LAMINITIS IN CATTLE UPDATE

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SUMMARY

Laminitis is defined as a diffuse aseptic inflammation of the corium of digits, usually involving more than one digit. Laminitis has been recognised as a disease of multifactorial aetiology as several factors are thought to be involved. In this review, current concepts on aetiology are discussed and these include factors produced during inflammatory processes, or carbohydrate fermentation in the rumen with subsequent production of histamine and/or lactic acid. The sudden introduction to cattle of feeds composed of large amounts of readily fermentable carbohydrates is associated with the occurrence of laminitis in both dairy and beef cattle. Other factors include epidermal growth factors, endotoxins and vasoactive mediators of the arachidonic acid metabolites such as thromboxanes A_2, prostaglandin E_2 and prostacycline I_2. The theories for the pathogenesis of the disease presented attempt to identify the primary site of attack based on radiographic findings, histological observations in the corium of the digits and experiments with epidermal growth factors. However, there is a lot of uncertainty regarding the actual aetiology and pathogenesis. Specific areas for further research in order to understand the actual aetiology and pathogenesis are outlined.

INTRODUCTION

Digital diseases are now common as an outcome of modern dairy and beef production systems. Digital diseases can cause lameness and subsequently lead to weight loss, decreased production, premature culling and great economic losses to the farmer. The economic losses which are realized are mainly due to decreased productivity, increase in cost of veterinary services or treatment and replacement of animals culled prematurely. In many countries, the estimated financial loses due to lameness have been reported to be enormous (Dijkhuizen, 1983; Choquette-Levy *et al.*, 1985; Harris *et al.*, 1988; Whitaker *et al*, 1988; Esslemont, 1990). In countries where cattle are raised intensively, lameness is comparable in importance to mastitis and reproductive disorders (Mortensen and Hesselholt, 1986; Whitaker *et al*, 1988; Harris *et al*, 1988). An association between lameness and reduced reproductive fertility has also been reported indicating that lameness aggravates this disorder (Lucey *et al.*, 1986; Mgasa *et al.*, 1990). In most reports on lameness, laminitis has been singled out as the major cause, particularly in intensively kept cattle.

DISEASE CHARACTERISTICS

Laminitis is as a disease of multifactorial aetiology as several factors could be involved (Mortensen and Hesselholt, 1982; Bazeley and Pinsent, 1984). However, there

is a general agreement that the sudden introduction of cattle to feeds composed of large amounts of readily fermentable carbohydrates is associated with the occurrence of laminitis in both dairy and beef cattle.

The disease may be divided into acute, subacute and chronic stages, but the existence of a sub clinical form has been recognized (Peterse, 1980; Mortensen and Hesselholt, 1982). The clinical picture of laminitis in cattle has been described in detail by Nilsson (1963), Maclean (1965, 1966) and Dirksen (1978). In acute cases pronounced signs are hoof tenderness, stiffness, a stronger pulse in the digital arteries, local venous distension and occasionally hoof deformations. Often the initial acute and subacute phases are not always observed and the occurrence of laminitis is first noticed in the chronic stage when changes in the claw characteristics are evident (Nilsson, 1963; Peterse, 1985). Mild signs of lameness which may be noted as stiffness in the gait may be the signs observed initially. However, in severe cases where serious hoof deformation and sole ulceration have occurred severe lameness is a characteristic feature. In chronic laminitis the claws are characterized by formation of ridges and concavity of the dorsal wall. Other signs in the claws include haemorrhages in the sole and white zone or yellowish discoloration and softening of horn in the sole (Nilsson, 1963; Anderson and Bergman, 1980; Toussaint-Raven, 1985; Mortensen and Hesselholt, 1986). A downward deviation of the pedal bone is often observed on radiography (Maclean, 1970a).

The clinical signs of subclinical laminitis are insidious. However, changes in the digits comprising haemorrhages in the sole and occasionally concavity of the dorsal wall may be evident (Andersson and Bergman, 1980; Mortensen and Hesselholt, 1986; Peterse, 1985). Sole haemorrhages have been considered an important stage of subclinical laminitis (Toussaint Raven, 1973; Peterse, 1985). Sole ulcer and white zone lesions which often occur as a sequel to subclinical laminitis are important causes of digital lameness (Maclean, 1971a; Mortensen and Hesselholt, 1982; Peterse, 1982; Greenough, 1985; Weaver, 1988; Bradley *et al.*, 1989). Based on these observations, early recognition and diagnosis of subclinical laminitis have been suggested as a measure to assess the susceptibility of individuals to future lameness (Mortensen and Hesselholt, 1982; Greenough and Vermunt, 1991).

HISTOPATHOLOGY

The histopathology of bovine laminitis has been described (Nilsson, 1963; Maclean, 1971b; Andersson and Bergman, 1980; Mortensen and Hesselholt, 1986; Boosman *et al.*, 1989; Mgasa *et al.*, 1990). In acute laminitis, hyperaemia, oedema and haemorrhages as well as infiltration of the corium with lymphocytes, histiocytes and fibroblasts is a common feature. Occasionally eosinophil infiltration may occur in the perioplic and coronary corium. Thrombosis in veins and arteries is also a common feature. In the epidermis the cells of the stratum basale and spinosum are enlarged and disoriented and there may be partial or complete disappearance of the keratogenic substance. Acidophilic bodies may also be observed. In cases of acute exacerbation of chronic laminitis, vacuolation and nuclear pyknosis in the stratum basale and stratum spinosum have been observed (Mgasa *et al.*, 1988; Mgasa 1991). Subacute cases of laminitis have been described with pathological changes intermediate between acute and chronic laminitis (Nilson, 1963).

In the chronic phase, the pathological

changes are dominated by vascular changes (Maclean, 1971b; Andersson and Bergman, 1980; Mgasa *et al.*, 1988) with hyperaemia and haemorrhages in the corium. Dilatation of capillaries and venules is a prominent feature. There is hypertrophy of the tunica media, proliferation of the tunica intima and fibrosis of the tunica adventitia (Maclean, 1971b). Similar pathological changes have been described by Andersson and Bergman (1980). Other findings in the corium include chronic thrombi and chronic granulation tissue as well as heavy perivascular accumulation of macrophages which contain haemosiderin (Andersson and Bergman, 1980). Mast cells have been reported to occur in large numbers in the chronic phase (Nilsson, 1963). However, other studies have described only a few mast cells and eosinophils localized in the perioplic and coronary corium (Maclean, 1971b; Andersson and Bergman, 1980). Other changes in the corium include sclerosis of the connective tissue in the solar corium and lamella (Maclean, 1971b; Andersson and Bergman, 1980).

Studies of the histopathology of laminitis are few in the literature and those that are available do not indicate the specific lesions which can be attributed to laminitis. In most cases the histology described seems to be an interaction between animal, age and disease factors. Apparently normal animals have been observed to have degenerative changes in the digits similar to those observed in laminitis (Andersson and Bergman, 1980). These observations indicate that the diagnosis of laminitis is largely subjective as no definite criteria are available. This is an area where research is needed in order to understand the pathogenesis of the disease and the aetiology.

PREDISPOSING FACTORS

A variety of nutritional and managemental factors have been implicated in the aetiology of laminitis. The increase of laminitis in recent years has been ascribed to high concentrate and low roughage rations (Anderson and Bergman, 1980; Peterse, 1982; Liversey and Flemming, 1984; Mortensen and Hesselholt, 1986; Mgasa, 1989; Greenough and Vermunt, 1991). Housing is another factor thought to exacerbate the clinical signs of the disease especially where hoof horn is weakened by standing in slurry or where cows have to twist and turn in poorly designed and narrow passages (Bazeley and Pinset, 1984). Laminitis and sole ulcers have been reported to be a common problem in heifers which spent most of the time standing in concrete cubicles with less straw bedding (Colam-Ainsworth *et al.*, 1988). Sudden introduction to cubicle housing, lack of exercises and poor cubicle housing are other suggested factors (Edwards, 1982).

In dairy cattle, laminitis has been associated with stress from many sudden changes occurring around the time of calving, such as feeding, social grouping and introduction to new environment when their body metabolism is changing very rapidly (Bazeley and Pinset, 1984). Sudden introduction to concentrate feeds at the time of calving has also been reported to predispose cattle to laminitis.

Acute inflammatory disease such as mastitis and metritis may predispose animals to laminitis (Nilsson, 1963; Maclean, 1965). These conditions are thought to predispose cattle through the release of toxic factors or histamine produced at the site of the inflammatory reaction. In free range beef cattle in the tropics, laminitis has been attributed to walking long distances on hot ground (Mgasa *et al.*, 1984). An inherited form of laminitis in Jersey cattle has also been reported (De Bloom *et al.*, 1968; Merrit and Riser, 1968; Edwards, 1972). In

summary, laminitis has been recognised as a disease of multifactorial aetiology (Mortensen and Hesselholt, 1982; Bazeley and Pinset, 1984) and an epidemiological approach is necessary in order to understand the aetiology.

AETIOLOGY

Laminitis has been induced experimentally by grain overload in cattle (Mortensen and Hesselholt, 1986). Similarly laminitis has been induced following intraruminal infusion of lactic acid in sheep (Telle and Preston, 1971; Morrow *et al.*, 1973). The role of lactic acid in laminitis of cattle has been doubted by other workers as attempts to repeat the experiments and induce laminitis by intraruminal infusion of lactic failed despite high levels of peak concentrations of lactate in the rumen (Andersson, 1981). This indicated that lactic acid itself may not be the solitary causative factor. However, extensive research in nutritionally caused laminitis in horses indicates lactic acidosis as a significant factor in the aetiology of the disease (Garner *et al.*, 1975; Garner, 1980) and it has also been considered relevant in cattle (Dirksen, 1983; Greenough, 1985; Weaver, 1988). In most cases the changes in the rumen microclimate and the release of other substances during rumen acidosis, together with the structural changes of the rumen are factors known to contribute in the pathogenesis of laminitis.

The relationship of laminitis to other feedlot ailments such as lactic acidosis and changes in the forestomach has been recognised (Dirksen, 1983). The structure of the forestomach has been observed to be altered in cases of rumen acidosis. Severe degenerative changes in the rumen mucosa such as clamping of papillae, hyperkeratosis, parakeratosis and acanthosis have been reported in association with rumen acidosis (Brownlee, 1956; McGavin and Morril, 1976; Landsverk, 1978; Sakata and Tamate, 1979; Garfi *et al.*, 1981; Dirksen *et al.*, 1985; Jensen 1988). Such changes in the forestomach have been reported to be associated with laminitis in bull calves fed on concentrates ad libitum (Mgasa, 1991). This indicate that the damage caused by rumen acidosis to the structure and morphology of the forestomach may assist in the absorption or dissemination of toxic factors involved in laminitis.

Histamine has been found in rumen fluid of lactic acidotic sheep (Dain *et al*, 1955). Nilsson (1963) thought that histaminosis could produce laminitis since histamine is known to cause oedema, hyperemia, haemorrhages and necrosis in various connective tissues when given in high amounts. Serum histamine levels have also been reported to be slightly elevated during acute laminitis of cattle maintained on high concentrate rations, with much higher levels being recorded in chronic cases (Maclean, 1970b). Laminitis has been induced experimentally in cattle following injection of high doses of histamine (Nilsson, 1963; Takahashi and Young, 1981). The response of laminitic animals to antihistamine therapy seems to support the histaminosis theory. However, histamine has been described to be poorly absorbed from the rumen particularly at the low pH dominating in rumen acidosis (Brent, 1976). In addition, histamine is a basic compound which should be highly dissociated at the pH of acidotic rumen; thus rapid absorption is unlikely (Brent 1976). The elevation of serum histamine reported in carbohydrate overloaded cattle is thought to be coincidental with histamine released from other sources (Maclean, 1970b). The possibility of laminitis arising from an allergic reaction to histamine has been discussed (Nilsson, 1963; Maclean, 1966). Other investigations have suggested that

histamine plays only a subordinate role in hypersensitivity reactions in cattle (Eyre *et al.*, 1973). There seems to be a lot of contradictions on the role of histamine in laminitis and clarification by more research is required.

Carbohydrate overload in ruminants has been associated with lactic acidosis (Dunlop and Hammond, 1965) and the appearance of endotoxins in the circulatory system (Dougherty *et al.*, 1975). Endotoxins have been extracted from ruminal bacteria as well as ruminal fluids (Mullenax *et al.*, 1966) and are thought to originate from dying and disintegrating Gram-negative bacteria due to low pH induced by overproduction of lactic acid in carbohydrate fermentation (Dougherty *et al*, 1975). Endotoxins have been found in the rumen of grain engorged cattle in concentrations which could be toxic if they were absorbed by the damaged mucosa (Mortensen and Hesselholt, 1986). In horses, development of laminitis has accompanied endotoxaemia (Sprouse *et al.*, 1987). In cattle, injection of endotoxins in digital arteries has been reported to induce mild clinical signs of endotoxaemia with mild clinical laminitis characterised by pronounced vascular lesions (Mortensen *et al.*, 1986).

Endotoxins have their effect on blood vessels in several tissues. However, there is uncertainty as to the role of endotoxins in laminitis as these cause several combinations of host responses in ruminants (Verheijden *et al.*, 1984), most of which are non specific because they are induced by non specific mediators released from activated macrophages (Dinarello, 1984). Furthermore plasma endotoxin clearance has been observed to be extremely rapid, such that during rumen acidosis only very low levels can be detected in the peripheral blood which may not be of any biological significance (Mortensen and Binder, 1985; Andersen, 1990). However, the primary effect of endotoxins is thought to be through their effect on the release of vasoactive mediators. The mediators are of the arachidonic acid metabolites such as thromboxanes A_2, prostaglandin E_2 and prostacycline I_2 which have been suggested to play a role in laminitis due to their relationship to the development of the clinical syndrome endotoxicosis (Jarlov *et al.*, 1988; Andersen, 1990). The role of endotoxins in bovine laminitis needs clarification because of the contradicting observations.

Epidermal growth factors which could be released from the gastrointestinal tract and uterus have been observed experimentally to inhibit the differentiation of keratinocytes and these have also been proposed as responsible in the pathogenesis of laminitis (Ekfalck *et al.*, 1987). The occurrence of severe outbreaks of laminitis in herds where there is no history to suggest a high incidence of acidosis or high amounts of concentrates or deficient fibre contradicts the above theories.

PATHOGENESIS

Many theories have been put forward to try and explain the chain of pathophysiological events associated with the local changes which can be observed in laminitis. The occurrence of symmetrical and bilateral lesions in feet of affected animals has led to the suggestion of a systemic disease (Greenough, 1982; Liversey and Fleming, 1984; Mortensen and Hesselholt, 1986). However, to date the pathogenesis of the disease is not clearly known. More research is therefore needed to elucidate its aetiology and pathogenesis.

Joly and Vivien (1901; Cited by Maclean 1971b) suggested that the primary attack is an osteitis. Obel (1948) indicated that the

changes in the epidermis are primary and that the deviation of the distal phalanx which is observed in laminitis results from lack of onychogenic substance in the laminae and consequent stretching of the laminae resulting in displacement of the bone. Experimental studies, in vitro, have indicated that epidermal growth factor which are found in the gastrointestinal tract and the uterus may be responsible in the inhibition of differentiation of keratinocytes (Ekfalck *et al*, 1987). These studies suggest that the vascular changes in the corium are secondary.

Histological studies have indicated that vascular changes are primary and cause oedema and haemorrhage in the acute phase, which are followed by secondary changes as a result of stagnant hypoxia, an inadequate supply of nutrients to keratin-producing cells (Nilsson 1963; Maclean, 1971b; Andersson and Bergman, 1980; Boosman *et al.*, 1989). Angiographic studies of laminitis in horses have also indicated vascular changes to be primary (Coffman *et al.*, 1970). Based on these observations, the pathophysiological process in the digits is thought to be a toxic influence on capillary walls causing an insufficient nutrient supply to the keratin-producing cells with a synthesis of structurally incompetent keratin, which together with the pull on the flexor tendon, results in separation of the horny and sensitive laminae and rotation of the pedal bone (Edwards, 1982).

The occurrence of laminitis together with polyarthritis and synovitis in cattle fed on concentrate diets has also been documented (Andersson and Liberg, 1980; Mortensen *et al*, 1986; Mgasa,1991). This simultaneous occurrence has been suggested to be an expression of different reactions to a common aetiological agent. The existence of a disease complex which may manifest itself in the forestomach, digits, joints and other lower limb areas should also be investigated.

CONCLUSION

Although many predisposing factors for laminitis are documented, there is a lot of uncertainity regarding the actual aetiology and pathogenesis of the disease. The theories put forward to try to explain the chain of systemic phenomenon and the occurrence of local changes in the tissues of digits are often conflicting. The literature available also indicates that many factors could be involved and therefore the disease is of multifactorial aetiology. In order clearly to understand this disease an epidemiological approach in research should be adopted.

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