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Gross, histologic, and computed tomographic characterization of nonpathological intrascleral cartilage and bone in the domestic goat (*Capra aegagrus hircus*)

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Abstract

Objective To characterize grossly, histologically, and via computed tomography (CT) the appearance of intrascleral cartilage, bone, or both in domestic goats with otherwise normal eyes and to correlate this with age, sex, and breed.

Animals studied Sixty-eight domestic goats (89 eyes).

Procedures Forty-nine formalin-fixed globes from 38 goats underwent high-resolution CT, and gross and light microscopic examination. An additional 40 eyes from 30 goats underwent light microscopy only. Age, breed, and sex of affected goats were retrieved from medical records.

Results Considering all methods of evaluation collectively, cartilage was detected in 42% of eyes (44% of goats) and bone in 11% of eyes (12% of goats); bone was never seen without cartilage. Goats in which bone, cartilage, or both were detected ranged from 0.25 to 13 (median = 3.5) years of age, represented 11 of 12 breeds of the study population, and had a male:female ratio of 11:19. Bone was detected in the eyes of significantly more males (n = 8) than females (n = 2). No sex predilection was noted for cartilage alone. Histology revealed intrascleral chondrocyte-like cells, hyaline cartilage, and islands of lamellar bone. Some regions of bone had central, adipose-rich, marrow-like cavities. CT localized mineralized tissue as adjacent to or partially surrounding the optic nerve head.

Conclusions This is the first report of intrascleral bone or cartilage in a normal goat and of intrascleral bone in an otherwise normal mammal. The high prevalence of intrascleral cartilage and bone in this study suggests that this finding is normal and likely represents an adaptation in goats.

Key Words: anatomy, caprine, chondrogenesis, os opticus, osseous metaplasia, osteogenesis

INTRODUCTION

In all vertebrate species, the sclera consists of a dense network of collagen fibrils and serves as a rigid substrate to maintain intraocular pressure and globe shape, protects delicate intraocular structures, and is a site of insertion for the extraocular muscles thus enabling globe movement.[1,2] However, there are many specific scleral adaptations. In monotremes, most fish, reptiles, and birds, and some amphibians, scleral collagen is augmented with variable proportions, extent, and arrangement of cartilage, bony ossicles, or both.[3–6] For example, birds have scleral cartilage and bone, cartilaginous fish species have scleral cartilage only, and some teleosts have intrascleral bone in addition to cartilage. The presence of intrascleral cartilage or bone is particularly variable in reptiles; lizards have scleral cartilage and bone; crocodiles have only scleral cartilage; and snakes have neither scleral cartilage nor bone.[2] These cartilaginous and bony elements of the sclera collectively form the 'ocular skeleton' and are believed to further augment preservation of globe shape when it is exposed to pressure changes associated with diving below water or flying at altitude, and facilitate visual accommodation by serving as less deformable anchor sites for the rapidly acting striated ciliary muscles found in many of these species.[3,6]

To the authors' knowledge, intrascleral cartilage or bone formation is reported very rarely in mammals that give live birth (therians) and, then, only in various experimental models, pathological conditions and aging in rats,[7] mice grafted with avian retinal pigment epithelium,[8] the organoid nevus syndrome in humans,[9,10] and in chronically phthisical human globes.[11] Osseous metaplasia is fairly common in nonscleral sites, including the aged canine lung (i.e., pneumoliths), several neoplasms (e.g., canine mixed mammary tumors[12] or feline gastrointestinal adenocarcinomas),[13] and intraocular sites (e.g., the canine uvea[14] or the guinea pig ciliary body).[15] However, to the authors' knowledge, intrascleral bone has never been reported in the normal globe of monotremes or therians, and cartilage has been reported in the normal eye of only one therian – a Suffolk ewe >24 months of age – and that individual was a member of the control group for a study in which sheep were orally infected with scrapie as neonates.[16] Therefore, the purposes of the present study were to describe for the first time the presence of cartilage and bone in the sclera of goats with otherwise normal eyes, to characterize this finding grossly, histologically, and via computed tomography (CT), and to report its frequency and determine whether its occurrence was correlated with age, breed, or sex of affected goats.

MATERIALS AND METHODS

The electronic medical record system at the University of California, Davis Veterinary Medical Teaching Hospital was searched for all goats that died or were euthanized between January 1999 and May 2012 and from which globes were archived for further assessment. Animals with systemic abnormalities likely to produce ophthalmic manifestations and those in which gross external scleral or orbital abnormalities were noted at necropsy were excluded. For each of these goats, the following information was then retrieved from the medical record: age, sex, breed, medical history, date of death, whether the patient died or was euthanized, and postmortem examination findings.

One or, when available, both globes from all goats meeting the entry criteria were retrieved from the archival collection. All globes had been preserved in 10% formalin since postmortem examination. After removal from formalin, all globes were positioned, cornea down, in circular holes cut into a commercial cardboard tray designed for shipping small containers of contrast agent (Isovue 370, Bracco Diagnostics Inc., Monroe Township, NJ), and imaged using high-resolution CT (Lightspeed16 General Electric Co., Milwaukee, WI) using 0.625-mm collimation and medium- and high-frequency algorithms. Regions of 250 Hounsfield units (HU) or greater were considered consistent with mineral deposition,[17,18] and the thickness, morphology, and attenuation of any such structures were measured using regions of interest. Multiplanar reformatting and three-dimensional reconstructions were performed occasionally to further characterize all mineralized tissue noted.

Following CT, all eyes were sectioned in the paramedian plane and examined grossly. Following gross examination, globes in which bone was noted grossly or by CT were decalcified. All globes were then routinely processed and paraffin-embedded, sectioned at 4 μM, and stained with hematoxylin and eosin (HE). In addition to goats for which whole globes were available, HE-stained sections of eyes from goats that met the same entry criteria were retrieved from archived collections and examined histologically. In all cases, evidence of bone or cartilage was recorded. Additional sections from four globes in which examination of HE-stained slides revealed a basophilic matrix in the posterior sclera were stained with the alcian blue technique for cartilage/glycosaminoglycan (GAG) matrix at pH 1.0.

Ages of goats with cartilage, bone, or either and those without cartilage, bone, or either were compared using the Mann–Whitney rank-sum test. Proportions of male and female goats with cartilage, bone, or either and those without cartilage, bone, or either were compared using chi-square analysis or, when <5 expected observations were encountered in any cells, Fisher's exact test. Goats for which age was listed in the medical record simply as 'adult' or 'juvenile' were omitted from all statistical analyses of age. For all analyses, $P < 0.05$ was considered significant.

RESULTS

Forty-nine eyes from 38 goats underwent CT, and gross and histologic examination. In addition, HE-stained sections from a further 40 eyes from 30 goats were examined using light microscopy only, for a total of 89 eyes from 68 goats. Goats in the study population ranged from 1 day to 13 years of age (median = 2 years) and represented 12 breeds: Boer (n = 14), Pygmy (n = 12), Nubian (n = 11), mixed breed (n = 8), Alpine and Nigerian Dwarf (n = 5 each), Toggenburg (n = 3), Saanen, LaMancha, and Angora (n = 2 each), and San Clemente and French Alpine (n = 1 each). Two records failed to specify breed. Thirty-eight (56%) of the goats were female.

Computed tomography revealed intrascleral mineralized tissue in 6/49 globes (5/38 goats) assessed; 1 each of Alpine (bilaterally affected), Boer, Toggenburg, French Alpine, and Nubian. Affected globes were obtained from goats ranging from 2 to 10 (median = 7) years of age; four were male, and one was female. The bilaterally affected goat was male (Table 1). Mineralized regions identified ranged from small, uniformly attenuating pinpoint

Table 1. Prevalence of scleral cartilage or bone as identified using light microscopy and CT

	Prevalence		Median (range) age (years)	Sex ratio (male:female)	Breeds (Number of goats)
	Eyes	Goats			
Cartilage evident on histology	37/89 (42%)	30/68 (44%)	2 (0.25–13)	11:19	Boer (n = 5, n = 2*) Nubian (n = 4, n = 2*) Alpine (n = 2, n = 1*) Toggenburg (n = 2, n = 1*) Pygmy (n = 2) Saanen (n = 2) Mixed breed (n = 2) Angora (n = 1) French Alpine (n = 1) LaMancha (n = 1) San Clemente (n = 1*) Unspecified (n = 1)
Bone evident on histology	10/89 (11%)	8/68 (12%)	7 (2–10)	6:2	Nubian (n = 2) Toggenburg (n = 2) Alpine (n = 1*) Boer (n = 1) French Alpine (n = 1) San Clemente (n = 1*)
Bone evident on CT	6/49 (12%)	5/38 (13%)	7 (2–10)	4:1	Alpine (n = 1*) Boer (n = 1) French Alpine (n = 1) Nubian (n = 1) Toggenburg (n = 1)

*Goats bilaterally affected.

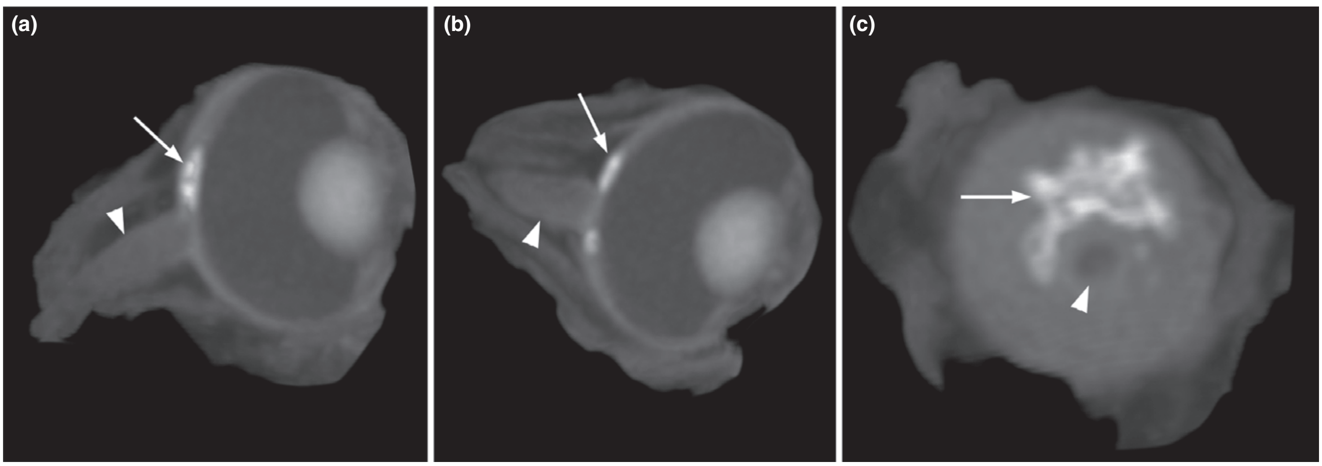

Figure 1. Three-dimensional multiplanar reconstruction maximum intensity projection computed tomographic images of a globe from a 7-year-old male castrated Alpine goat with mineralized tissue within the sclera (arrows). The window width is 350 and the window level is 40. Note in all panels the distribution of the mineralization surrounding much of the optic nerve (arrowhead). (a) Parasagittal projection, (b) dorsal projection, (c) transverse projection at the caudal margin of the sclera.

structures to multifocal regions of mineral-attenuating tissue with cortical and medullary structures. All were adjacent to and sometimes partially surrounding the optic nerve head (Figs 1 and 2, Video S1).

Gross examination findings largely corresponded to CT results, with one or multiple, pinpoint to 0.7 × 0.3 cm, ovoid, glistening tan-white foci in the posterior sclera, adjacent to, or partially surrounding the optic nerve head (Fig. 2b). Of the 89 eyes (68 goats) examined histologically, bone was detected in 10 eyes from eight goats (Table 1). All globes in which intrascleral mineral was identified by CT had osseous foci confirmed by histologic examination. Globes with scleral bone were from goats ranging from 2 to 10 (median = 7) years of age of which six were male and two were female. Both goats affected bilaterally were male. Decalcified sections showed, within

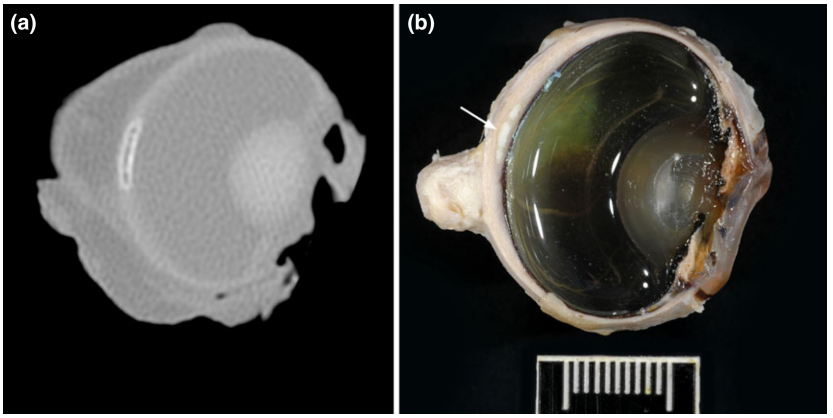

Figure 2. (a) Dorsal computed tomographic image of the same globe as shown in Figure 1 with mineralized tissue within the sclera. The mineralized tissue is located dorsal to the optic nerve. The window width is 350 and the window level is 40. Note that the mineralized tissue has a dense cortical region with a central, less attenuating medullary cavity. (b) Gross photograph of a parasagittal section of the same globe. Note the islands of white tissue (arrowhead) corresponding to the mineral-attenuating focus in Fig. 2a.

scleral collagen, distinct islands of lamellar bone, some with central adipose-rich, marrow-like cavities. Osteocytes were evident within lacunae. (Fig. 3). All globes with intrascleral bone also had islands of hyaline cartilage surrounding or adjacent to bony islands.

A total of 37 globes from 30 goats had histologic evidence of intrascleral hyaline cartilage (Table 1). Of these, 27 globes from 25 goats had cartilage in the absence of bone (two goats had cartilage and bone in one eye but cartilage only in the contralateral eye). The cartilage was always located within the inner posterior sclera, predominantly dorsal and adjacent to the optic nerve head. These goats ranged from 3 months to 13 years (median = 2 years) of age, 11 were male, and 19 were female, and they represented 11 breeds [seven Boers (two bilaterally affected), six Nubians (two bilaterally affected), three Alpines (one bilaterally affected), three Toggenburgs (one bilaterally affected), two each of Saanens, Pygmies, or mixed breed, and one each of LaMancha, French Alpine, San Clemente (bilaterally affected), Angora, and unspecified breed. Of the bilaterally affected goats, two were males and five were females. The cartilage distribution ranged from individual or small pairings of chondrocyte-like cells to large, basophilic clusters (Fig. 4a). After staining with the alcian blue technique, loose GAG-rich matrix admixed with scleral collagen was identified at the posterior pole, but not peripherally, on additional sections from all four globes (Fig. 4b); three globes had variable sized islands of GAG-rich hyaline cartilage with distinct lacunae, and one globe also had an island of mature bone. Two of the four globes were from different male Boer goats (2 months and 3 months of age), and the remaining two globes were from Toggenburg goats (7-month-old female, 5-year-old castrated male). The fibrous tunic and intraocular structures were otherwise normal in all examined sections from all goats.

Considering results from all detection methods collectively, cartilage was detected in 37/89 (42%) eyes (30/68 (44%) goats), bone in 10/89 (11%) eyes (8/68 (12%) goats), and bone or cartilage in 37/89 (42%) eyes (30/68 (44%) goats); bone was never seen without cartilage.

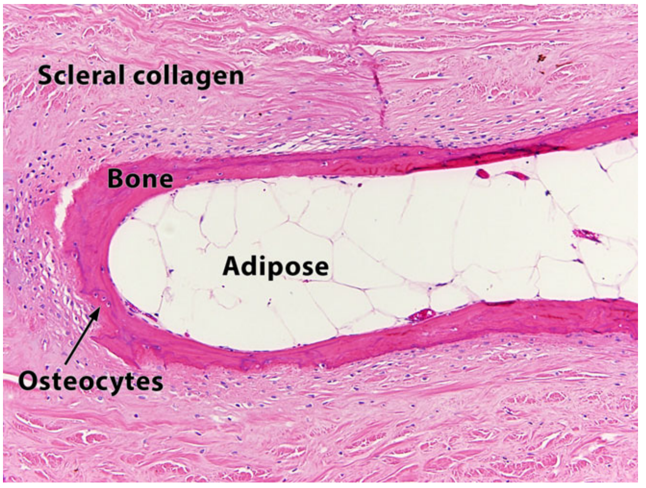

Figure 3. Photomicrograph of the posterior sclera of an adult male San Clemente goat that was bilaterally affected. Note the island of mature bone embedded in scleral collagen, and the adipose tissue-rich central cavity, which resembles bone marrow devoid of hematopoietic elements. HE, 10×.

Goats in which bone, cartilage, or both were detected ranged from 0.25 to 13 (median = 3.5) years of age, represented 11 of the 12 breeds within the study population, and had a male:female ratio of 11:19 (0.6:1). Considering data on a per-eye basis, bone was detected in significantly ($P = 0.04$) more eyes from male ($n = 8$) than female ($n = 2$) goats; no sex difference was noted for the presence of cartilage alone ($P = 0.09$) or either cartilage or bone considered together ($P = 0.09$). Considering data on a per-goat basis, no sex differences were noted for the number of goats in which cartilage alone ($P = 0.39$), bone alone ($P = 0.13$), or either cartilage or bone considered together ($P = 0.39$) was detected. The median and interquartile range age of goats in which cartilage (3; 0.9–7.3), bone (7; 3.9–8.5), or either (3; 0.9–7.3) was detected was significantly greater than that for goats in which cartilage (0.5; 0.2–3; $P = 0.001$) or bone (1; 0.3–4; $P = 0.03$) was not detected, or in which neither bone nor cartilage (0.5; 0.2–3; $P = 0.001$) was detected.

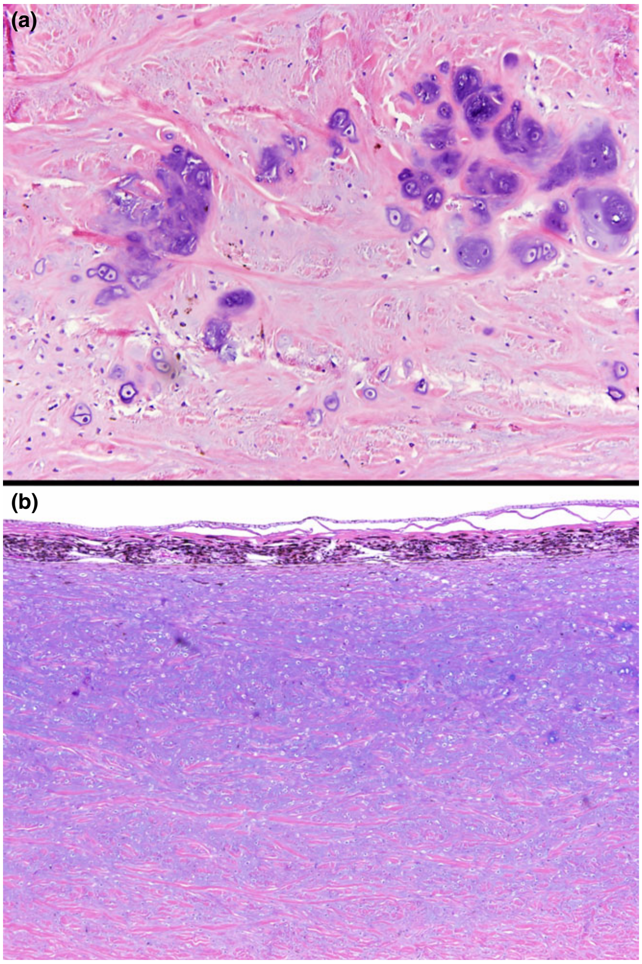

Figure 4. (a) Photomicrograph of the posterior sclera of an adult female Nubian goat whose opposite eye had intrascleral bone. Note the islands of hyaline cartilage and angular chondrocyte-like cell nuclei embedded in amphophilic (purple) matrix. HE, 10×. (b) Photomicrograph of the posterior sclera of a 3-month-old male intact Boer goat depicting fibrocartilage matrix highlighted by alcian blue stain for glycosaminoglycans. The pigmented choroid is toward the top of the image, and the retina is artifactually separated. Alcian blue, 4×.

DISCUSSION

Although bone, cartilage, or both occur as normal tissues within the sclera of many nonmammalian eyes[2–6] and have been reported with various induced and spontaneous pathologic conditions in eyes of multiple species,[7–11,14–16] to the authors' knowledge, the present study is the first to report intrascleral bone development in the normal globe of a mammal of any type, and the first to characterize intrascleral cartilage as a normal finding in any therian. To the authors' knowledge, there is only one previous report describing intrascleral cartilage in a single Suffolk ewe from the control group of a study looking at the effects of oral inoculation with scrapie.[16] Those authors also include the personal observation of intrascleral cartilage in 40% of eyes from Suffolk sheep and 12.7% of eyes from Cheviot sheep; however, those data were not obtained as part of the study design. As such, ours is the first report which fully characterizes intrascleral cartilage as a spontaneous phenomenon in a diverse population of a mammalian species free of ophthalmic disease. Specifically, reports of normal caprine ocular anatomy have failed to mention scleral bone or cartilage despite describing results of numerous techniques that have been used to detect bone in human eyes.[19–21] In the present study, and considering all methods of detection employed, cartilage was detected with a strikingly high prevalence - 42% of eyes (or 44% of goats) - while bone was detected in 11% of eyes (or 12% of goats). The prevalence of cartilage or bone in goat sclera might be even higher given the fact that cartilage or bone could have been missed in the archived samples that were already histologically sectioned and HE-stained at the time of evaluation and hence never imaged with CT. Affected goats represented both sexes and a wide range of breeds and ages; however, animals in which cartilage was detected tended to be younger (median = 2 years) than did animals in which bone was detected (median = 7 years), and all animals in which bone was detected also had cartilage evident. Taken together, these data suggest that cartilage and bone formation may represent stages of the same process in these goats. While heterotopic bone in many species and anatomic sites can occur without a persistent cartilage component or precursor, the concomitance of cartilage in all cases with intrascleral bone in the present study suggests that scleral ossification occurs through a cartilage precursor in the goat.

CT was used as a screening test to describe the frequency and distribution of mineralized tissue in the sclera. Although CT is not able to distinguish cartilage from soft tissue, the presence of mineral-attenuating tissue is indicative of mineralization or ossification. The multiplanar reconstructions and three-dimensional renderings were helpful in characterizing the distribution of mineralized tissue and to aid in planning of sections for microscopy.

In the present study, scleral cartilage and bone were typically located adjacent and often dorsal to or surrounding the optic nerve head. This is similar to the position in which bone is described in the eyes of albino rats exposed to chronic stress,[7] and in humans with organoid nevus syndrome,[9,10] but not in humans with phthisical globes.[11] The position of bone we discovered in goats is also remarkably similar to the os opticus, which has been described in 219 avian species from 35 families and nine orders.[22] Although typically horseshoe-shaped, the os opticus can be highly variable in size and shape, even within a single species. Unlike the avian ossicle, which is comprised of a sclerotic ring of bones, the os opticus is composed of cancellous bone with marrow-rich cavities and concentrically arranged lacunae, and is consistently found at the point where the optic nerve exits the globe.[3,22] Thus, the location, typical shape, and histologic appearance of the bone we describe in goats within the present study are all very similar to that of the avian os opticus.

Although not investigated in the present study, it is tempting to postulate the likely function of intrascleral bone and cartilage in normal caprine eyes. Typically, intrascleral bone or cartilage has been presumed to increase ocular rigidity to prevent globe collapse or intraocular pressure changes – especially in animals flying above the earth's surface or residing at depths below the surface of water. More specifically, the os opticus – given its location surrounding the optic nerve head – is proposed to preserve scleral rigidity and protect the eye against trauma, specifically the optic nerve where it inserts through the rarified and presumably weaker sclera of the lamina cribrosa.[22] Given the anatomic similarity between the os opticus in birds and the intrascleral bone and cartilage that we describe in goats in the present study, it is tempting to assign these structures a similar function in goats and birds. For example, goats engage in fighting behavior that involves rearing up on the pelvic limbs and then descending rapidly and with force against their foe.[23] Males regularly engage in this high-impact behavior during dominance combat, while females use their horns against predators.[24] In addition, goats of both sexes use their horns for lower impact activities such as clearing vegetation.[23] The effect of these intense impacts on cranial tissues is presumed to be similar to that caused by coup-contrecoup injuries in the brain.[25] As such, this has stimulated speculation regarding adaptations goats may have developed for 'shock absorption' during combat, including horn design and frontal bone and frontal sinus morphology.[26–28] It is plausible that intrascleral trabecular bone and cartilage near the insertion of the optic nerve in goats may reduce deformation of sclera during such encounters, thereby protecting the eye and optic nerve from repeated shocks by redistributing stress away from these vital structures. Alvarez refers to a pivotal change in fighting force, body mass, and horn structure when male Spanish Ibex reach maturity at around 6 years of age and begin to compete for access to females.[29] This seems to support our observation that cartilage, bone or both were seen more commonly in older individuals and male goats. However, the fact that this was a unilateral finding in a number of goats in the present study is curious and suggests either asymmetric impact or asynchronous development of this change in both eyes.

There are a number of mechanisms by which bone and/or cartilage form within ocular structures; these include (i) congenital ectopic (choristomatous) bone/cartilage formation,[30–32] (ii) osseous metaplasia as a pathologic response (e.g., post-traumatic or intratumoral),[33–36] (iii) an adaptive response to physiologic stressors within an individual's environment,[37] or (iv) as a normal developmental finding within all or the vast majority of individuals within a species. [2–6] Given the high prevalence of affected animals, and the lack of other ectopic tissues, it seems unlikely that our findings represented choristomatous cartilage or bone formation. Similarly, given the fact that no eyes in the present study had other observed histologic lesions, and specifically that all cartilage and bone formed in areas free of histologic lesions, it seems that these findings were unlikely to represent a pathologic response. However, all goats were euthanized or died for reasons unrelated to this study and complete clinical and ophthalmic examination findings were not always provided. Therefore, it is possible that some – but likely not all – goats we report had unrecognized or unrecorded ocular or systemic disease that predisposed them to osseous metaplasia. Given the broad range of breeds and ages of affected animals, the high prevalence in the study population, and the long period over which affected globes were collected, it seems likely that the intrascleral bone and cartilage formation we report represents an adaptive response to physiologic stressors either over the period of an individual's life as described in rats exposed to chronic stress,[7] or as an evolutionary adaptation of the species as a whole, as described for the avian os opticus.[22]

Regardless of cause, it is interesting to note the ability of caprine sclera to undergo fibrocartilaginous and sometimes osseous metaplasia. Although our study design did not permit a longitudinal analysis, it seems likely that chondroid metaplasia begins as deposition of GAG-rich matrix into the collagenous matrix of the sclera, with a subset of goats developing true hyaline cartilage and, in some cases, mature bone with marrow-like cavities. A study in mice also suggests that the mammalian sclera maintains the ability to differentiate into cartilage after birth and that the process can be mediated by grafted avian retinal pigment epithelium.[8] Proteoglycan accumulation and development of fibrocartilage or hyaline cartilage can also be seen in chronic desmitis in horses.[38] Thus, scleral cartilage and bone formation may represent an adaptive feature that was of significant enough advantage to certain species and individuals to become a normal anatomic feature (e.g., birds), while remaining an inducible adaptive feature acquired in response to aging or injury in other individuals and species, such as the goats we describe here. The fact that affected animals in the present population were common, as young as 3 months, represented both sexes, and represented a broad range of breeds suggests that any inducing stresses must be widespread or multiple and diverse, start early after birth and rapidly lead to this adaptive change. Therefore, assessing all rationale, it seems probable that intrascleral bone and cartilage formation within the present study was either a normal finding in these goats and perhaps the species as a whole or that many individuals of this species have a relatively low threshold to initiate chondrogenesis and, subsequently, osteogenesis in response to unrecognized environmental stimuli.

To the authors' knowledge, this represents the first report of intrascleral bone or cartilage in a normal goat eye, the first report of spontaneously occurring bone in an otherwise normal mammalian eye, and – other than a single sheep in an experimental study – the first report of spontaneously occurring cartilage in an otherwise normal therian eye. The high prevalence of this finding in goats free of ophthalmic disease suggests that clinicians, radiologists, and pathologists should consider intrascleral cartilage and bone in an otherwise healthy goat eye an incidental finding, presumably representing a normal variation. Our data can be used to inform future reports and clinical investigations of other species in which this may be a normal finding thereby perhaps better illuminating potential mechanisms responsible for the induction of such metaplasia. In particular, it would be informative to investigate this finding in closely related species and other animals that display head-butting dominance behavior.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Video S1. Three-dimensional, volume rendering of a globe from a 7-year-old male castrated Alpine goat with mineralized tissue within the sclera. Note the distribution of the mineralization largely surrounding the optic nerve.