Archaeological and Anthropological Sciences

How reliable is the assessment of Porotic Hyperostosis and Cribra Orbitalia in skeletal human remains? A quantitative verification by a new evaluation form

--Manuscript Draft--

Manuscript Number:	
Full Title:	How reliable is the assessment of Porotic Hyperostosis and Cribra Orbitalia in skeletal human remains? A quantitative verification by a new evaluation form
Article Type:	Original Paper
Section/Category:	Palaeoanthropology
Corresponding Author:	Nicoletta Zedda Università degli Studi di Ferrara Ferrara, Emilia-Romagna ITALY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Università degli Studi di Ferrara
Corresponding Author's Secondary Institution:	
First Author:	Natascia Rinaldo
First Author Secondary Information:	
Order of Authors:	Natascia Rinaldo
	Nicoletta Zedda
	Barbara Bramanti
	Irene Rosa
	Emanuela Gualdi-Russo
Order of Authors Secondary Information:	
Funding Information:	
Abstract:	Intra vitam porous lesions of the skull (Cribra Orbitalia and Porotic Hyperostosis) are pathological conditions due to genetic or acquired chronic anemia. They are the most reported skeletal lesions in human skeletal remains and are routinely used to assess health, hygiene and nutritional status of past populations. Despite the existence of a number of proposed classifications, there is no generally accepted classification system used by all, with clear advantages over the others. Here, we propose a new evaluation form (BoPLE-Bone Porous Lesion Evaluation) that takes in consideration all the observable features of bone porous lesions, integrating existing qualitative criteria for the evaluation of severity and healing's conditions with a new quantitative analysis based on the count of pores/cm2. Porotic Hyperostosis and Cribra Orbitalia were investigated using the newly developed evaluation forms on 189 cranial bones from several distinct archaeological sites. Reliability and reproducibility of both existing qualitative scoring criteria and the new quantitative method were statistically tested. We believe that the new proposed classification system, which takes into consideration diverse parameters like surface area of lesion, location of lesion on cranial vault, and number of pits per surface area, represents a progress in the objective evaluation of porous bone lesions Its use will allow the determination of the severity of the lesion, thus provide data to assess conditions of frailty in past populations.
Suggested Reviewers:	Maria Giovanna Belcastro, PhD Associate Professor, Universita degli Studi di Bologna maria.belcastro@unibo.it

	Scientific coordinator of the Museum of Evolution of the University of Bologna and expert in Paleopathology and Physical Anthropology.
	Christina Papageorgopoulou, PhD Democritus University of Thrace cpapage@he.duth.gr She is an expert in physical anthropology.
	Caroline Ahlström Arcini Lund National Historical Museum Caroline.ahlstrom.arcini@arkeologerna.com She is an expert in Osteology

How reliable is the assessment of Porotic Hyperostosis and Cribra Orbitalia in skeletal human remains? A quantitative verification by a new evaluation form.

Natascia Rinaldo, Nicoletta Zedda*, Barbara Bramanti*, Irene Rosa, Emanuela Gualdi-Russo

Department of Biomedical and Specialty Surgical Sciences, University of Ferrara, Corso Ercole I d'Este 32, 44121, Ferrara, Italy

*Corresponding authors:
Nicoletta Zedda, email: zddnlt@unife.it, Tel: +39 0532 293748;
Barbara Bramanti, email: brmbbr@unife.it , Tel: +39 0532 293743.

ORCID

Natascia Rinaldo 0000-0002-6972-3085
Nicoletta Zedda 0000-0003-2899-2884
Barbara Bramanti 0000-0002-5433-663X
Emanuela Gualdi-Russo 0000-0002-7274-547X

Acknowledgements

The authors would like to thank Filippo Scianò for his contributions and Roberta Neilson for her participation in the data collection

Abstract

Intra vitam porous lesions of the skull (Cribra Orbitalia and Porotic Hyperostosis) are pathological conditions due to genetic or acquired chronic anemia. They are the most reported skeletal lesions in human skeletal remains and are routinely used to assess health, hygiene and nutritional status of past populations. Despite the existence of a number of proposed classifications, there is no generally accepted classification system used by all, with clear advantages over the others.

Here, we propose a new evaluation form (BoPLE-Bone Porous Lesion Evaluation) that takes in consideration all the observable features of bone porous lesions, integrating existing qualitative criteria for the evaluation of severity and healing's conditions with a new quantitative analysis based on the count of pores/cm2. Porotic Hyperostosis and Cribra Orbitalia were investigated using the newly developed evaluation forms on 189 cranial bones from several distinct archaeological sites. Reliability and reproducibility of both existing qualitative scoring criteria and the new quantitative method were statistically tested.

We believe that the new proposed classification system, which takes into consideration diverse parameters like surface area of lesion, location of lesion on cranial vault, and number of pits per surface area, represents a progress in the objective evaluation of porous bone lesions Its use will allow the determination of the severity of the lesion, thus provide data to assess conditions of frailty in past populations.

Keywords Porotic Hyperostosis, Cribra Orbitalia, Bone Porous Lesions, Scoring Standards, Evaluation Form

Introduction

Intra vitam porous bone lesions (also called cribra) are the most commonly reported pathological conditions in archaeological collections of human skeletal remains (Walker et al. 2009). They appear as small dents or holes of various sizes and distribution, which primarily develop on the outer surface of the orbits (cribra orbitalia) and the vault of the skull (cribra cranii). Cribra can also be found on the proximal epiphysis of the humerus and femur (Ortner 2003). Independently of their localization, cribra's lesions have been attributed to Porotic Hyperostosis, a physiological reaction to different forms of hereditary anemia, as it was first described by Angel in 1966 (Angel 1966). Anemia, in fact, causes disruption of hematopoiesis (blood cell production) in the trabecular bone marrow of the skull. Porotic Hyperostosis causes expansion of the diploë, the cranial spongy bone, due either to marrow hypertrophy (increased size of cells) or to hyperplasia (increased number of cells). This process is coupled with an irregular remodelling of the outer cranial table, which becomes reabsorbed with time, thus thinner and with visible porous lesions. In the most severe cases, the spongy bone of the diploë may be exposed (Martin and Goodman 2002; Rivera and Mirazón Lahr 2017).

In more recent times, the term 'Porotic Hyperostosis', is commonly used to denote cribrotic lesions of the cranial vault, whereas the term 'Cribra Orbitalia', is still used for the lesions of the orbital roofs. This terminology is becoming increasingly popular because it highlights the possible independent occurrence of the two lesions as well as their likely distinct etiologies (Wapler et al. 2004; Walker et al. 2009; Rothschild 2012; Rivera and Mirazón Lahr 2017). Yet, some scholars still prefer to use the term 'cribra cranii' for the lesions on the cranium vault (Stuart- Macadam 1989; Salvadei et al. 2001; Facchini et al. 2004; Gaudio et al. 2015; Tosi et al. 2017). The confusion in the terminology is generated by the fact that the actual etiology (or etiologies) of these lesions is still debated (Walker et al. 2009; Oxenham and Cavill 2010; Rothschild 2012). In this study, we decided to use the terms 'Porotic Hyperostosis' (PH) referring to the porous lesions localized in the cranial vault and 'Cribra Orbitalia' (CO) with reference to the porous lesions of the orbital roofs. Considering the possible etiology, PH and CO are generally both considered as a manifestation of anemia (Martin and Goodman 2002; Rivera and Mirazón Lahr 2017). Yet anemia can have a genetic (e.g., Thalassemia, Sickle-Cell anemia) (Angel 1966) or an acquired origin, due to iron deficiency (Wapler et al., 2004; Oxenham and Cavill, 2010), magnesium deficiency (Polo-Cerdá et al. 2001), vitamin B deficiency (Walker et al. 2009), or to chronic disorders (Rivera and Mirazón Lahr 2017). Other pathological conditions, such as chronic scalp infections and scurvy, can also generate porosity of the external surface of the cranial vault and/or of the orbit surface (Ortner 2003; Walker et al. 2009). Thus, *intra vitam* porous lesions are extensively used in anthropological studies as non-specific indicators of poor hygienic and health conditions, and/or nutrient deficiencies in past populations (Lallo et al. 1977; Mensforth et al. 1978; Salvadei et al. 2001; Facchini et al. 2004; Walker et al. 2009; Masson et al. 2015). For its wide application in physical anthropology, it appears of primary importance to have on disposal standardized scores of severity for porous bone lesions, which may enable comparison among individuals or populations, and might help in better defining the actual etiology (Jacobi and Danforth 2002), as well as the genetic and/or environmental conditions behind it. Different coding criteria for the assessment of severity, and for determining the possible range of expression have been proposed previously. Stuart and Macadam (1985) identified four degrees of severity, from the least serious (Grade 1) with scattered fine foramina to the most severe (Grade 4) presenting outgrowth in trabecular structure from the normal contour of the outer bone table. Salvadei (2001) distinguished only three categories, Codebook (Steckel et al. 2006) four degree of severity from 0 to 3, while Hengen (1971) utilised seven categories. In addition, other scholars have proposed to distinguish between active or healed lesions: active lesions exhibit porosity interspersed with increasingly thin bridges of bone, without signs of bone remodelling; healing lesions present bone remodelling, described as a "smooth lamellar texture with bone filling of the peripheral pores" (Mensforth et al. 1978; Mittler and Van Gerven 1994). For lesion's healing, several degrees were described as well: according to Salvadei (2001), four categories can be observed ranging from active cribra without healing (Grade 1) to fully healed lesions (Grade 4).

All these classifications, anyway, are based on qualitative descriptions of the lesions. To facilitate the evaluation, B&W photographs are often, but not always, provided by the authors. Yet, the estimation remains subjective and may consistently change with the experience of the surveyor who performs the analysis. Jacobi and Danforth (2002), who compared inter-observer scoring patterns in PH and CO, showed a great variation between 22 scores' assignations, demonstrating the limits of the current methods.

Here, we suggest a combined method for the assessment of porous bone lesions (BoPLE, Bone Porous Lesions Evaluation). BoPLE consists of newly developed evaluation forms, which take into consideration all observable features related to PH and CO. Besides using existing qualitative evaluation criteria for presence, degree of severity (Stuart- Macadam 1985) and healing status (Salvadei et al. 2001), BoPLE also proposes a new quantitative evaluation criteria consisting in counting the pits (dents or holes) in 1 cm^2 of the porous bone. This newly developed evaluation criteria, which was also among the suggestions of Jacobi and Danforth (2002), appears reasonable to describe the lesions with more confidence, although a much more extended survey will be necessary to assess the actual association between the number of pits/cm^2 and the other variables considered. In this study, we describe BoPLE and use statistical tests for validation of reliability and reproducibility of each evaluation criteria considered in the sheets, demonstrating that the quantitative method is the most accurate and objective for the analysis of cranial bone lesions.

Material and Methods

Sample

For the development of the new methodology and the associated validation survey, we chose to analyse samples from different archaeological sites, all located near Imola (Bologna, North-Eastern Italy): mass graves from the Imola's Lazzaretto (1630-32 CE); single burials from the "L'Osservanza" monumental complex (Late Antiquity); single burials from the site of "Via Emilia" (Lombard period, 7^{th}-9^{th} c.); mass graves from the site of "Via Maghinardo" (14th c.). The use of individuals from different archaeological sites permits to assess the reliability of the method in diverse conditions of preservation. We analysed all the osteological material recovered, which includes cranial bones and orbital roofs for a total of 189 bones, of which 135 (more or less complete) bones of the cranial vaults and ~~16~~ 54 orbital roofs. The skeletal materials examined include individuals of both sexes at different ages at death (from juveniles to mature).

Evaluation form

BoPLE makes use of two distinct and newly developed evaluation sheets, one for the evaluation of PH's (Fig. 1) and one for the evaluation of CO's variability (Fig. 2). For the analysis of PH, we considered skulls with at least one cranial bone preserved. Lesions were recorded on frontal, occipital and parietal bones. To record more precisely the location of the lesions, every bone was virtually divided into four parts, as described below. With reference to the whole skull and subsequently to each cranial bone, PH can be evaluated indicating its presence/absence, degree of severity, degree of healing, size of the area of the cranial bone with lesions (less or more than 50% of the total area), the location of the lesions within the bone quarters and the number of pits/1 cm^2.

Only skulls with at least one orbital roof preserved were taken into consideration for the analysis of CO. For each skull and for each orbital roof, we recorded: presence/absence of CO, degree of severity, degree of healing, size of the area with lesions and number of pits/1 cm^2.

For the assessment of severity of both PH and CO, we used the evaluation scale proposed by Stuart-Macadam (1985), adding the score ‘0' to indicate the absence of lesions. A detailed description of the degrees of severity used is given in Table 1. Further, we integrated the description of each degree of the severity scale with new colour photos (Fig. 3 and Fig. 4).

For the degree of healing, a distinction between active and non-active porous bone lesions was made following the definition of Mittler and Van Gerven (1994) and using the classification proposed by Salvadei et al. (2001). A detailed description of the degrees of healing used is given in Table 1. Moreover, and, as far as we know, for the first time, we integrated the description of the four degrees of healing with colour pictures, both for PH and CO (Fig. 3 and Fig. 4).

In the newly developed evaluation forms BoPLE, we propose to collect additional information useful for the evaluation of PH and CO and for comparative purposes. One of the added parameters is the location of PH within the cranial bones. To obtain this score, we divided each cranial bone into four virtual parts and indicated in which quarter the lesions are present. Another important parameter is the size of the area affected. In particular, with regard to PH, we recorded if the affected area is more (code 2) or less (code 1) than 50% of the total area of the cranial bone (Table 1). As for CO, we suggest to directly measure the length and the width of the total area affected using a non-stretchable, flexible metric tape.

In the evaluation forms, we propose a new quantitative evaluation method of the frequency of the porous lesions (pits) counted for every cranial bone and orbital roof in a fixed area of 1 cm^2. For each bone, we need first to visually identify the area with more dents or holes and takes a zenith picture of the selected area after applying squared photo scales. These scales were specifically created for the orbital roof and for the cranial bones (Online Resource 1, S1 and S2) and were produced in flexible cardstock to better adapt to the rounded surface of the skull. Pictures were taken with a Fujifilm XE1 (15.5 Mpx, APS-C sensor - 23.6 x 15.6 mm - XTrans CMOS), with lens Fujifilm XF 18.55 mm (f/2.8-4R) LM OIS. We used a tripod, a led flash with trigger and a non-reflective backcloth to enhance the quality of the pictures. The pictures were then modified using Adobe Photoshop Portable version 13.0.1.1 to adjust their resolution and readability. The number of pits for each cranial bone and orbital roof was then counted with the image-processing program ImageJ (https://imagej.net/Welcome), using the counter option of the multi-point tool.

Statistical analysis

To test the reliability of the scoring system used in BoPLE for CO's and PH's severity and healing, we calculated the intra-observer and inter-observer error in association with rationalized qualitative (presence/absence, degree of severity and degree of healing) and quantitative (number of pores) variables. For each analysed individual, both scoring sheets (for PH and CO) were independently filled by two trained observers (A and B). Both operators are experienced anthropologists with practice in CO and PH evaluation. Intra-observer reliability was tested by comparing two independent scoring sessions carried out by the same operator (A1 and A2), one month apart. Inter-observer reliability was assessed by comparing the results obtained by the two observers (A1 and B). For the qualitative variables, weighted (degree of severity and degree of healing) and unweighted (presence/absence of the lesions) Cohen’s Kappa was used to test the internal consistency between the two observations. For the assessment of inter- and intra-observer agreement in the evaluation of presence/absence of the lesions, we considered all the cranial bones (n= 135) and the orbital roof (n=~~16~~ 54), for a total of 189 bones. For the analysis of degree of healing and severity, we considered only cranial bones (n= 70) and orbital roofs (n= 34), in which the lesions were observed by at least one operator, for a total amount of ~~27~~ 104 bones (Table 2). For the analysis of degree of severity, only the scoring categories from 1 to 4 were considered.

Grade "0", which indicates "absence of lesions", was omitted in this analysis because the parameter 'presence/absence' of the lesions was analysed separately.

For the assessment of bias and degree of concordance between the independent examinations (A1-A2 and A1-B) of the lesions frequency (quantitative variables), Bland Altman plot and Intraclass Correlation Coefficient (ICC) were calculated. ICC is based on a two-way model considering single measures and the same rater for all subjects. For this analysis, we compared the number of pitting lesions counted by the two operators in all the cranial bones and orbital roofs, for a total amount of 104 bones (34 orbital roofs and 70 cranial bones). We excluded bones in which no lesions were observed since a great number of scores equal to zero could inflate the agreement among observers.

We performed each analysis considering all the orbital roofs and the cranial bones as a whole category and then separately (Table 2).

Statistical analysis was performed using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium).

Results

We developed new evaluation forms for porotic lesions in skeletal material and evaluated the reliability of the forms by applying inter- and intra-observer statistical analyses on the data obtained from 189 samples, which stem from different archaeological sites and periods.

When we considered the lesions of the orbital roofs and the cranial bones as a whole category, the values resulted from Cohen's kappa intra-observer agreement remarkably showed an almost perfect agreement for presence/absence, a substantial agreement for the degree of severity and an almost perfect agreement for the degree of healing (as defined according to Landis and Koch classification (Landis and Koch 1977)) (Table 3). The inter-observer agreement resulted almost perfect in regard to the parameter 'presence/absence' of the lesions, and substantial when the degree of severity and healing were tested, showing the lowest values of agreement in the degree of severity (Table 3). The intra- and interrater concordance was almost perfect for the evaluation of presence/absence of the lesions separately in orbital roofs and cranial bones. The lowest values for concordance (moderate) on the analysis of the orbital roofs were found for the degree of severity, whereas for the cranial bones was the degree of healing that gave the lowest results, interpretable between substantial and moderate (Table 3).

Intrarater reliability for the frequency of the porous lesions (cranial bones and orbital roofs concurrently) calculated between ~~the~~ two independent replications of the analysis by the same operator (A1 – A2), showed an ICC of 0.95 (95% CI 0.9293 – 0.9671) (Table 4), with an average difference of 2.3 pits and a 95% confidence interval of -22.0 and +26.6 (Fig. 5). These results indicate that there is a bias of less than three pits between the two counts. The ICC calculated for interrater reliability between two different operators (A1 – B) showed the same ~~a~~ value of 0.95 (95% CI 0.9124 – 0.9711) (Table 4) with a mean difference between the two observations of -5.0 pits and a 95% confidence interval of -27.7 and ~~40.4~~ +17.6 (Fig. 6). In both cases, the ICC values indicated an excellent reliability (Koo and Li 2016).

When we consider separately orbital roofs and cranial bones, the ICC values remained excellent, with the exception of the inter-rater agreement on the orbital roofs' lesions that showed an ICC of 0.89 (95% CI 0.6798 – 0.9532) indicating a good agreement (Table 4). The average difference between the counts was less than seven pits (mean difference -6.9 and 95% CI -27.3 to +13.5), with only one value that lied slightly above the upper limit of agreement (Online Resource 1, S4). The Bland Altman Plot showing intra- and interobserver variation for the count of the pits' frequency in orbital roofs and cranial bones separately are reported in the Online Resource 1 (Online Resource 1 S3-S6).

Discussion

With the present study, we propose a new evaluation form (BoPLE) to standardise and objectify retrospective diagnoses of PH and CO employing two sheets for separate evaluation. By distinguishing between the two lesions, we take into account their possible different aetiology (Rivera and Mirazón Lahr 2017). This new evaluation form, which makes use of established scoring criteria for the determination of healing and severity degrees, includes also additional parameters, such as the location of the pits, the dimension of the area affected and the number of pits (pores) per cm^2.

Among the many scoring criteria developed for the evaluation of the degree of severity (Hengen 1971; Salvadei et al. 2001; Steckel et al. 2006), we appreciate in particular the clearness and flexibility of Stuart-Macadam' s (1985) four degrees of severity. In regard to the degree of healing, the only scholars who have proposed scoring criteria were Salvadei et al. (2001). Their classification was accurate and we have only added the degree "0" to indicate absence of cribra. Doing so, both scoring sheets can be applied also on skeletons without macroscopical lesions, thus can be routinely used in anthropological investigations.

Reliable and replicable scoring standards are of essential importance in anthropological studies (Jacobi and Danforth 2002). However, we could not find in the literature any definition of errors associated with standardized scoring methods for presence/absence and degree of healing/severity for PH and CO. Neither Stuart-Macadam (1985) nor Salvadei et al. (2001) associated any error to their coding criteria. An attempt to assess inter-observer agreement was made by Jacobi and Danforth (2002). They compared the results obtained from 22 individual scorers divided into groups based on their level of experience with skeletal material, calculating the "modal percent agreement" for each specimen. Yet, in such a way, they evaluated the replicability but not the reliability of the scoring criteria. Consistently with their results, we found a lower level of agreement for the degree of severity and for the degree of healing compared to the assessment of presence/absence in the inter-observer repeatability. Thus, to our knowledge, this is the first time that an assessment of reliability for these scoring criteria has been made. In our study, lower values of k for the agreement in grading severity and healing could be partially explained because the binary scoring (presence/absence of the lesion) is simpler than a grading scheme encompassing four scoring possibilities.

For BoPLE, we contribute with new coloured photographs (Fig. 3-4), which clearly depict each scoring option for the degree of both, severity and healing. As suggested by Jacobi and Danforth (2002), a visual representation can be in fact very useful to achieve a greater methodological standardization – if the photos are clear and let less place for subjective interpretation.

However, the major novelty of BoPLE is possibly due to the introduction of a new quantitative method based on the count of the porous lesions (pits) present in an area of 1 cm^2. The results of Bland Altman Plot and ICC, which were used for the validation of this new quantitative method, suggest a very high level of both intra- and interrater agreement, categorizing the ICC values (Cicchetti, 1994; Koo and Li, 2016) as excellent and showing no systematic bias in the Bland-Altman plot. These results demonstrate that a quantitative measurement is a reliable and reproducible method for a more accurate evaluation of *intra-vitam* porous lesions of the skull. Since the number of pores/unit area should be directly related to the diameters of the pores, this quantitative assay will indirectly inform also on the porosity size, thus on the severity of the (healed or not) lesions. Therefore, we can conclude that BoPLE takes into account all the observable features of PH's and CO's lesions.

CO and PH are among the most commonly reported pathological conditions in archaeological collections (Wapler et al. 2004; Keenleyside and Panayotova 2006; Walker et al. 2009). The presence of porous bone lesions is deemed essential to assess general conditions of frailty in past populations (Marklein et al. 2016), since the lesions are a consequence of pathological conditions, like anaemias, metabolic diseases, cancer, chronic scalp infections or other chronic infectious diseases (Ortner 2003), or are due to malnutrition. Nevertheless, the only condition of presence/absence should not be considered indicative of the health and/or nutritional status of the individuals at the age of their death, since healed lesions can be the result of situations of many years before, and the individuals could have been in good conditions for a long time before dying. As the osteological paradox theory suggests (Wood et al. 1992), researchers should be cautious when interpreting skeletal indicators of physiological stress, because some might actually indicate an illness, which has been overcome because of a general individual good health status, thus are not indicative of frailty.

To better understand whether lesions are due to a condition of frailty, accurate and combined indications on the severity of the (previous or in progress) lesions may be of great significance. Differences in the degree of severity could be a consequence of different speed progression from the onset of the pathology, different intensity of the illness or an expression of different aetiologies. Moreover, and in particular, when individual bone porous lesions are interpreted in the light of the environmental and nutritional conditions of past populations, an integrated, accurate and objective evaluation, like that offered by BoPLE, should be considered and routinely applied.

Considering the anthropological interest in this topic and the evident shortcomings in the current evaluation systems proposed by the individual authors, we believe that our proposal, based on a quantitative assessment of the lesions integrated with existing qualitative methods, is worthy of attention and represents a progress in the objective evaluation of cribra bone lesions. We encourage further testing of the new proposed method to enlarge the sample size. In such a way, we will resort to a larger variability to determinate the actual relationship between number of pores and other variables, and set cut-offs for the quantitative scores. For this reason, we hope to have BoPLE accepted in the majority of the labs for routine analyses.

Figure captions

Fig.1 BoPLE, Recording form for Porotic Hyperostosis

Fig.2 BoPLE, Recording form for Cribra Orbitalia

Fig.3 Degrees of severity- For Porotic Hyperostosis: a - degree 0; b - degree 1; c - degree 2; d - degree 3; e - degree 4 – For Cribra Orbitalia: e - degree 1; f - degree 2; g - degree 3; h - degree 4

Fig.4 Degrees of healing. For Porotic Hyperostosis: a - degree 1; b - degree 2; c - degree 3; d - degree 4. For Cribra Orbitalia: e - degree 1; f - degree 2; g - degree 3; h - degree 4

Fig.5 Bland Altman plot evaluating the intraobserver variation between the count of the frequency of the lesions. X-axis: average of the two measures; Y-axis: difference between the two measures

Fig.6 Bland Altman plot evaluating the interobserver variation between the count of the frequency of the lesions. X-axis: average of the two measures; Y-axis: difference between the two measures

Compliance with Ethical Standard

Disclosure of potential conflicts of interest: The authors declare that they have no conflict of interest.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Angel JL (1966) Porotic hyperostosis, anemias, malarias, and marshes in the prehistoric Eastern Mediterranean. Science (80-) 153:760–763. doi: 10.1126/science.153.3737.760

Facchini F, Rastelli E, Brasili P (2004) Cribra orbitalia and cribra cranii in Roman skeletal remains from the Ravenna area and Rimini (I-IV century AD). Int J Osteoarchaeol 14:126–136. doi: 10.1002/oa.717

Gaudio D, Betto A, Vanin S, et al (2015) Excavation and Study of Skeletal Remains from a World War I Mass Grave. Int J Osteoarchaeol 25:585–592. doi: 10.1002/oa.2333

Hengen OP (1971) Cribra orbitalia: pathogenesis and probable etiology. HOMO- J Comp Hum Biol 22:57–75

Jacobi KP, Danforth ME (2002) Analysis of interobserver scoring patterns in porotic hyperostosis and cribra orbitalia. Int J Osteoarchaeol 12:248–258. doi: 10.1002/oa.619

Keenleyside A, Panayotova K (2006) Cribra orbitalia and porotic hyperostosis in a Greek colonial population (5th to 3rd centuries BC) from the Black Sea. Int J Osteoarchaeol 16:373–384. doi: 10.1002/oa.831

Koo TK, Li MY (2016) A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med 15:155–63. doi: 10.1016/j.jcm.2016.02.012

Lallo JW, Armelagos GJ, Mensforth RP (1977) The role of diet, disease, and physiology in the origin of porotic hyperostosis. Hum Biol 49:471–483

Landis JR, Koch GG (1977) The measurement of observer agreement for categorical data. Biometrics 33:159–74

Marklein KE, Leahy RE, Crews DE (2016) In sickness and in death: Assessing frailty in human skeletal remains. Am J Phys Anthropol 161:208–225. doi: 10.1002/ajpa.23019

Martin DL, Goodman AH (2002) Health conditions before Columbus: paleopathology of native North Americans. West J Med 176:65–8

Masson M, Bereczki Z, Molnár E, et al (2015) 7000 year-old tuberculosis cases from Hungary - Osteological and biomolecular evidence. Tuberculosis 95: S13–S17. doi: 10.1016/j.tube.2015.02.007

Mensforth RP, Lovejoy CO, Lallo JW, Armelagos GJ (1978) Part two: the role of constitutional factors, diet, and infectious disease in the etiology of porotic hyperostosis and periosteal reactions in prehistoric infants and children. Med Anthropol 2:1–59

Mittler DM, Van Gerven DP (1994) Developmental, diachronic, and demographic analysis of cribra orbitalia in the medieval Christian populations of Kulubnarti. Am J Phys Anthropol 93:287–297. doi: 10.1002/ajpa.1330930302

Ortner DJ (2003) Identification of pathological conditions in human skeletal remains. Academic Press, USA

Oxenham MF, Cavill I (2010) Porotic hyperostosis and cribra orbitalia: the erythropoietic response to iron-deficiency anaemia. Anthropol Sci 118:199–200. doi: 10.1537/ase.100302

Polo-Cerdá M, Miquel-Feucht M, Villalaín-Blanco JD (2001) Experimental cribra orbitalia in Wistar rats: an etiopathogenic model of porotic hyperostosis and other porotic phenomena. In: La Verghetta M, Capasso L (eds)

Proceedings of XIIIth European Meeting of the Paleopathology Association. Edigrafital S.p.A., Chieti, Italy, pp 253–9

Rivera F, Mirazón Lahr M (2017) New evidence suggesting a dissociated etiology for cribra orbitalia and porotic hyperostosis. Am J Phys Anthropol 164:76–96. doi: 10.1002/ajpa.23258

Rothschild B (2012) Extirpolation of the mythology that porotic hyperostosis is caused by iron deficiency secondary to dietary shift to maize. Adv Anthropol 2:157–160. doi: 10.4236/aa.2012.23018

Salvadei L, Ricci F, Manzi G (2001) Porotic hyperostosis as a marker of health and nutritional conditions during childhood: Studies at the transition between imperial Rome and the early middle ages. Am J Hum Biol 13:709–717. doi: 10.1002/ajhb.1115

Steckel RH, Larsen CS, Sciulli PW, Walker PL (2006) Data Collection Codebook. The Ohio State University, Columbus

Stuart- Macadam P (1989) Porotic hyperostosis: relationship between orbital and vault lesions. Am J Phys Anthropol 80:187–193. doi: 10.1002/ajpa.1330800206

Stuart- Macadam P (1985) Porotic hyperostosis: representative of a childhood condition. Am J Phys Anthropol 66:391–398. doi: 10.1002/ajpa.1330660407

Tosi A, Badino P, Pezzoni B (2017) Medical conditions observed in osteoarchaeological remains: arthropathies, traumatic lesions, tumours, metabolic diseases and dental pathologies. Med Hist 1:29–34

Walker PL, Bathurst RR, Richman R, et al (2009) The causes of porotic hyperostosis and cribra orbitalia: A reappraisal of the iron- deficiency- anemia hypothesis. Am J Phys Anthropol 139:109–125. doi: 10.1002/ajpa.21031

Wapler U, Crubézy E, Schultz M (2004) Is Cribra Orbitalia Synonymous with Anemia? Analysis and Interpretation of Cranial Pathology in Sudan. Am J Phys Anthropol 123:333–339. doi: 10.1002/ajpa.10321

Wood JW, Milner GR, Harpending HC, et al (1992) The Osteological Paradox: Problems of Inferring Prehistoric Health from Skeletal Samples [and Comments and Reply]. Curr Anthropol 33:343–370. doi: 10.1086/204084

Table 1

Table 1 Detailed description of the degree of severity (Stuart-Macadam, 1985) and degree of healing (Salvadei et al., 2001) scales and the size of the affected area

Feature	Degree of expression	Description	Figure
Severity	0	Absence of lesions	Fig. 1a,f
	1	Presence of small, scattered holes	Fig. 1b,g
	2	Presence of small and large scattered holes	Fig. 1c,h
	3	Presence of holes that join within the trabecular structure	Fig. 1d,i
	4	marked development of the trabecular part of the bone surface, which protrudes toward the outside	Fig. 1e,l
Healing	1	Lesions with no healing activity (active)	Fig. 2a,e
	2	Lesions with a healed area of less than 50%	Fig. 2b,f
	3	Lesions with a healed area greater than 50%	Fig. 2c,g
	4	Fully healed lesions (non-active)	Fig. 2d,h
Extent of area affected (only for PH)	1	< 50% of the total area is affected by the lesion	
	2	> 50% of the total area is affected by the lesion	

Table 2

Table 2 Detailed description of the statistical analysis used in the assessment of intra- and inter-observer reliability

Intraobserver (A1 – A2) and Interobserver (A1 – B) reliability	Scoring categories	Statistical analysis	n	Eligibility criteria
Qualitative data				
General Absence/Presence of lesions	0-1	Cohen's Kappa	189	All orbital roofs and cranial bones in the sample
Absence/Presence of lesions in orbital roofs	0-1	Cohen's Kappa	54	All orbital roofs in the sample
Absence/Presence of lesions in cranial bones	0-1	Cohen's Kappa	135	All cranial bones in the sample
General degree of severity (all the orbital roofs and cranial bones)	1-4	Cohen's Kappa	104	Presence of lesions
Degree of severity in orbital roofs	1-4	Cohen's Kappa	34	Presence of lesions
Degree of severity in cranial bones	1-4	Cohen's Kappa	70	Presence of lesions
General degree of healing (all the orbital roofs and cranial bones)	1-4	Cohen's Kappa	104	Presence of the lesions
Degree of healing in orbital roofs	1-4	Cohen's Kappa	34	Presence of lesions
Degree of healing in cranial bones	1-4	Cohen's Kappa	70	Presence of lesions
Quantitative data				
Frequency of the lesions (all the orbital roofs and cranial bones)		ICC and Bland Altman Plot	104	Number of pit lesions ≠ 0
Frequency of the lesions in orbital roofs		ICC and Bland Altman Plot	34	Number of pit lesions ≠ 0
Frequency of the lesions in cranial bones		ICC and Bland Altman Plot	70	Number of pit lesions ≠ 0

Table 3

Table 3 Intra and inter-observer reliability statistics for presence/absence of the pathology, degree of severity and degree of healing

Error test	N	Feature score categories	Intraobserver error		Interobserver error	
			Kappa	Landis and Koch kappa "strength of agreement"	Kappa	Landis and Koch kappa "strength of agreement"
All cranial bones and orbital roofs						
Presence/absence of lesions	189	2	1.000	Almost perfect	1.000	Almost perfect
Degree of severity	104	4	0.776	Substantial	0.670	Substantial
Degree of healing	104	4	0.815	Almost perfect	0.726	Substantial
Orbital roofs						
Presence/absence of lesions	54	2	1.000	Almost perfect	1.000	Almost perfect
Degree of severity	34	4	0.603	Moderate	0.586	Moderate
Degree of healing	34	4	0.857	Almost perfect	0.645	Substantial
Cranial bones						
Presence/absence of lesions	135	2	1.000	Almost perfect	1.000	Almost perfect
Degree of severity	70	4	0.861	Almost perfect	0.703	Substantial
Degree of healing	70	4	0.619	Substantial	0.603	Moderate

Table 4 Intraclass Correlation Coefficient (ICC) values resulting from the repeatability and reproducibility tests of the frequency of the lesions and their related 95% CI

Parameters	**Intra-observer variability**	**Inter-observer variability**
	A1 – A2	A1 - B
All cranial bones and orbital roofs (n=104)		
ICC values	0.9517	0.9516
95% CI	0.9293 to 0.9671	0.9124 to 0.9711
Orbital roofs (n=34)		
ICC values	0.9488	0.8887
95% CI	0.9006 to 0.9740	0.6798 to 0.9532
Cranial bones (n=70)		
ICC values	0.9386	0.9496
95% CI	0.8995 to 0.9622	0.9139 to 0.9698

Figure 1

Click here to access/download;Figure;Fig.1.tif

BoPLE (Bone Porous Lesion Evaluation)

RECORDING FORM for POROTIC HYPEROSTOSIS

Observer ______________________ Date____________________

Skeleton code____________________ Stratigraphic Unit (US)______

Site____________________________ Collection________________

GENERAL INFORMATION

Ancestry: ______________________ Sex: ______________________

Age: ______________________ Stature: ______________________

INVENTORY (CRANIAL BONES) Codes: P – present / A - absent

FRONTAL: _____ RIGHT PARIETAL: ____

OCCIPITAL: _____ LEFT PARIETAL: ____

ASSESSMENT OF POROTIC HYPEROSTOSIS (PER INDIVIDUAL)

Presence/absence of PH ______________ (Codes: P – present / A – absent)

General degree of severity (0-4) ______________

General degree of healing (1-4) ______________

ASSESSMENT OF POROTIC HYPEROSTOSIS (FOR EACH CRANIAL BONE)

RIGHT PARIETAL			**LEFT PARIETAL**		
Presence of PH within the quarters	2	1	Presence of PH within the quarters	1	2
	4	3		3	4
Degree of severity (0-4)			Degree of severity (0-4)		
Degree of healing (1-4)			Degree of healing (1-4)		
Frequency of pits in 1 cm^2	n=		Frequency of pits in 1 cm^2	n=	
Size of the area affected by PH	<50%	>50%	Size of the area affected by PH	< 50%	>50%
FRONTAL			**OCCIPITAL**		
Presence of PH within the quarters	1	2	Presence of PH within the quarters	1	2
	3	4		3	4
Degree of severity (0-4)			Degree of severity (0-4)		
Degree of healing (1-4)			Degree of healing (1-4)		
Frequency of pits in 1 cm^2	n=		Frequency of pits in 1 cm^2	n=	
Size of the area affected by PH	<50%	>50%	Size of the area affected by PH	< 50%	>50%

Figure 2 Click here to access/download;Figure;Fig.2.tif

BoPLE (Bone Porous Lesion Evaluation)

RECORDING FORM for CRIBRA ORBITALIA

Observer ______________________ Date ____________________

Skeleton code ____________________ Stratigraphic Unit (US) ______

Site ___________________________ Collection _______________

GENERAL INFORMATION

Ancestry: ______________________ Sex: ______________________

Age: ______________________ Stature: ______________________

INVENTORY (ORBITAL ROOFS) Codes: P – present / A - absent

RIGHT ORBITAL ROOF _____ LEFT ORBITAL ROOF: ____

ASSESSMENT OF CRIBRA ORBITALIA (PER INDIVIDUAL)

Presence/absence of CO _____________ (Codes: P – present / A – absent)

General degree of severity (0-4) _____________

General degree of healing (1-4) _____________

ASSESSMENT OF CRIBRA ORBITALIA (FOR EACH ORBITAL ROOF)					
RIGHT ORBITAL ROOF			**LEFT ORBITAL ROOF**		
Degree of severity (0-4)			Degree of severity (0-4)		
Degree of healing (1-4)			Degree of healing (1-4)		
Frequency of pits in 1 cm^2	*n*=		Frequency of pits in 1 cm^2	*n*=	
Size of area with CO	Length _____mm	Width _____mm	Size of area with CO	Length _____mm	Width _____mm

Figure 3

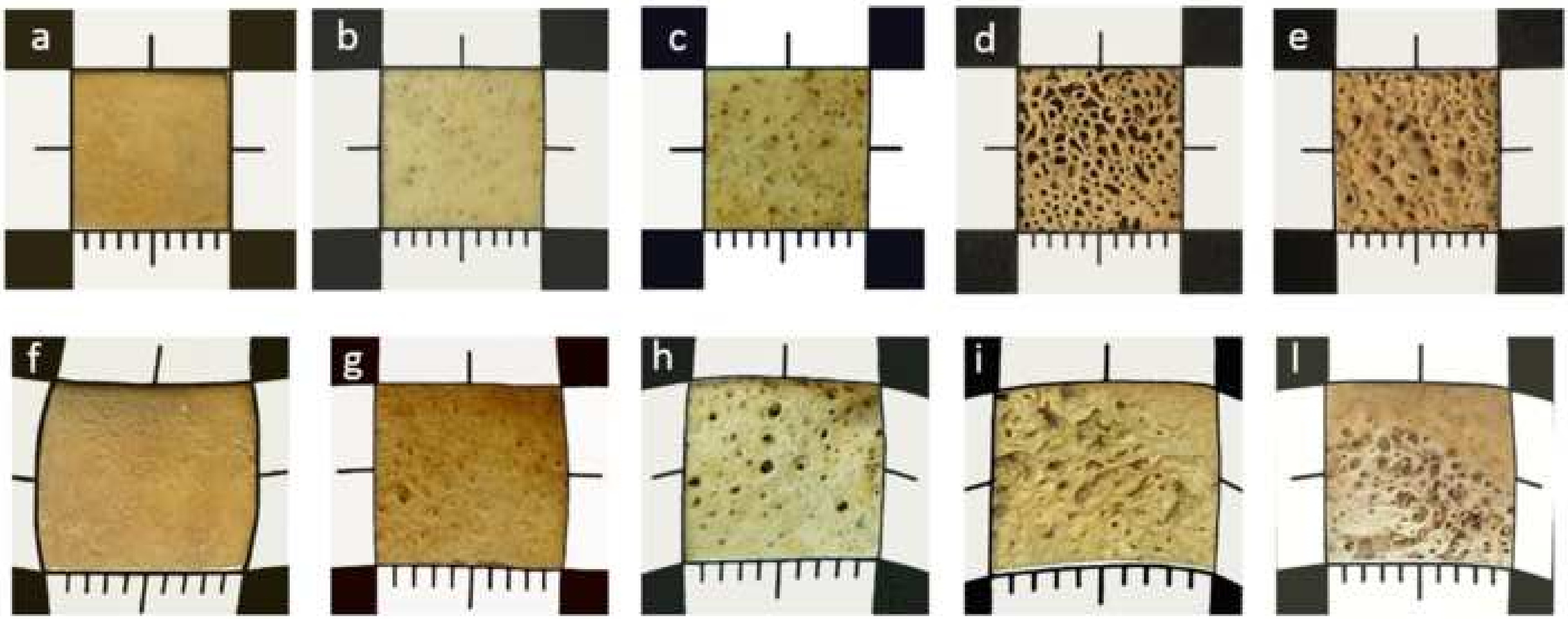

Figure 4

Click here to access/download;Figure;Fig.4.tif

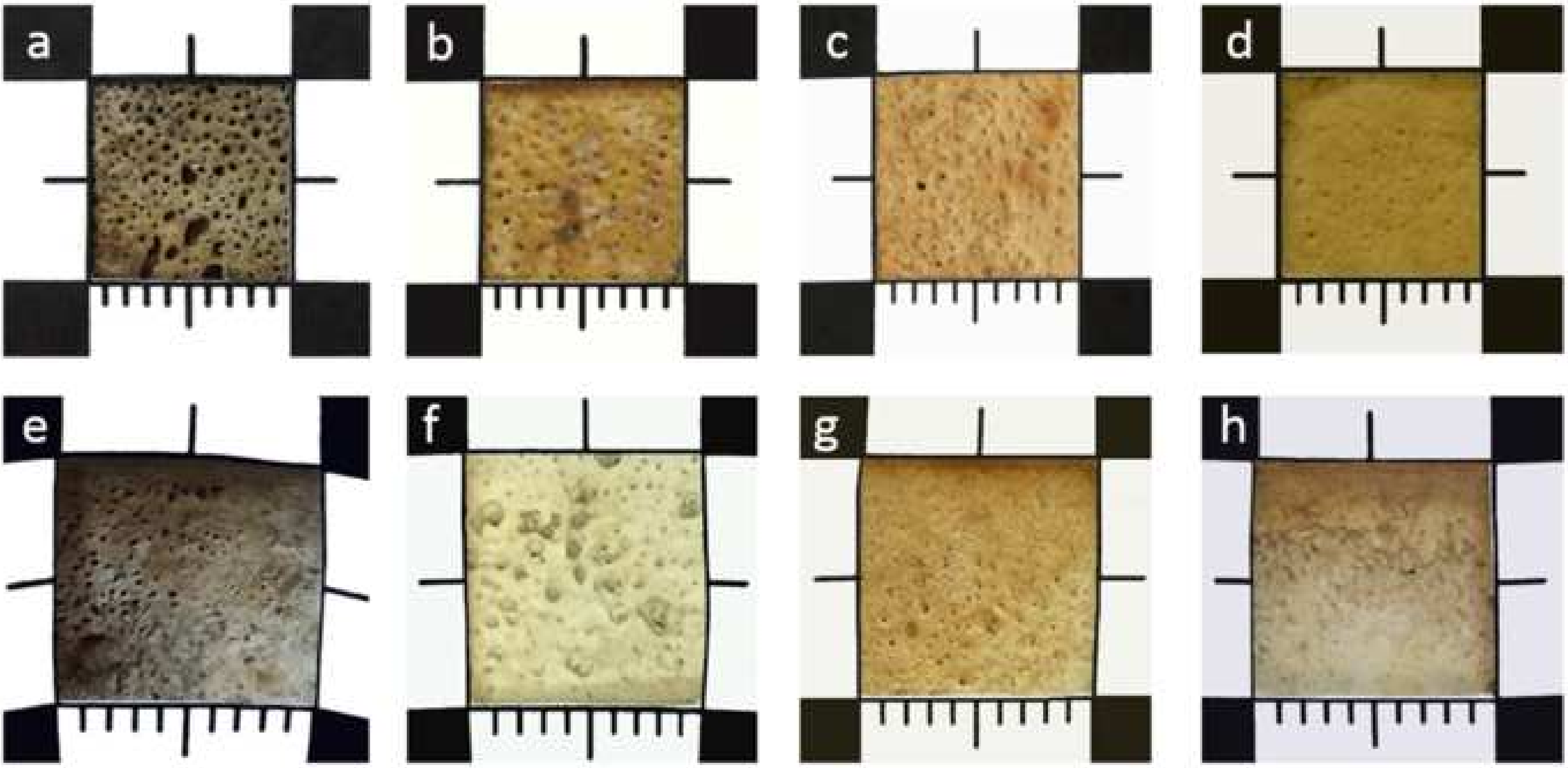

Figure 5

Click here to access/download;Figure;Fig.5.tif

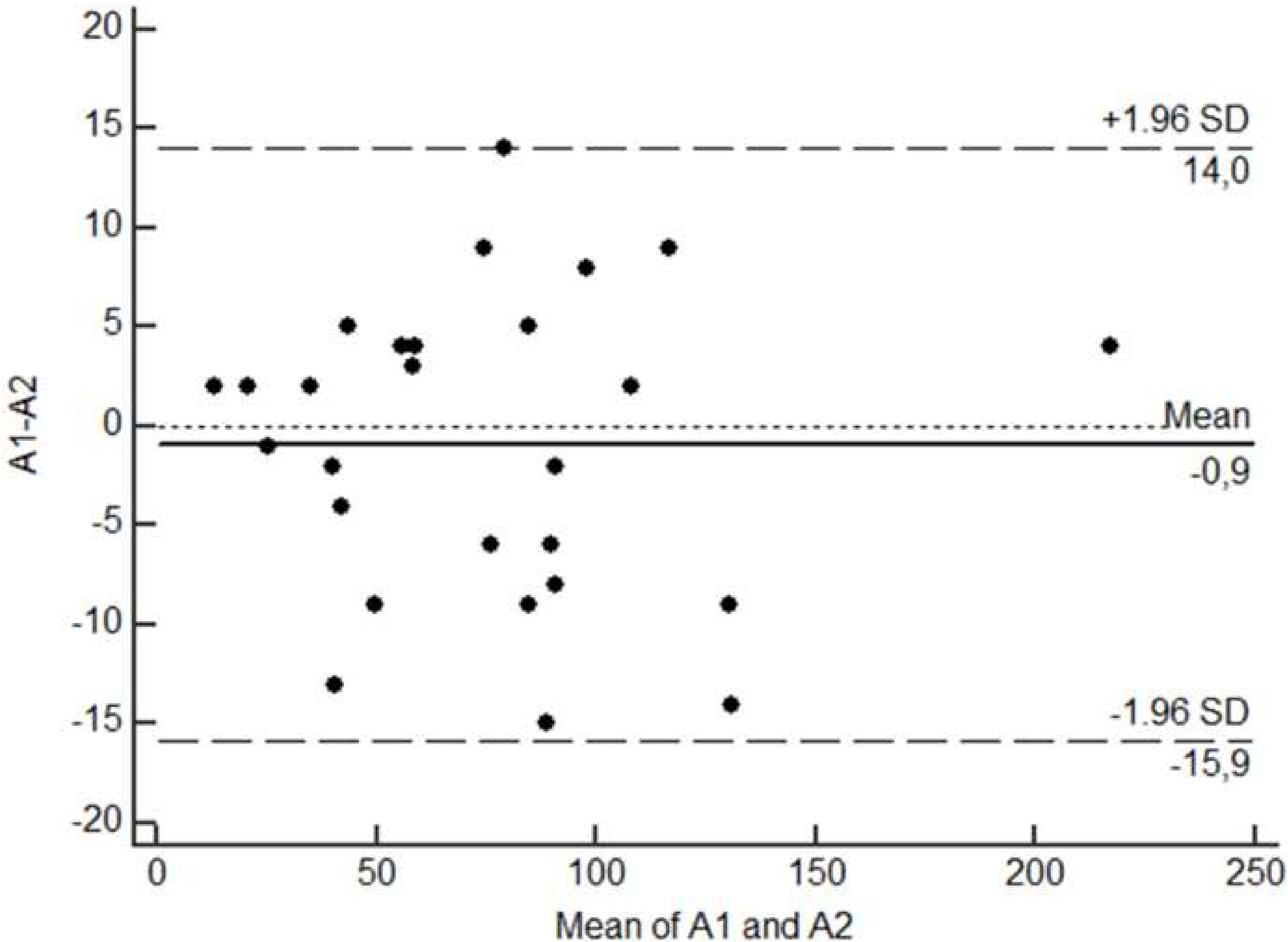

Figure 6

Click here to access/download;Figure;Fig.6.tif