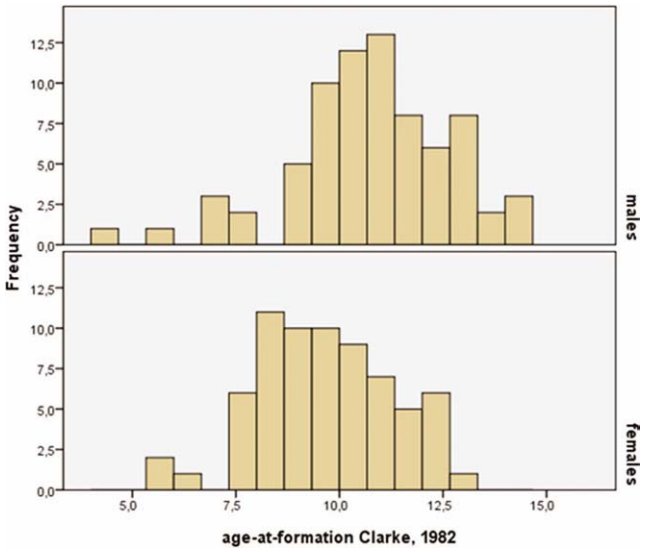

Fig. 2. Age-at-formation distribution of HLs of males and females at Tomils (11th–15th c. AD) based on the method of Clarke (1982). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

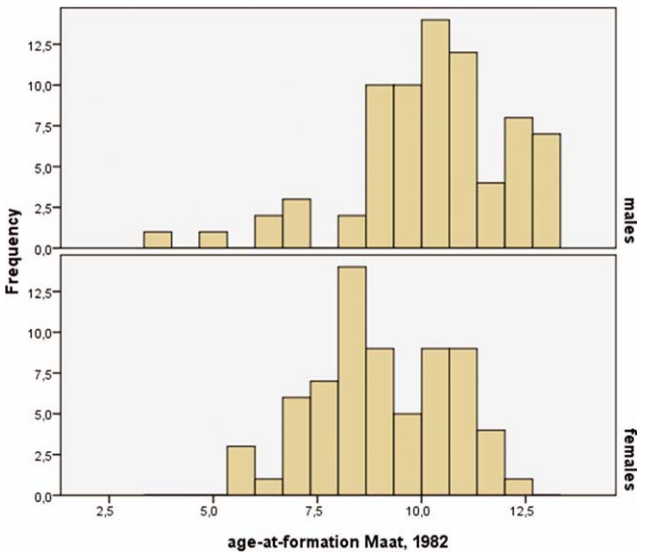

Fig. 3. Age-at-formation distribution of HLs of males and females at Tomils (11th–15th c. AD) based on the method of Maat (1982). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

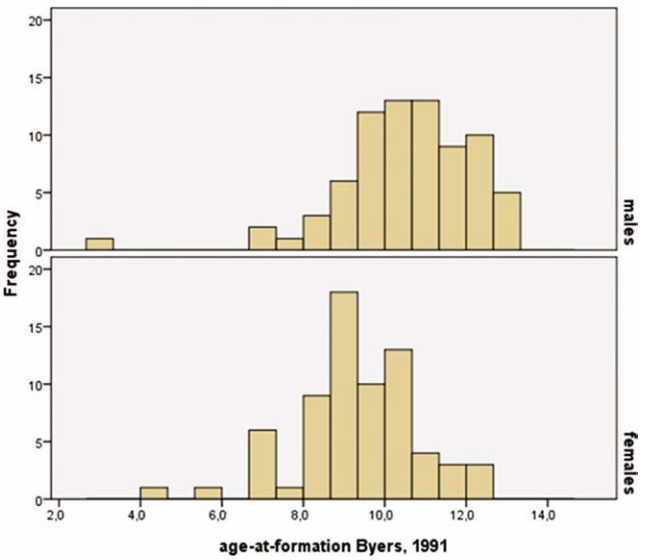

Fig. 4. Age-at-formation distribution of HLs of males and females at Tomils (11th–15th c. AD) based on the method of Byers (1991). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

0.97 ± 0.60 cm (n = 321 distances from 120 individuals), and between two HLs formed in directly successive years was 0.78 ±0.32 cm (n = 222 distances). No significant difference was found between the sex groups (t-test; distal end T −0.395, sig. 0.693; proximal end T 1.185, sig. 0.237). At subadults, the average distance between sequential HLs at the distal end of the tibia was 0.81 ± 1.13 cm (n = 57 distances from 36 individuals), and between two HLs formed in directly successive years was 0.39 ±0.45 cm (n = 5 distances).

The number of HLs per individual ranged from 1 to 40 lines with a mean of 6.3 HLs (SD 7.0, median 4.0, IQR 2.0–7.0). Subadults exhibited a mean of 3.8 HLs (SD 4.6, median 2.5, IQR 2.0–5.8) and adults a mean of 7.1 HLs (SD 7.4, median 5.0, IQR 2.0–7.0). Males exhibited a mean of 7.3 HLs (SD 8.1, median 4.0, IQR 2.0–9.0) and females a mean of 6.7 HLs (SD 6.5, median 5.0, IQR 2.0–6.0). The differences between sex (Mann-Whitney nonparametric tests, z score −0.041, sig. 0.967) and age (z score −0.900, sig. 0.368) were not significant.

The mean age-at-formation for adults and subadults according to the four methods is presented in Table 4. The highest incidence of HLs was found at the age of 8.3 to 9.3 for females and at the age of 9.5 to 10.5 for males, which was dependent on the method used (Figs. 2–4). The differences were statistically significant for all three methods.

For the subadults, the mean age-at-formation of a HL was 6.2 years of age (Table 4).

Table 5 shows the comparative summaries between each pair of methods of age-at-formation estimation and their differences. The differences between Clarke (1982) and Maat (1984) were not correlated with their means, wherefore they could be transformed by subtraction of their means (i.e. 0.500). A standard deviation of 0.363 gave a 1-sigma error for this transformation. A pairing of methods including Byers (1991), showed a significant correlation (Table 5), which from a statistical stand point does not allow a direct transformation. The regression formulas between the single estimations and the paired estimations are shown in Table 6. The mean difference after applying the regressions was zero with a standard deviation of 0.528 and 0.462 respectively, which gave a 1-sigma error for the transformations. Thus, a transformation between Clarke (1982) and Byers (1991) or between Maat (1984) and Byers (1991) is possible by applying the formula in Table 6 and this will result in an error of about 0.5 years.

Subadult individuals were aggregated into age groups as suggested by Hummert and van Gerven (1985). Table 7 shows the number of observed HLs in each age group (rows) in relationship to their age-at-formation (columns). From 36 subadults, 174 HLs were observed and resulted in a mean of 4.8 HLs per individual. The calculations were based on subadults ranging in age from 0 to 14–16 years (n = 36), using the tables of Hummert and van Gerven (1985). These tables were used for the estimation of the age-at-formation and gave a maximum age-at-formation 14 to 16 years. In all age groups, most of the observed HLs had been formed within the last 3 to 4 years of adolescence. Older individuals showed a significant lack of HLs from early years of life. The summarizing Table 8 shows that HLs steadily declined. Although in the last years of subadulthood new HLs are formed, the number of HLs is declining instead of increasing. In theory, the system of HL formation could be described as an initial period of new HL formation, followed by years of no remodeling and then followed by years of successive remodeling of older HLs.

TABLE 5. Mean and standard deviation of the difference between the three estimation methods (Byers, 1991; Clarke, 1982; Maat, 1984), their Pearson correlations and statistical significance

Difference	Mean ± std dev	Corr. coeff., sign
Clarke minus Maat	0.500 ± 0.363	−0.080, sign. 0.026
Clarke minus Byers	0.953 ± 0.589	−0.470, sign. 0.000
Maat minus Byers	0.453 ± 0.526	−0.471, sign. 0.000

TABLE 6. Regression formulas with slope and intercept comparing the estimation methods of Clarke (1982), Maat (1984), and Byers (1991)

Byers × 0.954 + 0.893 = mean Clarke/Byers	Byers × 0.959 + 0.594 = mean Maat/Byers
Clarke × 1.037 − 0.845 = mean Clarke/Byers	Maat × 1.034 − 0.544 = mean Maat/Byers
Difference: 0.006 ± 0.518	Difference 0.003 ± 0.462
Corr. coeff. −0.011, sign. 0.765	Corr. coeff. −0.003, sign. 0.934

Relationship between Harris Lines and other aspects of skeletal development

The number of HLs in adults did not correlate with tibia length T1 (Spearman's ρ 0.008, sig. 0.929,) in both males (Spearman's ρ 0.044, sig. 0.717) and females (Spearman's ρ −0.087, sig. 0.483). The frequency of HLs did not seem to affect the final stature of individuals (Spearman's ρ 0.017, sig. 0.859) neither in males (Spearman's ρ 0.072, sig. 0.595) nor in females (Spearman's ρ −0.127, sig. 0.348).

Relative to subadults, a one to one correlation between the number of HLs and tibia length (total length) would be biased, since younger subadults would have fewer HLs than older subadults. To eliminate this bias effect, we calculated the number of HLs per year for the subadults in order to detect individuals with few or many HLs for their age. We found a median of 0.46 HLs per year and an interquartile range (IQR) of 0.24 to 1.00. This IQR represented a HL frequency/rate of 50% for the subadult individuals. Individuals with fewer than 0.24 HLs per year or with 1.00 or more HLs per year represented the less frequent cases. Figure 5 shows the relationship between age and tibia length in Tomils. The symbols indicate whether an individual has abnormally few (≤0.24) or many HLs (≥1.00) for its age. The quadratic regression line shows the usual growth rate of the tibiae with age for Tomils (r^2 = 0.955). Symbols to the right of the line are individuals with longer tibiae for their age and symbols to the left of the line show individuals with relatively short tibiae for their age. There was no relationship between the deviation from normal growth and the number of HLs per year

TABLE 7. Number and age-at-formation of observed HLs in subadults, with individuals classified into the same age groups using the system of Hummert and van Gerven (1985)

Age at death[a]	*n*	Each cell shows the total number of observed HLs (*n* = 174) in relation to the age groups									
14–16	7	0	1	0	0	0	0	1	9	4	22	23
12–13	4	0	1	4	2	1	0	6	6	1	10	
10–11	3	0	0	1	1	2	1	5	8			
8–9	4	0	0	0	1	0	0	8	5			
6–7	3	1	1	4	1	2	3	5				
5	4	1	0	2	5	4	2					
4	3	0	0	1	3							
3	3	1	1	3	3							
2	4	1	4	2								
1	1	1										
Age-at-formation after Hummert and van Gerven		<1	1	2	3	4	5	6–7	8–9	10–11	12–13	14–16

[a]Age at death of subadult individuals.
n = number of subadult individuals.

observed. This was verified by an analysis of the residuals. The expected age-specific length of a subadult tibia in Tomils can be calculated as: 76.624 + (21.480 × age) − (0.583 × age2), with $r^2 = 0.955$. The residuals, i.e. the differences between the observed and the expected length of the tibia, are not correlated with the number of HLs per year (Spearman's ρ 0.176, sig. 0.353).

LEH was present in 35.3% of the total skeletal sample from Tomils. However, no correlation was found between the number of HLs and the percentage of LEH present in all adult individuals (Spearman's ρ 0.072, sig. 0.378) nor when calculated separately for males (Spearman's ρ −0.120, sig. 0.303) and females (Spearman's ρ −0.025, sig. 0.830). Subadult individuals also showed no correlation between the percentage of LEH and the number of HLs either (Spearman's ρ 0.333, sig. 0.104), respectively the number of HL per year (Spearman's ρ −0.148, sig. 0.523). The infant Group I (1–6 years old) was excluded from this calculation for the subadults, since permanent teeth in which LEH were recorded erupt only after the age of 6.

Hypothyroidism, a metabolic disease, occurred in Tomils at a high frequency (13.6%) and was used to test a probable connection between growth disturbances and the presence of HLs. Mann-Whitney U tests on the differences in the median number of HLs between adult male and adult female individuals with and without hypothyroidism showed no significant differences (Table 9). No test was conducted for subadults since the condition cannot be diagnosed with certainty on skeletal material of children and juveniles. Nevertheless, individuals with hypothyroidism, showed a significantly higher frequency of LEH versus individuals without hypothyroidism (Mann-Whitney U tests Z −3.390, sig. 0.001).

TABLE 8. Age of observed HLs calculated as a difference between age at death of the individual and age-at-formation of the HLs (restricted to individuals older than 5 years)

Age of the HLs (in yr)	0–1	2–3	4–5	6–7	8–9	10–11
n individuals	21	21	21	21	18	14
n HLs	43	44	20	21	4	6
HLs per 2-yr-span	2.05	2.10	0.95	1.00	0.22	0.43

Early formed HLs do not "survive" to an older age.

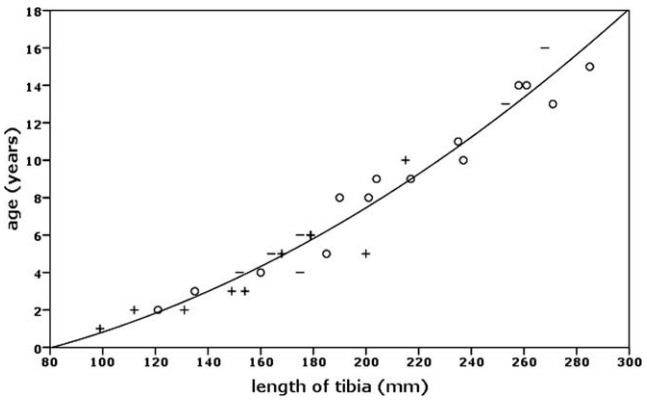

Fig. 5. The relationship between age (in years) and tibia length (in mm) at Tomils (11th–15th c.AD) [F1 after Martin (1928)]. The symbols indicate the relative frequency of HLs per year: − few HLs (< 0.27), ○ normal frequency of HLs (IQR: 0.27–1.00), + many HLs (>1.00). The line indicates the normal growth of F1 with age (quadratic regression, $r^2 = 0.955$).

To test the hypothesis, if an individual with a high number of HLs faces the risk of a shorter life expectancy than an individual with no HL or few HLs, we divided the individuals into two groups: Group A individuals with HLs and group B individuals with no HL. Group A had a life expectancy (a_{20}) of 42.2 years, while group B had a life expectancy (a_{20}) of 45 years. The difference between the groups was not statistically significant (χ^2 6.03, sig. 0.28) (Tables 10 and 11). Another classification was based on the presence of many or few HLs. The individuals were divided by the median (4) of the number of HLs per individual, i.e., Group C refers to individuals with HL numbers greater than 4, Group D refers to individuals with HL numbers of 4 or less. Group C had a calculated life expectancy (a_{20}) of 42.3, while Group D had a calculated life expectancy (a_{20}) of 43.3 (Tables 12 and 13). The difference was not statistically significant (χ^2 3.95, sig. 0.41). No relation between the number of HLs and life expectancy was found.

In terms of the mean age at death, there were no statistically significant differences between the adult age group with and without HLs (mean age at death 45.7 and 48.8 years, respectively; Mann-Whitney U test Z −1.203, sig. 0.229). In terms of many or few HLs, there was again no significant differences between mean age at death in the adult age group (mean age at death 45.8 and 46.9 years, respectively; Mann-Whitney U test Z −0.368, sig. 0.713).

DISCUSSION

A high prevalence of HLs was found in the medieval skeletal material of Tomils. More than three quarters of the examined individuals showed at least one HL. There was no difference observed between males and females, with regards to both the number of individuals affected and the mean number of HLs per individual. An analysis of archaeological and anthropological characteristics (Papageorgopoulou, 2008) has shown no evidence of socioeconomic differences in terms of gravegoods, place of interment, and type of burial among the individuals with and without HLs. Comparable results regarding the frequency of HLs in skeletal material of similar geographical and chronological settings were found in skeletal material from Switzerland (13th−14th c. AD) (Ameen et al., 2005), from medieval (10th–14th c AD) Poland (Gronkiewicz et al., 2001; Nowak and Piontek, 2002; Piontek et al., 2001) from medieval and early modern (5th–19th c. AD) Southern Germany (Haidle, 1997) and from North

TABLE 9. Relationship between the number of HLs and hypothyroidism. Each cell shows the mean, the standard deviation and the median

	Without hypothyroidism	With hypothyroidism	Mann-Whitney *U*-test
Males and females	Mean 5.4 ±4.3; median 4.0	Mean 4.4 ± 3.5; median 3.5	$Z = -1.213$, sig. 0.225
Males	Mean 6.1 ± 4.9; median 5.0	Mean 4.3 ± 3.8; median 3.0	$Z = -1.474$, sig. 0.140
Females	Mean 4.8 ± 3.5; median 4.0	Mean 4.6 ± 3.1; median 4.0	$Z = -0.032$, sig. 0.974

TABLE 10. Life table showing the life expectancy of individuals with HLs

Age group	a	D_x	d_x	q_x	e_x	a_x
0–7	7	18.0	84.0	84.0	**35.9**	35.9
8–14	7	12.0	56.0	61.1	31.9	38.9
14–20	6	11.0	51.3	59.7	26.7	40.7
20–30	10	54.1	252.4	312.2	22.2	**42.2**
30–40	10	29.3	136.7	245.8	20.0	50.0
40–50	10	30.0	140.0	333.7	14.9	54.9
50–60	10	31.8	148.4	530.9	9.9	59.9
60–70	10	27.1	126.5	964.4	5.4	65.4
70–80	10	1.0	4.7	1,000.0	5.0	75.0

a = number of years within this age class; D_x = absolute number of dead individuals in this age class; d_x = relative number of dead individuals at age x (i.e. the beginning of this age class), calculated to base 1,000; q_x = probability of dying at age x; e_x = further life expectancy at age x; a_x = total life expectancy of those individuals, which survived up to age x (l_x = relative number of surviving individuals at age x; T_x = total number of years to be lived at age x; L_x = total number of years lived at age x, are not included since such parameters do not apply to skeletal samples).

TABLE 11. Life table showing the life expectancy of individuals with no HLs

	a	D_x	d_x	q_x	e_x	a_x
0–7	7	13.0	207.7	207.7	**34.3**	34.3
8–14	7	3.0	47.9	60.5	35.4	42.4
14–20	6	1.0	16.0	21.5	30.4	44.4
20–30	10	8.6	137.4	188.6	25.0	**45.0**
30–40	10	6.6	105.4	178.4	19.7	49.7
40–50	10	13.6	217.3	447.4	12.9	52.9
50–60	10	9.7	155.0	577.4	9.2	59.2
60–70	10	7.1	113.4	1,000.0	5.0	65.0
70–80	10	0.0	0.0	1,000.0	5.0	75.0

a = number of years within this age class; D_x = absolute number of dead individuals in this age class; d_x = relative number of dead individuals at age x (i.e. the beginning of this age class), calculated to base 1,000; q_x = probability of dying at age x; e_x = further life expectancy at age x; a_x = total life expectancy of those individuals, which survived up to age x. (l_x = relative number of surviving individuals at age x; T_x = total number of years to be lived at age x; L_x = total number of years lived at age x, are not included since such parameters do not apply to skeletal samples).

TABLE 12. Life table showing the life expectancy of individuals with a high frequency of HLs (≥5)

	a	D_x	d_x	q_x	e_x	a_x
0–7	7	4.0	30.0	30.0	**38.5**	38.5
8–14	7	4.0	30.0	30.9	32.6	39.6
14–20	6	9.0	67.5	71.8	26.5	40.5
20–30	10	37.1	278.3	319.0	22.3	**42.3**
30–40	10	19.3	144.8	243.7	20.4	50.4
40–50	10	17.6	132.0	293.8	15.4	55.4
50–60	10	22.2	166.5	524.8	9.8	59.8
60–70	10	20.1	150.8	1,000.0	5.0	65.0
70–80	10	0.0	0.0	1,000.0	5.0	75.0

a = number of years within this age class; D_x = absolute number of dead individuals in this age class; d_x = relative number of dead individuals at age x (i.e. the beginning of this age class), calculated to base 1,000; q_x = probability of dying at age x; e_x = further life expectancy at age x; a_x = total life expectancy of those individuals, which survived up to age x. (l_x = relative number of surviving individuals at age x; T_x = total number of years to be lived at age x; L_x = total number of years lived at age x, are not included since such parameters do not apply to skeletal samples).

TABLE 13. Life table showing the life expectancy of individuals with a low frequency of HLs (≤4)

	a	D_x	d_x	q_x	e_x	a_x
0–7	7	27.0	188.0	188.0	**32.8**	32.8
8–14	7	11.0	76.6	94.3	32.5	39.5
14–20	6	3.0	20.9	28.4	28.6	42.6
20–30	10	25.6	178.3	249.5	23.3	**43.3**
30–40	10	16.6	115.6	215.6	19.4	49.4
40–50	10	25.9	180.4	428.8	13.4	53.4
50–60	10	19.4	135.1	562.3	9.7	59.7
60–70	10	14.1	98.2	933.8	5.7	65.7
70–80	10	1.0	7.0	1,000.0	5.0	75.0

a = number of years within this age class; D_x = absolute number of dead individuals in this age class; d_x = relative number of dead individuals at age x (i.e. the beginning of this age class), calculated to base 1,000; q_x = probability of dying at age x; e_x = further life expectancy at age x; a_x = total life expectancy of those individuals, which survived up to age x. (l_x = relative number of surviving individuals at age x; T_x = total number of years to be lived at age x; L_x = total number of years lived at age x, are not included since such parameters do not apply to skeletal samples).

America (McHenry, 1968; McHenry and Schulz, 1976; Rathbun, 1987) and South America (Alfonso et al., 2005; Allison et al., 1974). Lower frequencies of HLs (<50%) were observed in skeletal material from Italy (3rd–5th c. AD) (Berrocal-Zaragoza and Subirà, 2008), from the Canary Islands (Arnay-de-la-Rosa et al., 1994), from medieval (11th–17th c. AD) Ireland (Hughes et al., 1996), and medieval (11th–16th c. AD) Great Britain (Mays, 1995; Ribot and Roberts, 1996).

In the aforementioned studies, HLs were considered to be bone reactions to pathological or nutritional stress and were used as markers of non-specific stress for the reconstruction of life conditions and the health status of the examined skeletal material. However, in most of the studies, the researchers failed to correlate the presence or absence of HLs with specific stress markers (clinical studies: Dreizen et al., 1956; Garn et al., 1968; Ginhart, 1969; Marshall, 1968; Park, 1964; archaeological studies: Alfonso et al., 2005; McHenry and Schulz, 1976). Recent studies even suggested that HLs are a result of a normal rather than an abnormal growth process (Alfonso et al., 2005).

In the present study, a systematic association with other stress indicators and pathological conditions associated with growth disturbances was performed. One could argue that despite the stress indicators, individuals with many HLs could successfully compensate for stress via catch-up growth and therefore had no significant differences when compared to individuals where no HL exist. However, many clinical studies show that children with low birth weight or other growth inhibitions usually fail to reach the height of their healthy counterparts (Ford et al., 2000; Hack et al., 2003; Odberg et al., 2010).

On past HL studies, Wells (1967) found no correlation between HLs and stature. According to Himes (1978) and Huss-Ashmore et al. (1982), the lengthwise growth of long bones often adapts to stress at the expense of other features such as cortical bone thickness. However, Mays (1995) found no association between HLs, cortical index and long-bone length in medieval juvenile and adult skeletons from Great Britain (Mays, 1985). He attributed the lack of association with HLs to remodeling, in particular, for HLs found in adult individuals.

Clinical studies using X-rays and medical records of 201 children found neither a one-to-one relationship between severe illnesses and HL formation nor between HLs and the stature of the individuals (Gindhart, 1969). The only correlation between HLs and stature was observed in a study of 1,412 Guatemalan children, where children with

HLs were shorter in comparison to children with no HLs (Acheson et al., 1974; Blanco et al., 1974).

There has been no study reporting a correlation between HLs and life expectancy using life tables. Most researchers examine this aspect in terms of HL distribution within age groups. It has been shown that individuals with higher numbers of HLs have died earlier than other individuals (Grolleau-Raoux et al., 1997; McHenry, 1968; Nowak and Piontek, 2002). Nevertheless, this could be an artifact of the bone remodeling process and HL resorption. We could not reproduce this correlation either in terms of life expectancy or mean age-at-death.

LEH is seen as the dental analog of HLs (Goodman and Rose, 1990; Goodman et al., 1980) and many studies have tried to find an association between HLs and LEH (Alfonso et al., 2005; Clarke, 1982; Mays, 1985; McHenry and Schultz, 1976; Ribot and Roberts, 1996). Nevertheless, few studies have shown an association (Mays, 1995). Bone remodeling and different etiologies have been used in order to explain the absence of correlation between the two conditions (Mays, 1985; McHenry and Schultz, 1976). In the present study, there were no correlations between HLs and LEH; as individuals with HLs did not exhibit LEH and visa versa. As demonstrated in the present study, bone remodeling and thus HL remodeling in the first years of life may provide a reasonable justification for the lack of correlation between the two conditions (especially until the age of seven, which is the end phase of LEH formation). Some researchers suggested that dental development is much less affected by environmental stress than is bone growth. Thus, trivial stress episodes may lead to HLs, but not to LEH (Mays, 1995).

Hypothyroidism is a condition of mild to severe impairment of physical and mental development due to untreated thyroid hormone deficiency. Endemic hypothyroidism arises from a dietary deficient of iodine (Patrick, 2008). In Tomils and other European alpine regions, endemic hypothyroidism was very common up until the beginning of the 20th century, when the etiology was discovered and thereafter eliminated (Bürgi et al., 1990; Solca et al., 1999). The condition significantly affects skeletal growth and leads to growth disturbances (De Quervain and Wegelin, 1936; Guggenbühl, 1853; Ortner and Hotz, 2005; Weygandt, 1904; Wieland, 1940).

In Tomils, there was no correlation found between HLs and hypothyroidism. There are few studies that have investigated the presence of HLs in hypothyroidism (Boyages et al., 1988). There are more available notations about the presence of HLs in idiopathic hypoparathyroidism, a metabolic disorder caused by parathyroid hormone deficiency, which leads to variations in the rate of growth, bone remodeling, and epiphyseal closure. In three reports (Bronsky et al., 1958; Rosen and Deshmukh, 1985; Taybi and Keele, 1962), individuals with hypoparathyroidism showed HLs, but the authors failed to show a relationship between the etiology of the two conditions. In a one case of Cushing's syndrome, HLs were present in the vertebra, but not in the long bones (Bessler, 1982). HLs have also been noted in children with psychosocial short stature, a growth failure and growth hormone insufficiency without an organic cause, but rather in association with behavioral disturbances and psychosocial stress (Khadilkar et al., 1998).

In a previous study (Suter et al., 2008), we have shown that the HL detection tool provides a simultaneous and semi-automatic age-at-formation estimation based on three common methods (Byers, 1991; Clarke, 1982; Maat, 1984) for adults and one method for subadults (Hummert and Van Gerven, 1985). Estimation of age-at-formation using the method of Clarke (1982) and Maat (1984) showed a systematic difference of 0.5 years (6 months) and could be transformed with a low error of c. 0.36 years (c. 4 months; Table 5). Estimation of age-at-formation using Byers (1991) method showed a small, but significant distortion in estimations by using the method of Clarke (1982) and Maat (1984), which can be reduced by the formulas given in Table 6. The most important difference between these two pairs is given by the intercept of these regression formulas, which is about 0.9 years (c. 10 months) between Clarke (1982) and Byers (1991) and 0.5 to 0.6 years (c. 7 months) between Maat (1984) and Byers (1991); where the 1-sigma error is close to 0.5 years (6 months). Accordingly, we suggest that comparisons between methods should only be performed after an appropriate conversion to and from the corresponding method. These age-at-formation results probably derive from the differences within the growth tables used for each calculation method.

In Tomils, most HLs had been observed in male individuals using Byers' method at 9.5 years of age, using Maat's method at 9.9 years of age, and using Clarke's method at 10.4 years of age, respectively. For females, the mean age-at-formation according to the three methods ranged from between 8.3 and 9.3 years of age. The 1-year difference between males and females was steady, statistically significant and constantly observable. The absence of HLs after the age of 16 is symptomatic, which has also been reported by other researchers (Maat, 1984; Wells, 1967). After the age of 16, the growth of the tibia declines until the fusion of the epiphysis is almost completed. Most HLs in males occurred between 7.5 and 12.5 $\pm$ 0.5 years of age and in females between 7 and 11 $\pm$ 1 years of age, while no HLs have been observed after the age of 16 in males and after the age of 13 in females. Similar results have been found in prehistoric skeletal material of the same temporospatial setting (Gronkiewicz et al., 2001; Haidle, 1997; Nowak and Piontek, 2002), but also in skeletal material of different archaeological contexts (Alfonso et al., 2005; Arnay-de-la-Rosa et al., 1994; Clark, 1978; Goodman and Clark, 1981;). The only exception concerning this age distribution is the one of Hummert and Van Gerven (1985) in medieval Sudanese children, where they found a peak after 4 years of age. There is a large ongoing discussion about whether these high peaks after 7 years of age are an artifact of the remodeling process or reflect sociocultural and/or biological changes during the life of the individual.

A sociocultural change relates to the individual entering adulthood, which means less parental control, the beginning of education, more physical load, and eventually malnutrition and vulnerability to diseases (Bidon and Lett 2000; Dedet, 2008; Lohrke, 2004; Newman, 2007; Orme, 2003; Shahar, 2002; Simoneit, 1997; Ulrich-Bochsler, 1997). The sociocultural changes in association with the increased growth rate during puberty could be possible causes of the high peaks after this specific age.

Remodeling as a single factor cannot explain these peaks in the frequencies of HLs occurring within an age span. In Tomils up to an age of about 16, nearly every year a new HL was formed, while at the same time about every

2 years one of the older HLs was remodeled. Detailed analysis showed that the remodeling took place more frequent on earlier formed HLs than on later formed HLs. Therefore, the mean age-at-formation of HLs in subadult individuals tends to be close to the end of their lifespan and not in the middle. Consequently, nearly no HLs formed during infancy were left. This gives a specific distribution of the age-at-formation of HLs expected in adults, indicating most of the remaining HLs came from the last 4 years of bone growth. The histograms of mean age-at-formation of HLs in adult individual's show many HLs from age 8 to 11 years, but fewer from age 12 to 16 years. There are no arguments to explain, why the HLs of this specific age span would be preferentially excluded from subsequent remodeling (other than those from the age span 12–16). The observed peaks need an explanation based on the dominant formation of HLs.

Postnatal growth is dependent on normal growth hormone (GH) secretion and on proteins that influence GH secretion. Endocrinological studies suggest a GH secretion spurt occurs after the age of 7 and peaks between age 10 and 11 (Reiter and Rosenfeld, 1998). The earlier peak of HLs in females versus males is also present in growth curves and GH secretion curves, and correlates with the phenomenon of earlier biological maturation of females (Reiter and Rosenfeld, 1998). Also studies have reported growth curves and growth patterns that suggest a nonlinear growth pattern rather than a linear one, which is comprised of short periods of rapid growth (growth spurts) and short periods of little or no growth (growth stasis) (Butler et al., 1990; Gill et al., 2001; Hermanussen et al., 1988; Lampl et al., 1992; Tillman et al., 1998). Saltatory growth and seasonal variability—faster growth in spring and summer than in autumn and winter—additionally affect the growth pattern.

By observing the similarity of long bone growth curves (Anderson et al., 1963) and growth hormone (GH) secretion curves (Boron and Boulpaep, 2009; Reiter and Rosenfeld, 1998) in children and juveniles, we noticed a strong similarity with the HL age distribution. We therefore suggest that HLs are probably associated with a physiological growth process with spurts and stasis of human growth and that the age-at-formation distribution peaks reflect physiological growth spurts associated with increased GH secretion. These spurts and stasis could lead to HL formation, which may be more intensified under disadvantaged environments. Although pubertal growth spurts are not universal in non-westernised and preindustrialized populations (Boyd, 1980; Hermanussen and Kühl, 2006; Hermanussen et al., 1995) as well as in modern populations with poor environmental conditions (Méndez et al., 1963; Mueller et al., 1980; Sabharwal et al., 1966), growth hormone excretion may intensify the HL formation in some individuals in comparison to others. The way the human organism compensates for stress and growth is highly variable between individuals and populations. The extent to which it occurs depends in many factors including the timing and duration of the insult and the nature of the nutritional rehabilitation (Cooke, 2010). Many studies have shown that there is not a one-to-one relationship between growth and short-term changes in height and weight of normal children and children with growth disorders (Tillman et al., 1998, 2002). The lack of association between HLs and other stress indicators such as LEH and hypothyroidism, cortical thickness, stature, bone length and life expectancy, and their presence in both healthy and unhealthy children argues positively for a re-examination of HLs as purely nutritional or pathological stress indicators.

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