Acute– phase proteins increase with sarcoptic mange status and severity in Iberian ibex (*Capra pyrenaica*, Schinz 1838)

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Abstract

Sarcoptic mange is a contagious skin disease caused by *Sarcoptes scabiei*, affecting both domestic and wild mammals, including the Iberian ibex (*Capra pyrenaica*), a medium-sized mountain ungulate almost endemic to the Iberian Peninsula. Acute-phase proteins (APPs) could be an indicator of sarcoptic mange disease and severity in Iberian ibex. Serum samples from 131 healthy and sarcoptic mange-affected Iberian ibexes were collected from 2005 to 2012 in Sierra Nevada Natural Space in southern Spain. Serum alpha-1-acid glycoprotein (AGP), serum amyloid A (SAA) and haptoglobin (Hp) concentrations were quantified, and statistically significant differences according to sarcoptic mange disease and severity were assessed. Both AGP and SAA were significantly higher in the sarcoptic mange-affected ibexes than in the healthy ones as well as in the severely affected ibexes as compared to those with less than 50 % of the body surface affected. For the first time, changes in APP are reported in relation to sarcoptic mange in Iberian ibex. It is also reported for the first time that the intensity of APP increase depends on the severity of sarcoptic mange, which could be

related with the pathological secondary amyloidosis, leading to organ dysfunction in severely mange-affected animals. Species and population differences in the increase of APP in response to sarcoptic mange could indicate individual and population differences in the immune capability of each population to deal with mange, population prevalence and mortality being the last indicators of such sensitivity.

Keywords

Acute phase proteins
Capra pyrenaica
Iberian ibex
Sarcoptes scabiei
Sarcoptic mange

Introduction

Sarcoptic mange is a contagious skin disease caused by the mite *Sarcoptes scabiei* (Linnaeus, 1758). Sarcoptic mange is prevalent worldwide, affecting both domestic and wild mammalian species, and it is currently considered an emerging or re-emerging disease (Arlian 1989; Bornstein et al. 2001; Pence and Ueckermann 2002; Walton et al. 2004). Clinical signs include pruritus, skin drying and peeling, alopecia, scab formation, acanthosis and hyperkeratosis. Moreover, these skin lesions facilitate the development of secondary infections (Rahman et al. 2010). In chronic infestations, animal health is impaired and they may even die, although the last causes and conditions of death are not clear (Arlian et al. 1990).

The Iberian ibex (*Capra pyrenaica*, Schinz 1838) is a medium-sized ungulate, endemic to the Iberian Peninsula (Pérez et al. 2002) and economically relevant as a big game species (Fandos et al. 2010). Iberian ibex populations from Andalusia (southern Spain) have been affected by sarcoptic mange since 1987, reaching mortalities over 90 % (Fandos 1991; Pérez et al. 1999). Chronic sarcoptic mange induces detrimental effects on haematology, serum chemistry, body weight, body condition, oxidative stress and even metapodial development and testes mass in Iberian ibex (Serrano et al. 2007; De and Dey 2010; Sarasa et al. 2011; Pérez et al. 2015).

The acute-phase proteins (APPs) are a group of serum proteins whose concentration may increase (positive APP) or decrease (negative APP) in relation to trauma, infection, stress, neoplasia and inflammation (Conner and Eckersall 1988; Petersen et al. 2004; Cray et al. 2009). Positive APP can be further classified as major (those showing 10- to 100-fold increases) or moderate (those showing 2- to 10-fold increases) (Cerón et al. 2005). Moreover, the circulating concentration of APP is related to the severity of the disorder and the extent of tissue damage in the affected animal, therefore giving not only diagnostic but even prognostic value to the APPs (Petersen et al. 2004).

In Caprinae, haptoglobin (Hp), serum amyloid A (SAA) and alpha-1-acid glycoprotein (AGP) are the most common APP (Petersen et al. 2004) and their concentrations in goats increase after a pro-inflammatory challenge (González et al. 2008). Hp, SAA and AGP determination has been validated in Iberian ibex (Bach 2012). SAA and Hp increased following experimental infestation of sheep with *Psoroptes ovis* (Hering, 1838) and rapidly declined after the successful treatment of infested sheep with an endectocide (Wells et al. 2013). SAA and AGP are considered major APP and Hp and ceruloplasmin minor APP in the closely related Alpine ibex (*Capra ibex*, Linnaeus 1758) when affected by sarcoptic mange (Rahman et al. 2010). However, to the best of the authors' knowledge, APP changes have not been evaluated in scabietic Iberian ibex. Moreover, no correlation between the severity of sarcoptic mange and the intensity of APP variations has been previously investigated either in Alpine or Iberian ibex.

The aim of this study is to analyze the effect of sarcoptic mange disease and severity on APP concentrations in Iberian ibex, in order to better understand their use as a potential diagnostic and prognostic tool.

Materials and methods

Sample collection

Serum samples from 131 both healthy and sarcoptic mange-affected Iberian ibex, age ranging from 1 to 12 years, were collected from 2005 to 2012 in Sierra Nevada Natural Space (SNNS) (36° 00′–37° 10′ N, 2° 34′–3° 40′ W, southern Spain) (Table 1). The ibexes were darted using an anaesthetic rifle with a combination of ketamine and xylazine. Once the ibexes were immobilized, blood samples were collected from the jugular

vein.

Table 1
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Number of Iberian ibexes (*Capra pyrenaica*) sampled in SNNS according to their sex and sarcoptic mange status

Sarcoptic mange status	Sex		Total
	Males	Females	
Healthy	59	27	86
0–50 % of body surface affected	31	1	32
More than 50 % of body surface affected	9	4	13
Total	99	32	131

The captured ibexes were classified into three categories: 0 (clinically healthy), 1 (0–50 % of the body surface affected) and 2 (more than 50 % of the body surface affected) as previously described (Pérez et al. 2011).

Laboratory analyses

Blood samples were allowed to clot at room temperature. Then, the serum was obtained by centrifugation at 4750×*g* for 10 min and stored at −20 °C until analysis.

Serum concentrations of AGP were quantified as the mean of two determinations using commercial assays for cattle, based on the spectrophotometric measurement of protein concentration in the supernatant after precipitation with perchloric acid, as previously described (Tecles et al. 2007). Serum SAA concentrations were quantified as the mean value of two measurements using a commercially available ELISA kit (Tridelta Phase™ range serum amyloid A; Tridelta Development Ltd., Bray, Ireland). Serum Hp concentrations were calculated as the mean of two measurements quantified using a colorimetric assay based on peroxidase activity of the haptoglobin–haemoglobin complex with acid pH (Eckersall et al. 1999).

Statistical analysis

Since APP concentrations did not fit a normal distribution, as assayed using a Kolmogorov–Smirnov test, non-parametric tests were used to detect statistically significant differences between healthy and sarcoptic ibexes (Mann–Whitney test) as well as among healthy ibexes, ibexes with less than 50 % of the body surface affected and ibexes with over 50 % of the body surface affected (Kruskal–Wallis test). The effect of sex on APP concentrations was also assessed with a Mann–Whitney test. Statistical significance was accepted at $p < 0.05$. All the statistical analyses were performed using R software version 3.2.1 (R Development Core Team 2015).

Results

Both AGP and SAA were significantly ($p < 0.001$) higher in the sarcoptic mange-affected ibexes than in the healthy ones (Table 2). Among the sarcoptic mange-affected ibexes, both AGP and SAA were also significantly ($p < 0.001$ and $p < 0.002$, respectively) higher in those ibexes more severely affected than in the ibexes with less than 50 % of the body surface affected (Table 3). SAA concentration was under the detection limit in 96 ibexes (66 out of 86 among the healthy ones, 25 out of 32 among those with less than 50 % of the body surface affected and 5 out of 13 among those with more than 50 % of the body surface affected). Conversely, no statistically significant differences in Hp serum concentration were observed between healthy and sarcoptic mange-infested ibexes ($p = 0.6068$) or among the three classes of sarcoptic mange status ($p = 0.6068$) (Tables 2 and 3). No sex effect on APP concentrations was found.

Table 2

Serum AGP, SAA and Hp concentrations in healthy and sarcoptic mange-infested Iberian ibexes from SNNS

	Healthy			Infested		
	n	**Mean**	**SD**	***n***	**Mean**	**SD**
AGP (mg/mL)[a]	86	1.006	0.639	43	1.362	0.719
SAA (mg/L)[a]	20	1.806	2.431	15	5.953	4.973
Hp (g/L)	77	0.368	0.309	40	0.369	0.345

[a]Statistically significant ($p < 0.001$) differences between healthy and *Sarcoptes*

scabiei-infested ibexes

Table 3

Serum AGP, SAA and Hp concentrations in Iberian ibexes from SNNS according to their sarcoptic mange status

	Healthy			0–50 % of body surface affected			More than 50 % of body surface affected		
	n	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**
AGP (mg/mL)[a]	86	1.006	0.639	31	1.206	0.641	12	1.763	0.780
SAA (mg/L)[a]	20	1.806	2.431	7	2.871	1.340	8	8.649	5.488
Hp (g/L)	77	0.368	0.309	30	0.308	0.269	10	0.550	0.482

[a]Statistically significant ($p < 0.001$ for AGP and $p < 0.002$ for SAA) differences between healthy and *Sarcoptes scabiei*-infested ibexes

Discussion

To the authors' knowledge, this is the first time that changes in APP have been related to sarcoptic mange in Iberian ibex. According to these results, both AGP and SAA could be classified as moderate APP (Cerón et al. 2005) whereas Hp was apparently not affected by sarcoptic mange in Iberian ibex. Although APP can persist in the circulation beyond immediate inflammation, APP response pattern changes as pathological lesions become chronic, as is the case in sarcoptic mange. APP may be undetectable or very low levels in healthy individuals and subclinical conditions, showing only temporary elevations (Meling et al. 2012). Most APP half-lives are only 24 to 48 h (Cray et al. 2009), and bovine SAA, in particular, is elevated in acute rather than in chronic inflammatory conditions (Horadagoda et al. 1999), haptoglobin and SAA returning to baseline values before AGP (Eckersall et al. 2007). All these factors could explain the lack of an APP response (and particularly for SAA) found in a proportion of both the healthy (unaffected by mange) and scabietic (by probability mostly overcoming the acute phase of the disease and entering the longer chronic phase of the disease) Iberian ibexes sampled.

This study also shows for the first time in a wild caprine host that the

intensity of APP increase depends on the severity of sarcoptic mange. As in sheep infested with *P. ovis* (Wells et al. 2013), APP may increase in sarcoptic mange-affected ibexes either due to the immune response, the secretion of pro-inflammatory cytokines or the systemic inflammation related to the extensive skin lesions (Suffredini et al. 1999; De and Dey 2010; Rahman et al. 2010). Therefore, all the three causes could explain the statistically significant higher SAA and AGP concentrations found in the more severely sarcoptic mange-affected Iberian ibexes. Increased SAA concentrations have been related to pathological secondary amyloidosis (Ceciliani et al. 2002, 2012), which is a common finding leading to organ dysfunction in severely mange-affected animals (Tataruch et al. 1985; Arlian et al. 1990). This agrees with the higher APP values observed in the more severely affected Iberian ibexes and may contribute to elucidate the still incompletely unknown pathogenesis of sarcoptic mange in wild ruminants, as well as being useful as a prognostic indicator.

Sarcoptic mange induces an increase of inflammatory and immunoglobulin-secreting cells in the skin (Morsy and Gaafar 1989; Skerratt 2003) as well as an increase in circulating antibodies (Morgan and Arlian 1994). Cell-mediated immune response is thought to be more important than humoral antibody response as regards protective immunity (Arlian et al. 1994), although whether infestation by *S. scabiei* induces protection against future reinfestations is controversial and seems to depend on the species (Bornstein et al. 2001). In domestic sheep, a second challenge with *S. scabiei* induced less severe lesions than first infestation, with lower immunoglobulin G (IgG) but higher immunoglobulin E (IgE) concentrations (Rodríguez-Cadenas et al. 2010). In Iberian ibex, both a cellular (Pérez et al. 1999, 2006) and a humoral (Lastras et al. 2000; Sarasa et al. 2010) immune response against *S. scabiei* infestation have been previously reported. A sexual bias in serum IgG concentration trend in response to mange has been reported both for first and second challenges, females consistently showing higher IgG values than males, whereas male IgG concentration remained almost stable in the second challenge (Sarasa et al. 2010). Higher IgG concentration was detected in healthy Iberian ibexes which had been in contact with sarcoptic mange than in diseased ibexes (Lastras et al. 2000), suggesting that humoral response helped healthy ibexes to control sarcoptic mange whereas it was not competent enough in the sarcoptic mange-affected ibexes (Granados et al. 2008; Lastras et al. 2000). However, an inhibitory action of *S. scabiei*

on the immune response of the host has been reported (Lalli et al. 2004), so the lower humoral response of scabietic compared to the healthy exposed ibexes could also be one of the features of immune response of Iberian ibex to mange. Since sarcoptic mange-related ibex mortality in SNNS has been relatively low as compared to other Iberian ibex populations affected by mange (León-Vizcaíno et al. 1992, 1999; Granados et al. 2008), the relationship of individual and population differences in immune humoral response with mange susceptibility, clinical outcome and related mortality deserves further investigation. A high variation in sarcoptic mange-related mortality has been reported both in Iberian (León-Vizcaíno et al. 1992, 1999; Granados et al. 2008) and Alpine ibex (Rossi et al. 2007) populations. Therefore, the increase of APP in response to sarcoptic mange could be not only a species-related feature but also an early indicator of the immune capability of each population to deal with mange, population mange prevalence and mortality being the last indicator of such sensitivity.

A previous study on the effects of sarcoptic mange in APP in the closely related Alpine ibex revealed a higher increase of APP related to mange, AGP and SAA acting as major APP and Hp and ceruloplasmin as minor APP (Rahman et al. 2010). Previous infestation with *S. scabiei* reduces the intensity of the immune response (Sarasa et al. 2010), as well as the extent of the lesions and the number of mites as compared to primary lesions, and therefore decreases the intensity of the APP response (Wells et al. 2013). Thus, the differences in APP changes between Alpine and Iberian ibexes could be due to differences in previous exposure to sarcoptic mange (unknown) or differences in sarcoptic mange severity (unreported in the previous Alpine ibex study) in the sampled individuals as well as the aforementioned species and population features.

To summarize, SAA acted as a moderate APP and AGP as a minor APP in the Iberian ibexes affected by sarcoptic mange in the SNNS, whereas Hp did not. This APP response was more intense in the more severely affected ibexes. Further analysis of APP response in other sarcoptic mange-affected Iberian ibex populations, as well as in other species, is needed in order to clarify whether APP response to sarcoptic mange in wild ungulates is influenced by individual and population immune response and mortality related.

AQ3

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Conflict of interest

AQ4

The authors declare that they have no competing interests.

Compliance with ethical standards This study, accomplished with all Andalusian, Spanish and European legal requirements and guidelines regarding animal welfare, was approved by the Ethics on Animal Welfare Committee of the Universidad de Jaén and authorized by the Dirección General de Producción Agrícola y Ganadera of the Consejería de Agricultura, Pesca y Medio Ambiente of the Junta de Andalucía.

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AQ5

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