Applications of black bone disease in forensic anthropology: Using a dark side effect to shed light

by Brianne I. Bertram

Black bone disease can result from using a tetracycline-based prescription drug. In life, it is a cosmetic side effect that affects approximately 4% of users and often goes unnoticed unless it presents in teeth. This raises the important question of whether the presentation of black bone disease will impact forensic anthropologists conducting an investigation. In this paper, the presence of tetracycline staining is explored to examine how this information can be used in tandem with the well-researched development of tetracycline staining in teeth to determine if an individual was using tetracycline—or one of its derivatives—and how we can appropriately use that information to corroborate a positive identification of a deceased individual.

Tooth staining from tetracycline (fig. 1) use is a well-documented phenomenon in the field of dentistry, with multiple documented case studies dating back to 1956 (Salman et al. 1985; Cale, Freedman, and Lumerman 1988; Odell, Hodgson, and Haskell 1995; Bowles and Bokmeyer 1997). More recently, cases have been reported of similar staining occurring throughout the skeleton due to one of tetracycline's derivatives, minocycline (fig. 2) (Attwood and Dennett 1976; Hubbell et al. 1982; Rumbak et al. 1991). Minocycline staining has informally been called "black bone disease" and has received media attention due to its ability to stain newly formed bone and penetrate existing bone. Like its sister drug minocycline, tetracycline can cause soft tissue pigmentation; however, soft tissue is outside of the scope of most forensic anthropological investigations and will not be focused on in the present paper. This paper will look at tetracycline and minocycline staining to explore how these two drugs, primarily prescribed as anti-inflammatories, cause hard tissue staining and the variation of staining that can present. I will then look at how this knowledge can be applied to forensic anthropology to assist in the identification of unidentified human remains.

Brianne I. Bertram is an MA alum from the University of Alberta (Department of Anthropology, 13–15 HM Tory Building, Edmonton, Alberta, T6G 2H4 [bbertram@ualberta.ca]).

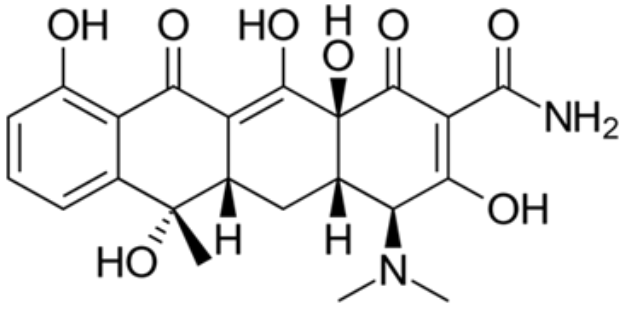

Figure 1. Tetracycline.

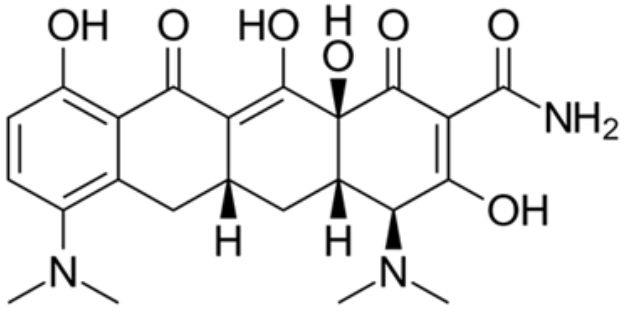

Figure 2. Minocycline.

Tetracycline and its Derivatives

Tetracycline staining in dentition has been thoroughly researched (e.g., see the excellent review by Warmling et al. 2024). Tetracycline creates complex calcium ions which are deposited in the dentin and enamel of forming teeth via unknown mechanisms (Sánchez, Rogers, and Sheridan 2004; Raymond and Cook 2015). Because of its affinity for calcium, tetracycline bonds with the newly deposited dentine and enamel, creating a calcium compound with the potential side-effect of staining. Tetracyclines as an antibiotic are effective against both gram-positive and gram-negative bacteria, like E. coli, making them a commonly prescribed antibiotic in the United States (Sánchez, Rogers, and Sheridan 2004).

Sánchez, Rogers, and Sheridan (2004) developed a table to describe the subtle differences in the presentation of tetracycline and its derivatives. While similar, minocycline produces a more blue-gray hue in comparison to other derivatives, which tend to appear more brown-yellow (Sánchez, Rogers, and Sheridan 2004:712). These colour distinctions can serve as an indicator of whether the individual was prescribed minocycline or a different tetracycline variant. The colour is described by others as a rust green/blue-tinged stain (McCklesky and Littleton 2004; Farahnik, Zaghi, and Hendizadeh 2015). Others have supported the name 'black bone disease' in publications by labelling the black appearance of the stain's deposition on the skull (Laure et al. 2009) and thyroid (Miller, Lewis, and Bentz 2006; Kandil et al. 2011).

Minocycline therapy has the known side effect of deposition of pigment in skin, nails, teeth, bones, and eyes (Wolfe and Reichmister 1984). This side-effect has been well known since the late 1990s, with calls for all patients who received minocycline for longer than a year to undergo screening for pigmentation deposit (Eisen and Hakim 1998). This call to action has rarely been acted upon, and as a result, the majority of recorded cases come from patients undergoing different, and often unrelated, procedures. Typically, the majority of patients present with pigmentation of the craniofacial area, including the oral cavity, with a variety of independent case studies throughout the post-cranial skeleton (Chan, Hicks, and Giordano 2012; Toffoli et al. 2019). Staining has primarily been found accidentally during routine surgery, but staining throughout the lower appendicular skeleton has also been reported frequently for a small number of case studies (Kerbleski, Hamptom, and Cornejo 2013; Middleton, Anawke, and McKinle, 2011; Reed, Gregg, and Corpe 2012; Treister, Magalnick, and Woo 2004). Minocycline has three potential mechanisms of staining. The first is an intrinsic theory, where the minocycline molecule is highly protein-bound and as a result, bonds with collagen-rich tissues like bone tissue and teeth (Raymond and Cook 2015:140). The second is an extrinsic theory, whereby staining occurs because the high minocycline concentration is excreted into gingival fluid and etches into the enamel when the minocycline is oxidized (Raymond and Cook 2015:140). The last method is described as occurring via the chelation of haemosiderin, otherwise understood as the mechanism whereby staining is caused by a product of minocycline's breakdown that interacts with iron ions and results in staining within the bone matrix (Raymond and Cook 2015:140). This varies slightly from other tetracycline derivative staining, allowing it to present in the sclera and existing bone throughout the body. Minocycline is unique in its presentation and in that there is no widely-accepted reason why pigments deposit across the skeleton.

Examples of Tetracycline Derivative Presentation

Cases of tetracycline therapy are few and far between with only 34 published cases in academic journals across several decades (Tilley et al. 1995; Wolfe and Reichmister 1984; Yang et al. 2012). These cases cover much of the human body including the skull, dentition, thyroid, and appendicular skeleton. A few cases will be presented below to exemplify the types of tetracycline derivative pigmentation.

After electing for anthroposcopy of the right hip as a treatment for chronic bilateral hip pain, a seventeen-year-old male athlete was found to have a brownish-black pigmentation on all visible osseous surfaces, including the femoral head and neck, and the acetabulum (Chan, Hicks, and Giordano 2012). The discolouration was not limited by bone type, with deposition occurring in both cortical and cancellous bone. The patient's bone was biopsied using a Jamshidi needle, which under histopathological analysis revealed normal bone tissue (Chan, Hicks, and Giordano 2012). Under ultraviolet light, there were linear bands of fluorescence which were believed to be evidence of minocycline staining. After the surgery, the patient was asked about their pre-operative medical history and it was revealed that he had been prescribed minocycline therapy for acne for a six-month period leading up to the surgery (Chan, Hicks, and Giordano 2012). This method of using an ultraviolet light test on the histological sample allowed them to confirm what was already suspected, as this technique has been used for tetracycline pigmentation in the past (Chan, Hicks, and Giordano 2012).

In the skull, two cases have been recorded, the first during an endoscopic brow lift on a 63-year-old female. Surgeons discovered an unexpected dark discoloration of the temporal and frontal bones (Vaswani et al. 2022). The integrity and density of the bones was normal, and the surgery was successful. In the postoperative visit, the patient revealed they had a history of tetracycline therapy for acne over a consecutive 3-year period (Vaswani et al. 2022). The second case was of a 52-year-old male, who exhibited a rusty green pigmented temporal bone during a routine surgery for revision tympanomastoidectomy (Farahnik et al. 2015). The patient had used tetracycline from the ages of 14–19 for acne vulgaris and had a history of stained molars from the drug. With a 30+ year gap between his tetracycline use and the temporal surgery, it highlighted how tetracycline pigmentation can be permanent in bone tissue (Farahnik et al. 2015)

A 53-year-old female in Indiana underwent surgery on her left foot on a hallux vagus deformity and a tailor bunion on the medial side of the foot (Nirenberg 2019). When they opened the foot, they found a brownish-black stained first metatarsal which, when cross-sectioned, showed that the pigmentation was not only in the cortical bone but also in the cancellous bone. This patient had taken minocycline for three years for acne treatment five years before the surgery (Nirenberg 2019). The patient’s black bone disease was first uncovered in the metatarsophalangeal joint, but this case is described to have uniquely less pigmentation in the fifth metatarsophalangeal joint than other cases. Nirenberg suggests this is due to micro cylinders anti-inflammatory capabilities being drawn to the higher inflammation in the first metatarsophalangeal joint, but the reason is still unconfirmed.

Following a motorcycle collision, a 28-year-old male victim suffered skeletal injuries including a chest wall trauma, four rib fractures, and an open diaphyseal forearm fracture (Toffoli et al. 2019). Pigmentation was discovered three months post-operation when the patient was

referred to a septic surgery department and additional testing showed no underlying pathologies. When they operated, they found a black-stained ulna and radius, which they attributed to the use of minocycline as an antibiotic for septic non-union. They photographed the individual and completed the operation as planned. They performed a clinical examination of the skin and oral cavity after the surgery to look for patterns of pigmentation but found nothing notable. The bone healed completely without residual pain (Toffoli et al. 2019).

As these published case studies have demonstrated, pigmentation from black bone disease can be deposited throughout the axial and appendicular skeleton in a seemingly consistent fashion (Ayangco and Sheridan 2003; Chan et al. 2012; Good and Hussey 2003). The staining seems to deposit evenly throughout the affected area and, with the exception of Nirenberg (2019), borders or fading in the staining were not uncovered by the surgeons: staining appeared to penetrate the entire area. None of the publications mentioned additional scans or work to discover the extent of the black bone disease beyond its presentation in their direct surgical field.

Applications in Forensic Odontology

Teeth are generally considered the most accurate method of age estimation used by biological anthropologists in creating an osteological profile. Because of this, the rate of tooth formation and eruption have been well studied with the current Western standards in forensic anthropology outlined in a dental atlas by AlQahtani, Hector, and Liversidge (2010). In addition to the atlas's imagery of the stages of dental development, they also included a scoring system for tooth formation. The developmental phases form at predictable intervals with the initial cusps of the tooth forming first, then the crown, and then the dentine. This is then followed by the initial root formation which closes at the apex later in life. AlQahtani, Hector, and Liversidge (2010) included a scoring system for the stages of root resorption in deciduous teeth. This method provides an age at the midpoint of plus or minus 6-month standard deviation after 1 year. What makes this atlas unique is the variety in the population of modern Londoners which was used to create it.

In a case study by Raymond and Cook (2015), the authors were presented with a 21-year-old female whose third-molar had erupted with noticeable discoloration. The patient was on 50mg of minocycline for six months for acne at age 16. According to the London Atlas, the third molar crowns are typically already partially formed at 16 years however, third molars are the most variable tooth and carry a standard deviation of ±3–4.5 years (Raymond and Cook 2015:140). This case study is an excellent example because the staining did not touch the roots of the teeth, which typically finish forming by 18–25 years, therefore the individual discontinued minocycline use before their teeth entered this stage. To use this staining in age estimation, third molar crown formation is the last tooth to form and is typically completed between the ages of 12–16. If the staining only affects the third molar, it can be said that the individual was prescribed a tetracycline derivative-based drug after the age of 13.5 years (Raymond and Cook 2015:141). Attempts to narrow this down further would be potentially problematic to an investigation due to the variability of third molar growth. To combat this, providing the information that the individual was prescribed a tetracycline derivative-based anti-inflammatory between the ages of 11.5 and

20.5, could be used to corroborate an identification.

This is not the only example of precise tetracycline and tetracycline-derivate staining during tooth formation. Antonini et al. (2010) performed a study on a variety of 17 discoloured molars from nine different individuals, all of whom were prescribed minocycline-based anti-inflammatory drugs for acne between ages 15 and 22. This study took place between 1996 and 2009 and found that the entire enamel layer of tetracycline-stained teeth was fluorescent. Root staining was more common than crown staining in the teeth examined, with a variety of intensities of colour across all teeth. They found that one tooth had distinct horizontal banding in the apical half of the root. Two teeth had a distinct greyish brown band around the cementoenamel junction. Another tooth had crown pigmentation, greyish staining, a brown band on the cementoenamel junction, and faint brown rings horizontally occurring across the root of the tooth (Antonini and Luder 2011:416–417). When exposed to fluorescent light, the described teeth showed small hooks that were bent coronally and followed the incremental lines of the cementum (Antonin and Luder 2011:416–418).

A more extreme case can be seen by looking at the now rare use of tetracycline in children. A 23-year-old male received tetracycline therapy between the ages of 2 and 3 years for tonsillitis (Fleming, Witkop, and Kulman 1987). This case demonstrated another example of linear staining in the hypoplastic enamel. The staining affected the labial surfaces of all incisors and the lingual aspect of all incisors, canines, and first permanent molars (Fleming, Witkop, and Kulman 1987). To confirm that the staining was from tetracycline, they exposed the teeth to UV light (270mU) and found the lines fluoresced yellow—a positive sign for tetracycline (Fleming et al. 1987).

Fleming, Witkop, and Kuhlmann's (1987) study demonstrated tetracycline staining may be accompanied by enamel hypoplasia. Enamel hypoplasia is the failure of enamel to develop completely, resulting in hypoplasia, a type of defect that can be split into four categories: hypoplasia, hypoplasia pits, hypoplasia grooves, and hypoplasia missing enamel (Clarkson and O'Mullane 1989). Evidence of enamel hypoplasia is typically reported because it is an individualizing factor, however, it is inappropriate for the forensic anthropologist to comment on the reason behind the hypoplasia because of the number of variable causes and times it can develop. Enamel hypoplasia can be the result of numerous issues during development including rickets, intestinal issues, and dietary stress (Schultz et al. 1998). Schultz et al. (1998) reported that enamel hypoplasias most commonly occur between the ages of 2 and 4 years, perhaps because of the dietary shift associated with weaning from breast milk to solid foods; this is due to the number of ameloblasts that are active during that period. Enamel defects like hypoplasias can also be the result of trauma, genetics, fluoride intoxication, and developmental disturbances. Because of its variety of causes, it is hard to attribute the hypoplasia described by Cohlan (1977) and Flemming (1987) to the use of a tetracycline derivative alone; thus, this is not a reliable indicator of black bone disease.

Tetracycline is often prescribed for infections or genetic diseases like cystic fibrosis, and there is potential for other pathological presentations in addition to the staining. Minocycline, on the other hand, is most commonly prescribed for forms of inflammatory acne, something that traditionally does not have any effect on the skeleton. The continued use of these drugs increases the risk of pigmentation (Pandit and Hadden 2004; Lynn 1996; Mehrany et al. 2003; Hepburn, Dooley, and Hayda 2005). The presentation of staining from

tetracycline and its derivatives in addition to other skeletal pathologies can be used to infer whether an individual may have had a genetic disease in life for which they were prescribed tetracycline. In the absence of other skeletal symptoms, and if black bone disease is expressed throughout the skeleton and not just in teeth, it might be reasonably suggested the individual had been prescribed minocycline. However, while it was probable they suffered from a condition like inflammatory acne, the reason for the prescription cannot be known with certainty.

Limitations and Future Research

The most significant limitation to using black bone disease to contribute to medical history is the regular removal of wisdom teeth for primarily medical reasons. Third molars are not always present; only 96% of individuals are born with them and all four may not be present (Hyam 2018). Approximately a third of the population has naturally impacted molars which are often removed preventatively in first-world countries. Additionally, in first-world countries like Canada, if these teeth erupt with significant staining, individuals can opt to have them removed. Estimates in Canada range from 22–66% of individuals having impacted wisdom teeth which when translated into the population is approximately 8.5 million people at the low end, as of 2013 (Boughner 2013). Another limitation to this method is that with the accessibility of modern dentistry, teeth that erupt with staining are often removed or covered: crowns are a common solution for this issue.

These cases all demonstrate black bone disease discovered in living individuals, however the discovery of black bone disease by forensic anthropologists has yet to be recorded and shared on public forums. One factor in determining post-mortem interval (PMI) is soil staining. By looking at the level of penetration of staining, we can estimate how long bones have been in the ground. While this is a method variable and dependent on the environment in which the remains are located, soil staining penetrates in a predictable way. Penetrative staining can cause confusion for investigators, confusion that can be alleviated, in part, by awareness of black bone disease as something we may begin to encounter more frequently in forensic cases. Dentists have discovered that tetracycline staining fluoresces when exposed to UV light in teeth. In dental patients with extended tetracycline use, there is fluorescence throughout the tooth, allowing us to determine that tetracycline is the cause of staining rather than other sources, like diagenetic soil deposition. In teeth, this method is well documented and small differences in the fluorescent spectrum can be identified to determine what tetracycline derivate was used. Semisynthetic derivatives of tetracycline, like minocycline, do not have the exact same fluorescence under UV light as tetracycline. Using this information, we can look at the fluorescence and begin to determine what tetracycline variant was used.

While the fluorescent levels can be measured precisely for tetracycline in teeth, the same cannot yet be measured for bone. First, through fluorescence, it should be determined if tetracycline staining is present in the skeleton. From there, we have a simple solution to determining if the staining is the result of older remains undergoing taphonomic processes or from tetracycline treatment in life. Should black bone disease not present with fluorescence under UV light, further steps would need to be taken to understand the chemical composition of tetracycline-impacted bone in order to identify its presence over taphonomic staining.

Conclusion

Tetracycline and its derivates have a unique presentation in the body in the form of staining. Because of this, we can use the way it presents to make inferences about the medical history of an individual. In cases with minocycline, the presentation of black bone disease allows us to infer that an individual used minocycline at some point in their life. This, combined with other symptoms, syndromes, or side effects, can help us infer a medical history that can be used by the police in identification. For minocycline, this is especially useful as black bone disease regularly goes undetected in life, but the actual prescription of the drug is documented and can be used as a secondary identifier. For tetracycline and its other derivatives, the precise ring staining in teeth can be used to provide an age estimation of when the drug was administered, which can be compared to known medical histories of missing persons or persons of interest and thus used as a secondary identifier. The presence of major staining in dental remains is rare due to modern dental aesthetics, resulting in many people having stained teeth removed or capped. Despite this, minor staining is well recorded as a result of compounds within the tooth matrix rather than just as a topical stain, since tetracycline staining persists throughout the tooth matrix past traditional whitening methods.

Knowledge of the existence of black bone disease, combined with the lack of longitudinal research, means that the impacts of tetracycline staining on the forensic record are limited. Despite this, we can draw conclusions from the persistence of tetracycline staining in teeth and the depth of pigmentation deposition in the presented surgical cases to show that black bone disease penetrates the bone matrix in a way that suggests it will persist after an individual's death. Without awareness of this condition, forensic anthropologists may experience confusion should they encounter an unidentified individual with black bone disease, as they may not recognize the chemical staining from taphonomic staining and its possible use as an identifier. Thus, there is a need for more research and dissemination of knowledge of this area of study.

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