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Invited Review

Use of statistical modelling to investigate the pathogenesis of claw horn disruption lesions in dairy cattle

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ABSTRACT

Claw horn disruption lesions (CHDLs) in dairy cattle account for a large proportion of lameness. The aim of this review is to provide an update on the evidence surrounding the pathogenesis of CHDLs, in the context of how statistical modelling has contributed to the validity of available evidence and current thinking. Historically, 'subclinical laminitis' has often been used to describe the commonly accepted underlying pathology associated with these lesions, however progress in understanding the aetiopathogenesis of CHDLs and a lack of clear evidence to support the traditional laminitis hypothesis, means use of this terminology has been challenged. With advancements in statistical modelling capabilities within the veterinary field, the multifactorial and complex nature of CHDLs can be more fully explored. This has led to an increased understanding of environmental and animal-based risk factors and their role in the pathogenesis of CHDLs, as well as highlighting future research areas. There is still a need for further research using intervention studies to demonstrate causality for identified risk factors to date, as well as quantifying the impact of these risk factors at the population level. Some important considerations when using and interpreting statistical models in lameness research are discussed with a critical assessment of the key statistical issues in published research investigating the pathogenesis of CHDLs.

Introduction

Lesions of claw horn disruption, primarily sole ulceration, sole haemorrhage and white line disease (haemorrhage and separation), account for a large proportion of lameness in dairy cattle (Manske et al., 2002; Sogstad et al., 2005). Sole ulceration was first described as Rusterholz disease in the 1920s and since then studies investigating the aetiopathogenesis of claw horn disruption lesions (CHDLs) have led to the identification of a wide range of risk factors (Hirst et al., 2002a). These can be broadly generalised into two categories; animal based risk factors (i.e. internal factors originating within the animal; predominantly factors related to the structure and function of the claw) and environmental risk factors (i.e. external factors which operate beyond the individual; predominantly factors which directly or indirectly increase the pressure on the hoof capsule).

One of the earliest hypotheses describing the pathogenesis of CHDLs was related to the occurrence of 'laminitis' (Nilsson, 1963); a proposal which was principally based on the symptoms and pathogenesis described for equine laminitis at that time. Studies investigating laminitis became predominant throughout the lameness literature in the subsequent years. However limitations in statistical analysis and techniques used were evident at this time, such that the multifactorial nature of CHDLs could not be fully explored. More recently, with the advancement and availability of statistical software and computing power, statistical modelling has been used to further our understanding of the complex nature of CHDLs in cattle by conducting multivariable analyses. Risk factors related to the environment have been investigated alongside animal-based risk factors and alternative hypotheses that may explain associations previously identified in the literature have been suggested.

To evaluate how statistical modelling has been used to investigate the pathogenesis of CHDLs, consideration must extend from the study design that generates data through to interpretation of results generated by models. All models are a simplification of reality, therefore both transparency and accuracy regarding model assumptions and reporting are important to enable understanding of the disease epidemiology (Huppert and Katriel, 2013). This review aims to provide an update on the current evidence surrounding the pathogenesis of CHDLs from the perspective of how statistical modelling has contributed to the evolution of our understanding of CHDLs and associated risk factors, since the laminitis hypothesis was proposed in the 1960s.

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Since the scope of the paper focuses on the use of statistical modelling, a comprehensive review of all the available literature on the pathogenesis of CHDLs is not provided. For reviews on the lameness literature readers are referred to Hirst et al. (2002a) and Potterton et al. (2012).

General considerations for statistical modelling in lameness research

Statistical methods can be used to analyse relationships between measurements on groups of animals and statistical models to provide a mathematical description of these relationships (Dobson, 1983). The process of statistical modelling can be described in three stages (Dobson, 1983); (1) specifying the equations and distributions that describe the primary features of the outcome, (2) estimating parameters (e.g. risk factor that is being investigated and confounding factors) and (3) making inferences. No model is perfect, but in order to evaluate how well a model describes the data (and therefore the validity of reported findings), there are a number of areas to consider from study design through to making inferences. This section describes some general considerations that are specific to lameness research with some examples, whilst further critical assessment of how statistical modelling has contributed to current evidence and thinking are discussed in subsequent sections.

Study design

Within the totality of peer-reviewed lameness literature, observational and cross-sectional studies are the most commonly reported study design (Hirst et al., 2002a; Potterton et al., 2012). Whilst variables that are found to be significantly associated with a lameness outcome may be causally linked, in general, results from these types of study provide weak evidence for causality. Dohoo et al. (2003) outlines a set of criteria for demonstrating causality including; time sequence, plausibility and experimental evidence. Cohort studies and randomised controlled trials (RCTs) can provide stronger evidence to support causality, yet they are under-represented in studies investigating the pathogenesis of CHDLs. This is likely due to the high resource demands with this type of study design, including cost and time and the accompanying relative lack of funding for lameness research.

Sample sizes and sampling procedures (e.g. randomization) are an important aspect of study design, however they are very commonly under-reported in the lameness literature. This is particularly evident in experimental research investigating laminitis where often relatively small numbers of animals were included e.g. Danscher et al. (2010) where group sizes were less than 10 animals. Sample size calculations indicate the number of animals required in each study group to demonstrate a significant difference; without this information it is not possible to interpret the relevance of negative findings with any confidence. However, sample size calculations for correlated data (e.g. repeated measures), such as that commonly encountered when investigating lameness, are not straightforward and bespoke software is often required (for example, GLIMMPSE (Kreidler et al., 2013)) (Liu and Liang, 1997; Guo et al., 2013).

Data analysis and statistical modelling techniques

Besides study design, statistical modelling can help to control for confounding factors in lameness studies investigating CHDLs. Potential confounders therefore need to be considered, identified and measured for data to be analysed appropriately. Regression analysis is a commonly used statistical technique that enables a number of variables to be incorporated into the model simultaneously (e.g. days in milk, milk yield, body condition score (BCS)); 'multivariable' models therefore enable confounding factors to be controlled for. Univariable statistics on the other hand do not allow for control of confounding factors. This is a major limitation for many of the early studies investigating laminitis, which were primarily observational studies and/or conducted under field conditions where confounding factors will almost inevitably exist (e.g. Bazeley and Pinsent (1984); Manson and Leaver (1988b)). It was more recently (post-2000) that the use of multivariable statistics has increasingly been used to explore the multifactorial nature of CHDLs, helping to progress understanding of animal-based risk factors, such as BCS (Green et al., 2014; Randall et al., 2015; Newsome et al., 2017b), as well as environmental risk factors such as alley and track surface (Barker et al., 2009; Burow et al., 2014).

Data gathered for lameness research commonly have a hierarchical (clustered) structure, for example, repeated measures of lameness (e.g. lameness score or treatment events (level 1) within a cow (level 2) within a farm (level 3)). Where this occurs, similarities may exist between the units at each level such that outcomes may be correlated. It is important that statistical modelling recognises and accounts for this to avoid biased parameter estimates (Woodhouse and Goldstein, 1988; Rabash et al., 2009). Modelling techniques that account for such correlations (e.g. mixed effects or multilevel) should therefore be used in any lameness studies with this data structure, however until more recently when software such as SAS (e.g. GLIMMIX procedure) or MLWin (Rabash et al., 2009) became more widely available, this has not been the case. In much of the early lameness research this was a major limitation, contributing to the publication of a large body of work providing weak evidence in support of the laminitis hypothesis.

Reporting of model assumptions and evaluation of model fit (i.e. how well the model fits the data) is a critical step and is another aspect to modelling that is under-reported in the lameness literature investigating CHDLs e.g. Haskell et al. (2006), Vanegas et al. (2006) and Bergsten et al. (2015). Statistical models that have a poor fit to the data can lead to erroneous conclusions being drawn. Key principles for evaluating model fit include; (1) checking model assumptions, (2) assessment of model fit by comparison of model predictions with observed data and (3) using cross-validation to determine likely generalisability of models (ideally a new data set although this is rarely possible). Appropriate methods for assessing model fit in mixed effects models have previously been described elsewhere (Gelman et al., 1996; Green et al., 2009).

A particularly pertinent issue in the lameness literature is the interdependence between risk factors and outcomes. Identifying the direction of causality can therefore be complex; for example lying times impact on lameness, which in itself impacts on lying times. Complete historical data and appropriate statistical modelling is particularly important in longitudinal studies in order to understand these temporal associations. This is relevant for studies investigating both animal-based (e.g. BCS or body weight (BW)) and environmental risk factors (e.g. those related to lying times) for CHDLs.

Reporting results and interpretation

Odds ratios (OR) estimated from logistic regression models (where the outcome is binary) are very commonly reported in studies investigating the pathogenesis of CHDL. Odds ratios and relative risk (RR) are similar, however when the disease event is common (e.g. lameness incidence rates of between 20 and 80 cases per hundred cows are not uncommon), OR may be substantially different to the RR and care is needed when interpreting results.

For example, Randall et al. (2016) reported an OR of 3.48 for the risk of future lameness in heifers associated with more severe white line lesions (WLL) post-calving compared with no lesions. This might be interpreted as heifers with WLL being 3.5 times more likely to become lame. However, the calculation of RR from posterior predictions was actually 1.6.

Extrapolation of results from one study to a larger population (external validity) is another important aspect of interpreting results regardless of how statistical modelling has been conducted. For example, is it appropriate to generalize findings from a study conducted on one dairy herd to the national dairy herd population? Detailed descriptions need to be provided such that the reader can make inferences regarding the extrapolation of findings (Polit and Beck, 2010). As research investigating CHDLs is still fairly limited (Potterton et al., 2012) and commonly carried out on data from a relatively small number of farms and/or animals this is another particularly relevant consideration in the lameness field.

Interpretations and future considerations

The increased availability of statistical software to fit multivariable models that can account for correlated data means that appropriate statistical modelling should be a core component of lameness studies; particularly for investigating CHDLs which are multifactorial in nature and the majority of the research is conducted under field conditions. Whilst identifying risk factors in observational and cross-sectional studies is an important aspect of investigating the pathogenesis of CHDLs, demonstrating causality and quantifying the impacts of these risk factors at the population level using intervention studies is *vital* if progress is to be made.

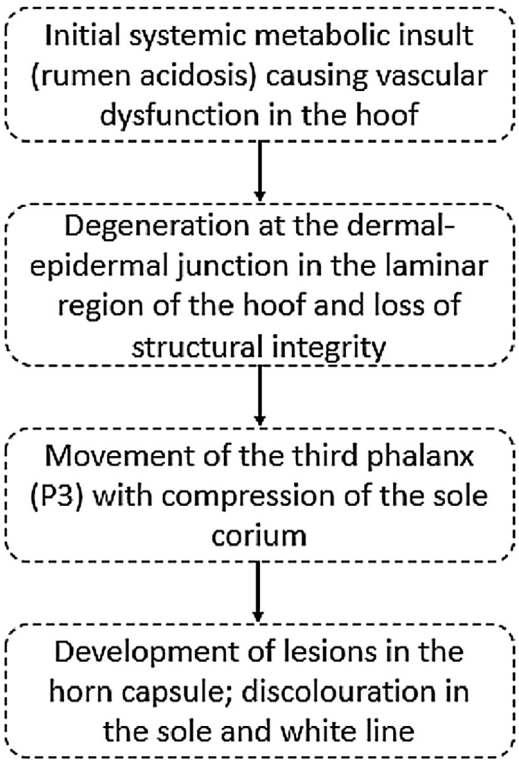

Fig. 1. Hypothesised causal pathway for the development of claw horn disruption lesions which have historically been described as 'subclinical laminitis' (Ossent and Lischer 1995, 1998); the available evidence to support this hypothesis is currently relatively weak.

Laminitis and claw horn disruption lesions

Introduction; terminology and definition of laminitis

Use of the terminology *laminitis* to describe the presence and diagnosis of CHDLs has a long history stretching back to the 1970s (Maclean, 1971; Peterse, 1979). With that description comes an implied nutritional aetiology based on an extrapolation from the described pathogenesis for equine laminitis. By definition laminitis refers to inflammation of the hoof laminae (rather than the presence of CHDLs). Historically, a number of forms of laminitis have been described including acute, subacute, chronic and subclinical (Bradley et al., 1989; Bergsten, 1994). Whilst a common hypothesised pathway has been described (see Fig. 1) (Ossent and Lischer, 1995, 1998), classically CHDLs have been thought of as a manifestation of a subclinical form, believed to be associated with a lowered rumen pH (or subacute ruminal acidosis (SARA)) in dairy cows (Nocek, 1997; Nordlund et al., 2004; Stone, 2004). There is a large body of work investigating laminitis; this section discusses the current evidence in the context of how statistical modelling has contributed towards validity of this evidence.

Associations between dietary factors and claw horn disruption lesions

Early literature provided weak evidence from case studies or expert opinion to identify associations between dietary factors (primarily associated with feeding concentrates) and CHDLs (Bazeley and Pinsent, 1984; Greenough, 1985). Since then, very few blinded RCTs and no systematic reviews to substantiate hypotheses have been reported. The vast majority of studies have been conducted under field conditions, however statistical modelling rarely controlled for confounding factors or correlated data (Livesey and Fleming, 1984; Peterse et al., 1984; Bergsten, 1994). Manson and Leaver (1988a, 1988b, 1989) used univariable analyses to investigate associations between clinical lameness and quantity of concentrates fed, concentrate:silage ratio or protein intakes. Confounding factors such as stage of lactation and parity were not controlled for and consequently, inferences regarding dietary effects need to be interpreted with caution. Bergsten and Frank (1996) described laminitis as having a potentially complex aetiology, and interactions between nutritional factors and environmental factors have been suggested (Cook et al., 2004b), highlighting the importance of appropriate multivariable analysis in field studies to elucidate possible associations. Whilst studies have used experimental design to control for some confounding factors, for example Bergsten and Frank (1996) and Livesey et al. (1998) used 2×2 factorial design and controlled for parity by investigating interactions between diet and underfoot conditions in heifers, a lack of multivariable approaches to statistical analysis meant factors such as milk yield were not controlled for.

Effects of forage type on development of CHDLs is another aspect of diet that has been investigated. Feeding wet silage-based diets in the rearing period was found to be associated with poorer claw health (measured 20 weeks post-calving) in two groups of eight heifers (Offer et al., 2001). A follow up longitudinal study concluded youngstock diets should not be heavily based on wet grass silage (less than 25% dry matter (DM)) (Offer et al., 2003). Limitations with regards statistical analysis controlling for potential confounding factors such as BCS and milk yield mean these results need further substantiation. Webster (2001) explored alternative mechanisms associated with calving as well as effects of diet on CHDLs. Whilst significant differences in CHDL between dietary treatments (low- or high-dry-matter forage) at 4 and 8 weeks post-calving were reported, statistical analysis could not control for the differences in milk yield (18%

lower for dry diet). Authors suggested that mechanisms other than inflammation of the laminae may be involved in the process of CHDL development (e.g. weakening of the suspensory apparatus associated with calving) which required further research. To date, there is a lack of compelling evidence to demonstrate a causal link between feeding high concentrate diets (or other direct nutritional factor contributing to lowered rumen pH) and the development of CHDLs.

Rumen acidosis, inflammation of the laminae and claw horn disruption lesions

A key step in the laminitis hypothesis is lowered rumen pH (rumen acidosis) triggering processes leading to inflammation of the laminae. However, studies have rarely investigated whether either of these pathological processes actually occur as a precursor to CHDLs. Experimental oligofructose (a readily available carbohydrate) overload models have successfully induced acute laminitis in profoundly acidotic animals with systemic clinical signs (Thoefner et al., 2004; Danscher et al., 2009) and accompanying histopathological changes in the lamellae (Danscher et al., 2010). However, it has not yet been demonstrated that this translates into the non-acute scenario (SARA) commonly seen on-farm or importantly whether the resulting inflammation of the laminae manifests clinically as CHDLs. Danscher et al. (2010) was unable to demonstrate an effect of oligofructose overload in an RCT investigating changes in biomechanical properties of the laminae in heifers. Physiological support of suspensory tissue (measured using a mechanical testing frame fixed by the horn and bone and loaded to failure) were measured at 24 and 72 h. This finding could potentially be due to insufficient study power ($n = 16$). How this level of acute overload might equate to diets commonly fed to high yielding dairy cattle on-farm was not characterised or discussed. As experimental studies have yet to provide strong evidence to support the laminitis hypothesis following acute acidosis, its role in the non-acute scenario (SARA), manifesting as CHDLs also remains unproved. One randomized intervention study investigated the effect of transition diets varying in levels of rumen-soluble carbohydrate, energy and fibre (Donovan et al., 2004) on haemorrhages in the sole. Rumen acidosis was defined as rumen liquor pH $\leq$5.8. Generalised linear models were used to control for confounding factors such as parity, season and days in milk, although methods for including repeated measures in models were not described. Whilst diets lowered rumen pH, no association between rumen acidosis and CHDL was found. Further robust studies should be carried out to substantiate the results reported, however accumulated study findings challenge the causal assumption that lowered rumen pH (or SARA) is involved in the pathogenesis of CHDLs.

Interpretations

The quality of available evidence to support a causal relationship between lowered rumen pH (or SARA) and CHDLs as well as inflammation of the laminae as a precursor to CHDLs is relatively weak and cannot currently substantiate the hypothesised laminitis causal pathway. Continued use of the terminology 'subclinical laminitis' to describe CHDLs adds to the bulk of literature with an implied nutritional aetiology; consequently this terminology should be reserved exclusively for studies demonstrating inflammation of the laminae, as suggested by previous authors (Livesey et al., 2003; Laven, 2006). It is incumbent on the research community to conduct high quality, robust intervention studies to provide stronger causal evidence in this currently disputed area.

Environmental risk factors

Introduction; hypothesised mechanisms for environmental risk factors

Mechanisms associated with environmental risk factors that may contribute to CHDLs are primarily related to increased forces acting at the claw-environmental surface interface. Increased biomechanical forces are believed to overwhelm the innate anatomical defence mechanisms in the hoof causing traumatic damage to the corium, leading to the development of CHDLs (Webster, 2001; Tarlton et al., 2002; Somers et al., 2005). Environmental risk factors therefore relate to (i) the surface the cow is standing, rising or walking on and/or (ii) the duration of time spent standing or walking. This section discusses the current evidence in view of how statistical modelling has contributed towards understanding in this area.

Associations between standing/walking surface and claw horn disruption lesions

Floor surface may influence biomechanical forces on the claw as a direct effect of compressibility or indirect effects related to abrasiveness (altered claw wear and growth rates leading to medial-lateral foot imbalance, thin soles or increased sole surface contact area) (Cook et al., 2004b; Telezhenko et al., 2009; Bergsten et al., 2015) or the coefficient of friction altering locomotion (Phillips and Morris, 2001; van der Tol et al., 2005). With different flooring surfaces, direct and indirect effects may vary and interactions with management factors such as cow handling, cow flow and the amount of slurry on the flooring surface could also be important.

A number of randomized trials have explored associations between flooring surfaces and CHDLs. Bergsten et al. (2015) reported that slatted concrete alleys resulted in an increased risk of CHDL vs. slatted rubber; OR (95% confidence interval) of sole haemorrhages/ulcers and white line haemorrhages were 2.19 (1.00–4.97) and 2.82 (1.28–6.43), respectively in heifers after calving. Confounding factors of cohort, breed and days in milk were controlled for in logistic regression models. In contrast, Vokey et al. (2001) used univariable statistical methods to compare rubber and concrete alleys in combination with different stall surfaces and was unable to detect significant differences. Statistical limitations were acknowledged by authors, as group differences in parity were observed which could impact findings. Vanegas et al. (2006) were also unable to detect a significant effect of flooring surface (rubber ($n = 82$) vs. concrete ($n = 81$)) on CHDLs up to 130 days post-calving. Although sample sizes were larger than those reported by Vokey et al. (2001), a different methodology for lesion scoring was used and this finding may be related to study power.

Mixed effects modelling has been used in observational studies to explore flooring surface as a risk factor for CHDLs with conflicting findings. For example Sogstad et al. (2005) identified an increased risk of white line haemorrhage associated with solid concrete alleys vs. slatted concrete, whereas Barker et al. (2009), did not find a significant risk of white line lesions associated with slatted concrete vs. solid concrete alleys. Differences in study design and lesion recording methods (foot trimming vs. farmer treatment records) may account for differences in these findings. Barker et al. (2009) however did report a significant association between solid grooved concrete alleys and white line disease (OR (95% confidence interval) = 2.50 (1.31–4.78); reference category = non-grooved).

Differences in growth and wear associated with flooring surface on claw imbalance or CHDLs have also been explored. Telezhenko et al. (2009) used generalised linear models to demonstrate differences in growth and wear rates with flooring systems over a 4

month period. No differences in claw asymmetry, however, were found. Previous lameness may also have impacted on claw conformation as a potential confounding factor. As an alternative hypothesis, Muggli et al. (2016) suggested anatomical disparity between the hindlimb lateral and medial digit length could contribute toward CHDL development. It has been suggested that this could explain the predisposition of the lateral hind claw to develop CHDLs and may have relevance for cattle exposed to hard flooring surfaces (Nuss, 2014). Although the clinical relevance of this has yet to be demonstrated.

Track surface (materials and maintenance) has been investigated as a risk factor for lameness in a number of observational studies (Harris et al., 1988; Chesterton, 1989; Barker et al., 2009; Burow et al., 2014). Chesterton (1989) and Burow et al. (2014) used multivariable statistical methods and demonstrated track cover and maintenance, respectively, as risk factors for lameness, although lesions were not explored. Barker et al. (2009) used multilevel modelling in a longitudinal study of 27 farms and reported the use of roads or concrete tracks as a risk factor for sole ulcers (OR (95% confidence interval) = 2.14 (1.10–4.16); reference category = no concrete tracks).

Findings from studies provide some evidence towards demonstrating an association between flooring surface (including track surface) and CHDL. Although further research using well-designed intervention studies is needed to understand the role of surface compressibility, abrasiveness and coefficients of friction in the aetiopathogenesis of CHDLs in order to determine optimum surfaces, alongside a better understanding of interactions with other risk factors.

Associations between standing/lying times and claw horn disruption lesions

As lameness impacts on lying behaviour (Solano et al., 2016), understanding the temporal relationships between environmental risk factors increasing lying times and CHDLs is complex. Standing/lying times could increase biomechanical forces on the claw due to (i) increased standing time per se or (ii) standing half in cubicles (perching) leading to increased pressure on the hind feet. Multiple factors may influence standing/lying times, including cubicle design, bedding surfaces, stocking density and social and behavioural aspects (Cook and Nordlund, 2009) which should be considered in study design and statistical analysis. Whilst numerous studies have demonstrated associations between lameness and cubicle design, comfort and bedding surfaces (Faull et al., 1996; Cook, 2003; Cook et al., 2004a; Sogstad et al., 2005; Espejo and Endres, 2007; Chapinal et al., 2013) as well as access to pasture or straw yards/open pack (Webster, 2001; Somers et al., 2005; Haskell et al., 2006; Fregonesi et al., 2009), few have measured lying times.

Cook et al. (2004b) used mixed effects modelling in a study of 12 herds, demonstrating that mattress cubicles were associated with an increased time standing in the cubicles per day compared with sand cubicles. Lameness prevalence was higher with mattress vs. sand cubicles (least square means 24 vs. 11%, respectively). The cross-sectional nature of this study means that cause and effect cannot be established, and effects on CHDL were not explored, however findings suggest cubicle comfort may impact on lying times and lameness. Proudfoot et al. (2010) used multivariable analysis in a study of 26 Holstein dairy cows, reporting that sole lesions in mid-lactation were associated with increased standing times in the 2 weeks before and 24 h after calving; time spent half-in cubicles and an increase in standing bout duration were significantly increased. Time periods were analysed separately, therefore cause and effect cannot be elucidated and it is possible that previous lameness history may have confounded results. Other studies have however also supported these findings (Galindo and Broom, 2000). Further work to understand the temporal associations between standing/lying times and the development of CHDLs are needed to identify how environmental and management factors may be improved to reduce the occurrence of these lesions.

Interpretations

A substantial body of literature provides evidence to support associations between environmental risk factors and CHDLs. However, less information is available regarding the underlying pathological processes, which requires further research. High quality intervention studies are required to demonstrate causality, identify underlying mechanisms and to quantify the relative importance of environmental risk factors at the herd level so that these can be effectively managed to reduce lameness.

Animal-based risk factors

Understanding temporal associations is paramount when investigating many of the animal-based risk factors; CHDLs themselves can impact on these risk factors and common causal pathways may exist. Appropriate study design and statistical modelling is therefore an important consideration. The use of multivariable and multilevel modelling in studies investigating animal-based risk factors has aided an advancement in our understanding of the pathogenesis of CHDLs, however further research using intervention studies are still required to demonstrate causality and substantiate previous findings.

Associations between body weight and claw horn disruption lesions

Body weight (BW) can influence mechanical forces acting through the claw and it therefore appears plausible that increased BW would be associated with increased risk of CHDLs (Gearhart et al., 1990; Bergsten, 2001). A number of confounding factors and interactions need to be considered when investigating this risk factor. For example, age and BCS both impact on BW as well as potentially having direct impacts on CHDLs themselves via alternative causal pathways. Likewise, BW itself may influence for example social hierarchy and lying times/feeding times which could impact on CHDLs. Other confounding factors may also need to be considered, for example hoof size (which may influence distribution of forces). Perez-Cabal and Charfeddine (2016) demonstrated a positive relationship between BW and CHDLs, however modelling did not control for a milk yield effect and BW was estimated. In contrast, mixed effects modelling has been used in a number of studies to control for clustering and confounding, and negative associations between BW and lameness have been identified (Onyiro et al., 2008; Norring et al., 2014; Randall et al., 2015). Although these studies did not provide information on CHDLs specifically, this finding might suggest that other factors such as social hierarchy may be involved. Further work to understand these complex associations will aid in understanding how BW may impact on CHDL development.

Suspensory apparatus and the calving effect

Hormonal and metabolic changes associated with calving are thought to contribute towards changes in the connective tissues of the hoof wall suspending the pedal bone (suspensory apparatus) resulting in instability of the distal phalanx (Webster, 2001, 2002; Tarlton et al., 2002) and development of CHDLs. Univariable statistical analyses were used in an experimental study of 6 pregnant and 3 maiden heifers, with findings suggesting

biomechanical and histopathological changes in the laminae that were consistent with fibrogenic processes rather than inflammatory changes around the time of first calving (Tarlton and Webster, 2002). Although study design controlled for some confounding factors the consequences of, for example, nutritional differences could not be distinguished. Knott et al. (2007) similarly reported calving as having an effect on connective tissue laxity in an experimental study of 48 heifers. The research so far appears to provide some evidence to suggest calving may be a potentially important primary factor involved in the pathogenesis of CHDLs through changes to connective tissue, although the causal mechanisms have yet to be fully understood, including how interactions with environmental risk factors may influence this process.

Supportive apparatus and digital cushion thickness

Energy balance has been highlighted as playing a key role in hoof health; as milk yield increases to peak lactation a concurrent decrease in BCS is seen, coinciding with an increase in CHDL risk. One hypothesis suggests that with reduction in BCS the digital cushion becomes thinner reducing its force-dissipating capacity (Bicalho et al., 2009), contributing to development of CHDLs. Understanding temporal associations is again important as lameness itself may directly impact on BCS (potentially through alternations to feeding behaviour (Norring et al., 2014; Thorup et al., 2016)) or via associated factors including milk yield and digital cushion thickness. A number of longitudinal studies have used mixed effects modelling to explore temporal associations between low BCS and lameness whilst controlling for milk yield and other confounding factors (Green et al., 2014; Lim et al., 2014; Randall et al., 2015). The association between low BCS and lameness has been shown to be present for the first lifetime recorded lameness event in cows (parity 2 and above) i.e. the effect of BCS loss precedes lameness, although this effect was not present in heifers (Randall et al., 2015) and CHDLs were not specifically investigated. To explore the underlying mechanisms, Newsome et al. (2017b) used survival analysis in a prospective cohort study of 158 cows to explore associations between changes in sole soft tissue thickness (corium and digital cushion) and CHDLs. Whilst a thinner sole soft tissue thickness increased the likelihood of future lesions, a change in thickness, i.e. thinning, did not influence the likelihood of lesion occurrence. These findings challenge the notion that BCS loss is the primary cause of a decrease in digital cushion thickness that leads to development of CHDLs. Other factors may contribute to a thin digital cushion including changes to the suspensory apparatus associated with calving or laminar pathology as well as previous lameness events (Tarlton et al., 2002; Knott et al., 2007; Newsome et al., 2016; Newsome et al., 2017a). Further work, including intervention studies, are required to understand whether controlling body condition loss does indeed reduce lameness caused by CHDLs as well as the underlying biological mechanisms.

Claw conformation and posture

Inappropriate claw conformation may alter weight distribution which could increase biomechanical forces through the hoof during limb loading. Maintaining appropriate distribution of weight across claws is one of the aims of routine foot trimming to prevent claw disease. Likewise, inappropriate postures, such as 'cow-hock', may influence biomechanical forces acting on the hoof.

Capion et al. (2008) used multilevel modelling in a longitudinal prospective study of 147 heifers from 5 farms to explore the dynamics of abnormal hind leg conformation, asymmetric claws, lameness and foot lesions. Authors highlighted that cause and effect relationships were not clear; for example cow-hock posture may be both a cause and effect of a foot lesion. Increased severity of white line lesion was associated with greater claw asymmetry whereas lameness score and sole haemorrhage appeared more severe in symmetric claws; the latter potentially an indicator of the early stages of this cycle. Further studies are required to support this hypothesis. Other postural and claw conformation factors suggested to be associated with CHDL include foot/claw angle, bone structure and hock angle (Perez-Cabal and Charfeddine, 2016). Currently, there is a lack of evidence for the role of claw conformation and posture in the pathogenesis of CHDLs, although the increase in biomechanical forces is biologically plausible and has been demonstrated to be present in areas associated with injury (Van der Tol et al., 2002).

Lameness history and pathological changes to hoof anatomy

A positive association between CHDLs and future lameness risk has been demonstrated in numerous studies (Hirst et al., 2002b; Randall et al., 2016; Newsome et al., 2017b), indicating potential underlying long-term pathological changes. The increase in lameness prevalence or risk with increasing age that has been widely reported would support this hypothesis (Barker et al., 2009; Randall et al., 2015; Solano et al., 2015). Development of new bone 'exostosis' on the distal phalanx has been shown to be positively associated with CHDL during life in a study of 282 hind claw from 72 Holstein-Friesian dairy cows examined at slaughter (Newsome et al., 2016). Linear regression models controlled for confounding factors including age and previous locomotion scores. Although with this type of study design caution should be taken with regards to causal inferences, findings provide some evidence to support the hypothesis that long term pathological changes in the hoof are associated with CHDLs and may contribute to the development of future lesions.

Recent research has shown that previous lameness events may contribute towards an overwhelming proportion of the total lameness in dairy herds (Randall et al., 2018). Whilst this study only investigated two herds, findings highlight the potential importance of previous lameness as a risk factor. Quantifying the contribution of risk factors could be used more widely in lameness research to investigate other risk factors; this would help to inform where resources should be prioritised in order to make most impact on-farm.

Interpretations

An increased use of statistical modelling to investigate animal-based risk factors has helped to advance our knowledge regarding the aetiopathogenesis of CHDLs; in particular the role of the structure and function of support structures in the hoof. In addition, some new areas for future research have been identified, as well as the need for further high quality intervention studies and prioritisation of interventions through quantifying the relative importance of risk factors at the herd level.

Conclusions

The use of statistical modelling in studies investigating the pathogenesis of CHDLs has helped to progress lameness research from a large volume of weak evidence related to the laminitis hypothesis becoming the received norm of understanding, towards stronger evidence to support the identification of potentially important and causal environmental and animal-based risk factors. The complexities of field-based data commonly used in lameness research means there is a requirement for the use of statistical techniques that can control for multiple confounding

factors and hierarchical (clustered) data. Additionally, recognising the interdependence between risk factors and outcome, in particular the effect of previous lameness history is important and must be controlled for wherever possible. In order to progress the field, future research should focus on intervention studies that can provide evidence towards causality for, and the relative importance of the potential risk factors identified in the literature to date.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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