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Physiological disturbances in inflammatory and metabolic regulatory pathways leading to Equine Laminitis

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Abstract

Equine laminitis is a complex and debilitating condition that severely compromises hoof health and equine welfare. This thesis investigates the physiological disturbances in inflammatory and metabolic pathways that lead to the development of laminitis, with a focus on the roles of vascular compromise, inflammation, enzymatic activity, and metabolic dysfunction. These pathways are discussed to highlight their impact on the laminar structures within the hoof capsule.

It begins with a detailed summary of the anatomy and physiology of the equine hoof, emphasizing the role of the laminae in providing structural support and distributing mechanical forces during locomotion. The vascular and metabolic systems are assessed to establish their contributions to laminar health and more importantly how their dysregulation leads to pathological changes. This thesis also highlights the key causes of laminitis, including endocrinopathic conditions such as Equine Metabolic Syndrome (EMS) and Pituitary Pars Intermedia Dysfunction, the inflammatory triggers linked to gastrointestinal disturbances and systemic infections, and mechanical stress from excessive weight-bearing in supporting-limb lameness.

By analysing the stages of laminitis, from the developmental phase to chronic structural failure, the study provides insights into the mechanisms contributing to the progression of this condition. Treatment strategies, targeting inflammation, vascular health, metabolic stability, and mechanical support, are evaluated alongside preventative measures such as dietary regulation, endocrine management, and hoof care. The thesis discusses the importance of early intervention and consistent management strategies to control the progression of the disease.

Prevention remains one of the most effective methods of combating laminitis, given the limitations in treatment options and the irreversible nature of advanced cases. Proactive approaches, including dietary regulation to manage carbohydrate intake and routine endocrine screening for at-risk horses, are essential. Advances in molecular biology have identified biomarkers, such as matrix metalloproteinases (MMPs) and cytokines, which hold potential for improving diagnostic accuracy and treatment outcomes.

This thesis investigates the pathophysiology of laminitis in depth, leading to a better understanding of its development. It emphasizes the need for multifactorial approaches to improve diagnosis, management, and prevention. Further research into the molecular

pathways and emerging therapies is essential for reducing the burden of this complex disease while enhancing equine welfare worldwide.

1. Introduction

Equine laminitis is a devastating and potentially life-threatening condition affecting the hoof of horses, ponies, and other equids [1]. Characterized by the inflammation and structural disruption of the laminae, the interlocking tissue that anchors the hoof wall to the underlying pedal bone, laminitis poses significant challenges to equine health and management. Laminitis affects approximately 15-20% of horses globally at some point in their lives, with recurrence rates exceeding 50% in at-risk populations [2]. The condition is often acute but can quickly progress to chronic stages, leading to severe pain, lameness, and in advanced cases euthanasia may be required. Despite many years of study, laminitis remains a complex and catastrophic disease with significant gaps in understanding its pathophysiology [3].

The aetiology of laminitis is diverse and involves metabolic, mechanical, and inflammatory pathways. It is frequently associated with systemic disorders such as endocrine dysfunctions (e.g., Equine Metabolic Syndrome [EMS] and Pituitary Pars Intermedia Dysfunction [PPID] [4], and gastrointestinal disturbances following carbohydrate overload [5]. Emerging concerns include the impact of climate change on forage quality, as increased sugar content in grasses during drought periods has been linked to heightened laminitis risk [4]. Other predisposing factors include excessive weight-bearing on a limb due to contralateral limb injury, as well as exposure to environmental toxins such as black walnut shavings [1]. The synergy of these factors complicates both prevention and treatment strategies, necessitating a multidisciplinary approach to management [6].

From an economic and welfare perspective, laminitis is one of the most significant diseases affecting equids, bringing to mind the phrase “no hoof, no horse” [2]. The condition not only impacts the quality of life of affected animals but also places substantial emotional and financial burdens on owners and caretakers. Economic costs include veterinary care, specialized shoeing, loss of use, and in severe cases, euthanasia, which imposes emotional distress to all involved [7]. Advances in imaging technologies, molecular biology, and biomechanical analysis have shed new light on the mechanisms contributing to laminitis. For example, thermography and computed tomography have improved the ability to detect subclinical laminitis, while molecular studies on biomarkers such as cytokines and matrix metalloproteinases (MMPs) have provided insights into disease progression [3, 5]. However, these findings have not yet fully translated into universally effective treatments [8].

This thesis aims to explore key aspects of pathophysiology of equine laminitis, focusing on the metabolic and inflammatory changes within the hoof that lead to the development of this disease. By investigating these pathways, this work seeks to contribute to the broader understanding of laminitis and possibly contribute to the development of better preventative measures, which remain the most effective approach to combating this condition [4, 6].

2. Anatomy and Physiology of the Equine Foot

2.1. Overview of the Equine Hoof

The equine hoof is a specialized structure that forms the terminal portion of the limb. Its unique anatomy allows it to withstand significant mechanical forces while providing sensitivity and protection [9]. The hoof capsule, surrounding tissues, and internal structures work together to support proper biomechanics and health of the foot. Understanding its anatomy is crucial for comprehending the physiological changes and pathological processes that occur during laminitis [10]. Below is an overview of the hoof's anatomy, with a focus on its role in laminitis development.

2.1.1. External Structures

The external hoof wall protects the inner structures and absorbs mechanical stress. It is divided into several regions as illustrated below in **(Figure 1).**

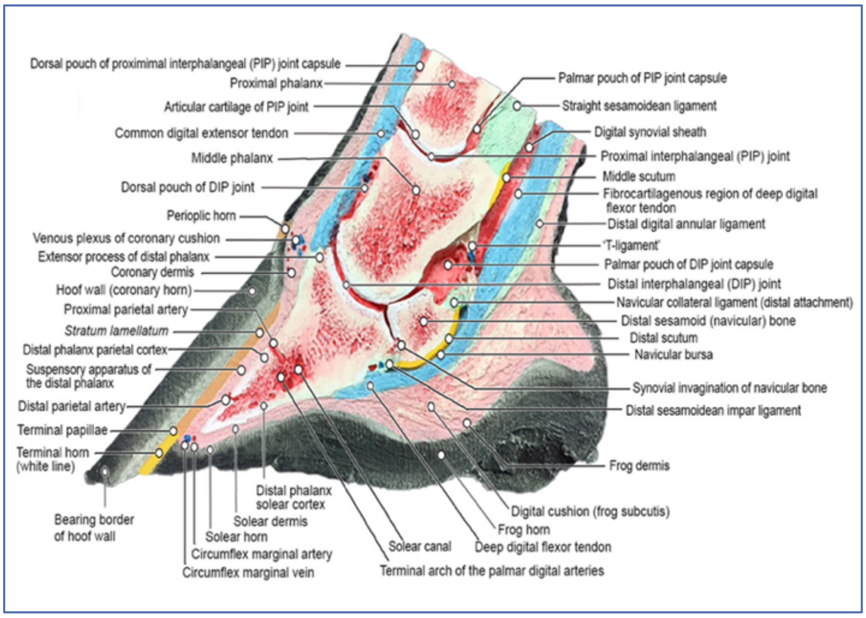

Figure 1: The anatomy of the equine hoof [11].

The hoof wall defines the rigid keratinized outer layer of the hoof that bears weight and protects the delicate internal structures. Originating from the marked junction between the soft tissue of the distal limb and the hardened keratinized layer of the hoof wall, the hoof grows continuously from the coronary band and is vital for supporting the horse's weight and resisting external forces [12]. Cells in this area generate the tubular and intratubular horn structures that make up the hard outer wall of the hoof. The coronary band is extremely sensitive due to its dense network of nerves and blood vessels. Damage to the coronary band can affect hoof growth and its integrity [13]. The periople is a thin, waxy layer near the coronary band that protects the hoof wall and maintains its moisture balance. Its damage can lead to cracks that compromises hoof integrity [14]. The bottom of the hoof, a concave surface providing protection to the sensitive internal structures while contributing to weight distribution and grip of the foot is referred to as the sole of the hoof [13]. The junction between the sole and hoof wall, composed of soft, non-pigmented horn is known as the white line. It serves as a marker of laminar health. Widening or haemorrhaging of the white line can be an early indicator of laminitis [15]. The frog is a V-shaped, rubbery structure on the underside of the hoof that aids in shock absorption, circulation, and traction [16].

2.1.2. Internal Structures

The internal structures of the hoof provide a framework for its mechanical function and vascular support. The coffin bone (P3), or distal phalanx, is the primary skeletal component within the hoof. It plays a vital role in structural support and weight-bearing, while being suspended within the hoof capsule and adhering to the hoof wall via the laminae [1]. This connection ensures stability and biomechanical integrity between the bony component of the hoof and its supporting structures [1]. The collateral cartilages are fibrocartilaginous extensions of the coffin bone. They contribute significantly to flexibility and shock absorption in the foot [16]. They help the hoof adapt to mechanical stresses encountered during locomotion. However, their degeneration or calcification, a condition termed sidebone, can exacerbate laminar damage and compromise hoof function [16].

Located caudally to the coffin bone, the navicular bone facilitates the movement of tendons within the foot and aids in force distribution [17]. By maintaining the proper alignment of the deep digital flexor tendon (DDFT) and the coffin bone, the navicular bone supports the hoof mechanisms and contributes to balance and motility. Its structural role is essential for force distribution during locomotion [17]. The digital cushion, a fibro-fatty structure situated beneath the coffin bone and the navicular apparatus, serves as a shock absorber, and promotes venous return. Its function is particularly critical during weight-bearing and locomotion, reducing impact forces and facilitating vascular circulation within the hoof [16]. The tendons and ligaments located within the hoof space, including the deep digital flexor tendon and the collateral ligaments, provide stabilization of the foot and facilitate motion. These structures ensure the coordination and flexibility necessary for effective locomotion [13].

Lastly, the laminae are the structures that link the hoof wall to the coffin bone and are central to the hoof's vascular and mechanical stability. The Primary and Secondary Laminae as seen in **(Figure 2)** are interdigitating structures that connect the hoof wall to the coffin bone. These laminae interdigitate to form a strong bond, suspending the coffin bone within the hoof capsule, distributing weight and providing suspension [14]. The Corium of the Laminae is a vascular layer essential for nutrient supply and waste removal. In laminitis, the laminar tissue becomes inflamed and structurally compromised, leading to displacement or rotation of the coffin bone, along with associated pain, and impaired function [14].

These anatomical structures give an insight to the complexity of the varied elements of the hoof and the integral roles they play, which are is necessary for optimum hoof health. It highlights the importance of the equine hoof as a dynamic and weight-bearing organ.

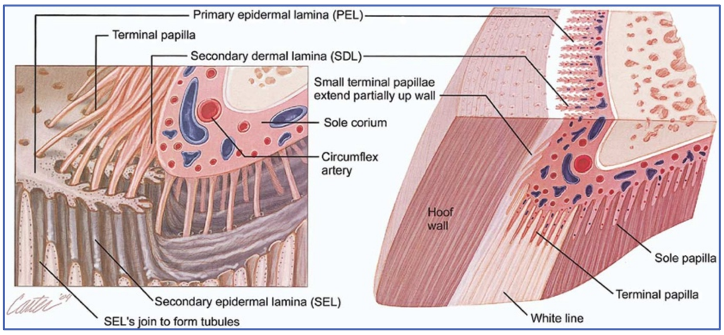

Figure 2: Laminae anatomy [18].

2.1.3. Circulatory System

The equine hoof possesses an intricate network of blood vessels that supply oxygen and nutrients to the tissues. This vascular network is critical for maintaining tissue health, facilitating recovery from injury, and ensuring proper thermoregulation [8]. The arterial supply to the hoof is primarily derived from the medial and lateral digital arteries, which are branches of the palmar arteries. These arteries form an anastomotic network that supplies the laminae, ensuring the delivery of essential nutrients and oxygen to the hoof [1].

The venous drainage within the hoof mirrors the arterial supply and plays a pivotal role in maintaining circulation. Unlike typical veins, these vessels lack valves, relying instead on the mechanical compression of the venous network during locomotion to facilitate blood return to the heart [16]. This adaptation is essential for sustaining circulation within the hoof, particularly during periods of high activity.

Within the corium, the microcirculation consists of a dense capillary network that supports the hoof's metabolic demands and eliminates waste products. This network is essential for the proper function and health of the hoof's internal structures [14]. Additionally, the presence of arteriovenous anastomoses (AVAs) allows blood to bypass the capillaries during rest [19]. However, during activity, these shunts must close to ensure adequate perfusion of the laminar tissues. Dysfunction of these shunts is implicated in the pathophysiology of laminitis, where excessive shunting can result in reduced perfusion and ischemic damage to the laminar structures [19].

During motion, laminar perfusion is enhanced by the mechanical action of the digital cushion and frog [16]. These structures compress the veins during weight-bearing, aiding venous return and reducing congestion within the hoof. Impairments in the function of these structures, particularly during laminitic episodes, can worsen causing venous congestion and thus contributes to further vascular compromise [16]. The combination of compromised vascular perfusion and inflammatory signalling in laminitis leads to ischemia, escalating tissue damage and further progressing the condition [8].

This complex vascular network, combined with its reliance on biomechanical and hemodynamic interactions, shows the intricacy of equine hoof physiology. Dysregulation within this system, particularly during conditions such as laminitis, highlights the critical role of vascular health in maintaining hoof integrity.

2.1.4. Suspensory Apparatus

The laminar structures of the hoof serves as the primary suspensory mechanism for the coffin bone, playing a crucial role in the structural and functional integrity of the hoof [9]. Its structure is designed to distribute the forces exerted during locomotion while simultaneously supporting the weight of the horse. The laminar system ensures proper alignment of the coffin bone within the hoof capsule, which is essential for supporting overall hoof health and biomechanical efficiency [9].

Disruption of the laminar surface, as seen in conditions such as laminitis, has profound implications for hoof structure and function [1]. Inflammatory processes weaken the bond between the sensitive and insensitive laminae, compromising the suspensory mechanism. This weakening can lead to rotation or sinking of the coffin bone, a pathological condition commonly referred to as founder [1]. These changes not only affect the biomechanical stability of the hoof but also have systemic consequences, impacting the horse's overall mobility and welfare.

The integrity of the laminae is critical for the hoof's ability to withstand mechanical stress and maintain proper skeletal alignment. Understanding the pathological processes that disrupt this system provides valuable insights into the prevention and management of laminitis and related disorders.

2.1.5. Sensory and Neurological Components

The hoof contains sensory nerves that detect pressure, pain, and temperature changes. Innervation is provided by the digital nerve branches, which are important for proprioception and pain signalling [17]. Pain perception and the inflammatory response are heightened during laminitis, leading to clinical signs such as lameness and heat in the hoof [3].

The anatomy of the equine hoof reflects its critical role in locomotion and structural support. The connection between its mechanical, vascular, and neurological systems is essential for health and function. Understanding these anatomical features provides a foundation for investigating the pathophysiology of laminitis and its underlying metabolic and inflammatory pathways [3].

2.2. Physiology of the Laminae

The laminae of the equine hoof are highly specialised tissues that play a crucial role in the suspension of the coffin bone (P3) within the hoof capsule. These structures are essential for maintaining the integrity of the hoof, ensuring proper weight distribution, and enabling efficient locomotion [15]. In addition to providing mechanical support, they function as a shock absorber and form the connection between the sensitive and insensitive layers of the hoof [14].

2.2.1. Anatomy of the Laminae

The laminae are classified into two primary types: the sensitive laminae (dermal laminae) and the insensitive laminae (epidermal laminae). The sensitive laminae consist of soft, highly vascularized tissues that are directly attached to the coffin bone (P3). These tissues are rich in blood vessels, nerves, and connective tissue, playing a vital role in the nutrient supply, innervation, and integrity of the hoof [13].

In contrast, the insensitive laminae are composed of keratinized tissues that form the inner surface of the hoof wall. These layers are produced by the epidermal layer and are firmly anchored to the sensitive laminae, creating a strong bond. This interconnection is critical for the hoof's weight-bearing function and for withstanding the mechanical stresses associated with locomotion [13].

Together, the sensitive and insensitive laminae interdigitate to form the complex laminar tissues. This arrangement includes approximately 600 primary laminae, each of which branches into around 150 secondary laminae [15]. This complex interlocking structure significantly increases the surface area of the laminae, maximizing the strength of the bond and enabling effective distribution of forces across the hoof [15]. The precise alignment and interaction of these laminae are essential for the performance and health of the hoof.

2.2.2. Physiological Functions

The laminae of the equine hoof perform multiple critical physiological roles that are essential for maintaining both the mechanical and metabolic functioning of the hoof. One of their primary functions is the suspension of the coffin bone within the hoof capsule, ensuring proper alignment of the distal limb. This suspension mechanism allows for the even distribution of weight across the hoof during locomotion and plays a vital role in maintaining the structural integrity of the hoof under mechanical stress [2].

Another significant role of the laminae is force distribution. During locomotion, the laminae help dissipate the forces exerted on the hoof as it strikes the ground. The sensitive laminae absorb compressive forces and transfer them through the hoof wall, minimizing stress on the coffin bone and other bony structures within the hoof. This function is crucial for preventing localized stress and potential injury to the foot's internal components [16].

The nutrient supply to the hoof is another critical role carried out by the laminae. The sensitive laminae are highly vascularized, ensuring a steady flow of oxygen and nutrients to the hoof wall and coffin bone. This vascular network supports the metabolic needs of the laminae and facilitates the continuous growth of the hoof wall from the coronary band [1].

Additionally, the laminae are richly innervated, enabling them to detect changes in pressure and pain. This sensory capability serves as a protective mechanism, alerting the horse to potential injury or inflammation. The ability to perceive mechanical stress is essential for maintaining hoof health and responding to damage or overloading [17].

These diverse and critical roles highlight the laminae's importance in maintaining the functionality of the equine hoof. Their ability to integrate mechanical support, metabolic functioning, and sensory protection is central to the hoof's overall health and performance.

2.2.3. Clinical Relevance: Laminitis and Dysfunction of the Laminae

The physiology of the laminae is fundamental to understanding the pathophysiology of laminitis, a condition characterized by inflammation and structural failure within the laminar tissues. Laminitis results in severe pain and significant functional impairment, often leading to long-term disability or euthanasia in affected horses [15].

One of the primary pathological changes in laminitis is the inflammation and weakening of the laminar bond. Inflammation, often triggered by metabolic disorders such as Equine Metabolic Syndrome (EMS) or Pituitary Pars Intermedia Dysfunction (PPID), as well as by toxins or mechanical overload, which disrupts the bond between the sensitive and insensitive laminae. This weakening compromises the suspensory function of the hoof, resulting in instability of the coffin bone within the hoof capsule [5].

As laminar integrity deteriorates, rotation or sinking of the coffin bone may occur, a condition commonly referred to as founder. Founder is a severe and often irreversible consequence of laminitis that leads to extensive structural damage within the hoof. In advanced cases, the coffin bone may sink to the extent that it protrudes through the sole of the hoof, drastically worsening the prognosis for recovery [1].

Vascular changes also play a significant role in the progression of laminitis. Compromised blood flow to the sensitive laminae leads to tissue ischemia and hypoxia, resulting in necrosis of the laminar tissues. This further weakens the laminar bond and contributes to the displacement of the coffin bone [8]. In addition to vascular compromise, enzymatic degradation further deteriorates the structural failure during laminitis. Increased activity of matrix metalloproteinases (MMPs) breaks down the extracellular matrix of the laminae, accelerating the loss of tissue integrity [5].

Metabolic dysregulation is another critical factor in the development of laminitis, particularly in cases of endocrinopathic laminitis. Conditions such as hyperinsulinemia disrupt glucose metabolism within the laminae, reducing cellular energy production and impairing the repair processes necessary for continued laminar health [4].

The laminae are essential for the proper functioning and structural stability of the hoof, playing critical roles in suspending the coffin bone, distributing mechanical forces, and supplying nutrients to the hoof tissues. Disruption of this system, as seen in laminitis, can lead to devastating consequences, including permanent damage to the laminar bond and the coffin bone [15]. Further research into the molecular mechanisms underlying laminar dysfunction holds promise for the development of improved management strategies and therapeutic interventions.

3. Pathophysiology of Equine Laminitis

Equine laminitis is a multifactorial condition involving complex pathological processes that disrupt the structural and functional integrity of the laminae in the hoof. The pathophysiology is characterized by a series of events involving vascular compromise, inflammatory responses, enzymatic degradation, and metabolic dysregulation, resulting in the failure of the suspensory apparatus of the coffin bone [20]. Below is an in-depth exploration of the physiological mechanisms underlying laminitis.

3.1. Stages of Laminitis

Laminitis is most commonly divided into three clinical stages which outline the changes in the conditions during the development of disease. The developmental stage is the time between the initial triggering event (e.g., systemic disease, mechanical overload) and the onset of clinical signs, lasting hours to days depending on the cause. Triggering events such as systemic inflammation, mechanical overload, or endocrine dysfunction initiate pathological changes in the hoof. These pathological changes include vascular and metabolic disruptions, to the physiology of the hoof [21].

The acute phase begins with the appearance of clinical signs (e.g., lameness, pain and increased hoof temperature) and may last up to 72 hours. The acute phase is marked by inflammatory and enzymatic degradation of the laminae, resulting in progressive structural damage [15].

The chronic phase occurs if the laminar damage is not resolved during the acute phase and the condition continues to progress while the health of the laminae further deteriorates. Prolonged or unresolved damage leads to structural failure, including rotation or sinking of the coffin bone (founder), due to the breakdown of the laminar bond [22].

3.2. Vascular Physiology and Hemodynamic Changes

The dysregulation of blood flow in the hoof is a defining feature of laminitis, with vasoconstriction and vasodilation playing critical roles in its pathophysiology. The condition often begins with vasoconstriction, which reduces oxygen and nutrient delivery to the sensitive laminae [23, 24]. This reduction in blood flow is mediated by endotoxins, cytokines, and systemic inflammatory mediators. While initially protective, prolonged vasoconstriction leads to hypoxia and metabolic disruption in laminar tissues. Following this phase, vasodilation occurs, marked by the production of reactive oxygen species (ROS).

These ROS heighten oxidative stress, leading to additional tissue damage. Reactive vasodilation may also contribute to tissue oedema and, in some cases, thrombosis, further impairing laminar function [23, 24].

Reduced perfusion within the laminae plays a central role in the ischemic damage observed in laminitis. Impaired blood flow results in cellular hypoxia, disrupting normal cellular processes and leading to tissue injury. Although reperfusion is necessary to restore blood flow, it can increase the damage by triggering the oxidative stress mechanisms. This phenomenon, known as ischemia-reperfusion injury, contributes to further degeneration of the laminar tissues [25].

Oedema formation is another critical consequence of vascular dysregulation in laminitis. Increased vascular permeability, driven by inflammatory mediators, causes plasma to leak into the interstitial spaces within the laminar tissues. This fluid accumulation results in laminar oedema, which, when confined within the rigid hoof capsule, exerts compressive forces on sensitive structures. Such compression increases tissue damage and contributes to the pain and clinical aspects associated with laminitis [26]

Finally, thrombosis within the microvasculature of the laminae worsens ischemia by further reducing nutrient and oxygen delivery. The formation of microvascular clots prolongs hypoxia, resulting in cellular death and further structural compromise of the laminar interface Together, these vascular alterations create a cycle of ischemia, inflammation, and tissue damage that drives the progression of laminitis [24]

3.3. Inflammatory Processes

Systemic or local inflammation (e.g., systemic inflammation or bacterial toxins) stimulate the release of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukins (IL-1β, IL-6). These cytokines amplify inflammation, causing further damage to the laminae and trigger the activation of enzymes like the matrix metalloproteinases (MMP) [21]. MMPs, particularly MMP-2 and MMP-9, are enzymes that degrade the extracellular matrix within the laminar tissues. Excessive MMP activation, often triggered by inflammation, weakens the laminar bond. Overactivation of MMPs is a characteristic of laminitis [27]. The radical oxygen species (ROS) generated during reperfusion injury and inflammation also cause cellular damage, further impairing the function of the laminar cells and exacerbating tissue injury [28].

3.4. Metabolic Dysregulation

Insulin and glucose dysregulation are key features in laminitis. Insulin resistance, commonly seen in equine metabolic syndrome (EMS) and Cushing's Diseases (PPID), is considered a predisposing factor in laminitis. High insulin levels (hyperinsulinemia) disrupt normal cellular function in the laminae. Insulin also alters vascular tone, promoting prolonged vasodilation and increasing the risk of oedema [29, 30]. Laminar epithelial cells rely on glucose for energy. Vascular compromise due to ischemia or metabolic dysfunction reduces glucose availability, impairing cell function and integrity [31].

3.5. Mechanical Stress and Structural Changes

Supporting-limb laminitis occurs as a consequence of excessive weight-bearing on one limb, typically due to an injury in the opposite limb. This redistribution of weight places prolonged mechanical stress on the overloaded limb, leading to ischemia within the laminar tissues. Over time, sustained pressure exacerbates vascular compromise, resulting in progressive laminar damage and further weakening of the hoof's structural integrity [32].

The condition is often associated with suspensory failure, where the laminar bond between the sensitive and insensitive laminae is compromised due to inflammation and enzymatic degradation. This failure leads to two significant pathological outcomes. First, rotation of the coffin bone occurs as the pull of the deep digital flexor tendon (DDFT) causes the coffin bone to rotate downward, away from the hoof wall within the hoof capsule. This misalignment disrupts the biomechanics of the hoof and increases the risk of irreversible structural damage [15]. Second, sinking of the coffin bone may result from the complete loss of laminar integrity, leading to the downward displacement of the coffin bone. This displacement compresses the underlying sensitive structures, causing severe pain and compromising hoof function [22].

Additionally, pressure imbalance within the hoof further exacerbates tissue damage. Increased pressure from laminar oedema, coffin bone displacement, or both contributes to the compression of sensitive tissues, intensifying pain and functional impairment. These mechanical and vascular changes create a cycle of inflammation, structural degradation, and mechanical failure that significantly worsens the prognosis for affected horses.

3.6. Neural and Pain Responses

Nociception plays a central role in the clinical presentation of laminitis, as damage to the laminar tissues stimulates pain receptors, or nociceptors, within the hoof. This nociceptive signalling contributes to the characteristic lameness observed in laminitic horses. Affected horses often adopt a "laminitic stance," where they shift their weight to the hind limbs or other less-affected limbs to minimize pressure on the painful areas. This pain response is not only a significant welfare concern but also an important diagnostic indicator of laminitis progression [23].

The activation of the sympathetic nervous system (SNS) further the condition. Pain and stress associated with laminitis trigger the SNS, leading to heightened vasoconstriction in the hoof. This vasoconstriction furthers ischemia and impairs tissue perfusion, perpetuating the cycle of hypoxia and tissue damage. The interplay between nociception, SNS activation, and vascular dysregulation highlights the multifactorial nature of laminitis pathophysiology and underlines the importance of effective pain management and vascular support in treatment strategies [24].

3.7. Clinical Correlation

The clinical presentation of laminitis reflects the underlying inflammatory, vascular, and mechanical changes within the hoof. Affected horses often exhibit a reluctance to move, weight-shifting or adopt a "rocked-back" posture to alleviate pressure on the painful limbs. These signs are primarily a result of inflammation, oedema, and increased mechanical pressure within the hoof capsule. The presence of increased hoof temperature and bounding digital pulses further indicates heightened vascular activity and inflammation within the affected hoof [15].

Radiographic findings provide critical diagnostic insights, particularly in advanced stages of laminitis. Common observations include rotation or sinking of the coffin bone, which result from the progressive failure of the laminar bond. Additionally, a widened white line visible on radiographs is indicative of laminar separation, reflecting the structural compromise of the hoof's suspensory apparatus [22].

The pathophysiology of equine laminitis is a sequence of vascular, inflammatory, metabolic, and mechanical factors that ultimately compromise the laminar interface. Each of these mechanisms contributes to the progressive degeneration of laminar integrity, leading to significant clinical and structural consequences.

Understanding these processes is essential for early diagnosis, effective management, and the prevention of long-term damage. Advances in research continue to improve our understanding of the mechanisms underlying laminitis, offering hope for the development of improved therapeutic strategies and preventative measures in the future.

4. Prominent causes of Equine Laminitis

Equine laminitis has several recognized causes, as referenced in both (**Figure 3)** and **(Table 1)**, each with distinct pathophysiological mechanisms. These causes can be broadly categorized into endocrinopathic, inflammatory (sepsis-associated), and mechanical forms. Understanding these mechanisms is essential for effective diagnosis, treatment, and prevention.

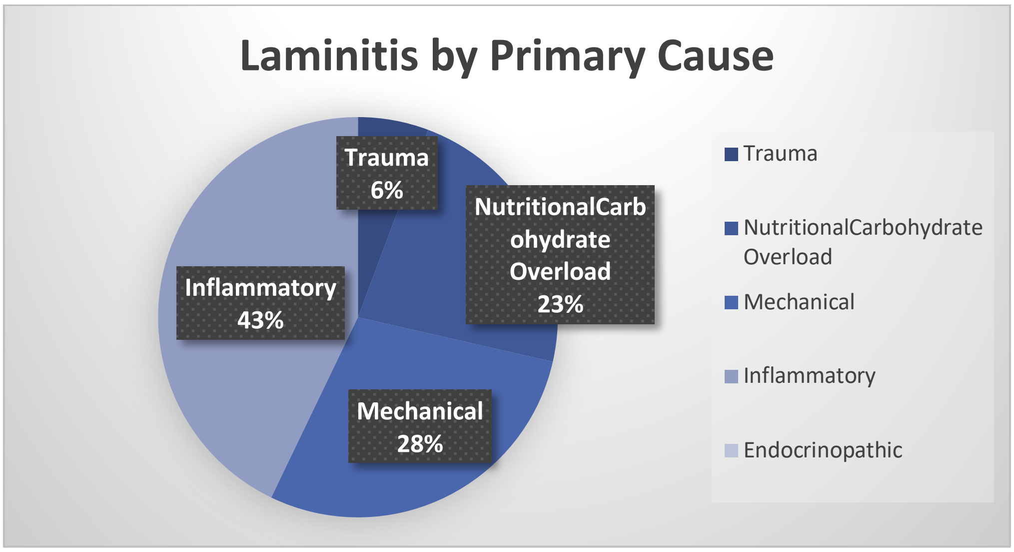

Figure 3: Primary causes of laminitis [20]

4.1. Endocrinopathic Laminitis

Endocrinopathic Laminitis is primarily associated with hormonal imbalances, commonly observed in conditions such as Equine Metabolic Syndrome (EMS), Pituitary Pars Intermedia Dysfunction (PPID, or equine Cushing's disease), obesity, or chronic hyperinsulinemia. Hyperinsulinemia, characterized by elevated insulin levels in the bloodstream, is a hallmark feature of endocrinopathic laminitis [33]. Although the exact mechanisms are still not fully understood, several pathological processes have been identified. Vascular dysfunction induced by insulin dysregulation leads to excessive and prolonged vasodilation in the laminar capillaries, increasing capillary permeability and resulting in tissue oedema and compression within the hoof capsule [1, 29]. Insulin also alters laminar cell function by disrupting glucose uptake and metabolism in laminar epithelial cells. This impairment weakens cellular repair mechanisms, increasing susceptibility to structural damage [4]. Additionally, increased matrix metalloproteinase (MMP) activity in response to hyperinsulinemia contributes to the degradation of the extracellular matrix, further weakening the bond between the hoof wall and coffin bone [5].

4.2. Inflammatory (Sepsis-Associated) Laminitis

Sepsis-Associated Laminitis occurs secondary to systemic inflammatory conditions, including colitis or enteritis (e.g. from grain overload or bacterial infections), pneumonia or pleuropneumonia, retained placenta in post-parturient mares, or other severe infections leading to endotoxemia. Endotoxin release, particularly from Gram-negative bacterial infections, triggers systemic inflammation by introducing lipopolysaccharides (LPS) into circulation. Endotoxins activate immune receptors, initiating an inflammatory cascade involving cytokines such as TNF-α and IL-1β, as well as prostaglandins [3]. This systemic inflammatory response leads to vascular changes, including vasodilation and increased vascular permeability, resulting in laminar oedema and ischemia. Ischemia deprives laminar cells of oxygen and nutrients, while subsequent reperfusion generates reactive oxygen species (ROS), exacerbating tissue damage [28]. Matrix metalloproteinase activation is another critical factor, as inflammatory cytokines upregulate MMP activity, promoting extracellular matrix degradation and laminar detachment [21]. In severe cases, disseminated intravascular coagulation (DIC) may occur, with microthrombi forming in the laminar capillaries, further restricting blood flow and contributing to progressive laminar damage [10].

4.3. Mechanical (Support-Limb) Laminitis

Mechanical (Support-Limb) Laminitis arises from excessive weight-bearing on a single limb, typically due to injury or lameness in the contralateral limb, prolonged immobility, or poor hoof care. Prolonged compression of the weight-bearing limb's laminae leads to localized ischemia by compressing blood vessels. This reduction in vascular perfusion results in hypoxia and impaired cellular metabolism within the laminar tissues [14]. As the condition progresses, vascular dysregulation occurs with ischemia followed by reperfusion injury, which exacerbates oxidative stress and tissue damage [15]. Additionally, structural fatigue of the laminar bond can develop under sustained mechanical stress, even in the absence of systemic inflammation or metabolic dysfunction [32].

4.4. Nutritional/Carbohydrate Overload

Carbohydrate Overload is a significant cause of laminitis, often resulting from the overconsumption of fermentable carbohydrates, such as grains or lush pasture. The pathophysiology begins with gut dysbiosis, where the rapid fermentation of carbohydrates in the hindgut produces excessive lactic acid, leading to a reduction in pH. This acidic environment disrupts the balance of gut microbiota, killing beneficial bacteria and compromising the integrity of the intestinal lining. The breakdown of gut barrier function allows endotoxins and bacterial byproducts to enter systemic circulation, initiating a cascade of inflammatory events [34].

The endotoxemia triggers systemic inflammation, characterized by widespread vasodilation, vascular leakage, and laminar oedema. These changes impair the hoof's structural stability and function [28]. An inflammatory cascade, mediated by cytokines and other inflammatory mediators, stimulates matrix metalloproteinase (MMP) activity, which degrades the extracellular matrix of the laminae and weakens the bond between the hoof wall and coffin bone [5]. Simultaneously, vascular changes driven by endotoxemia include vasoconstriction and the formation of microthrombi in the laminar capillaries. These events lead to ischemia causing further damage to the laminar tissues [1].

4.5. Trauma or Direct Injury

Trauma or Direct Injury to the hoof is another recognized cause of laminitis and occurs following excessive concussion on hard surfaces or penetrating injuries. The pathophysiological response to trauma involves an inflammatory response, where physical injury induces localized inflammation, increased vascular permeability, and laminar oedema. This inflammation disrupts normal laminar function and contributes to pain and tissue damage [1]. Additionally, mechanical disruption caused by direct damage to the laminae or surrounding structures can physically weaken the bond between the hoof wall and the coffin bone. This mechanical compromise aggravates the loss of structural stability, further impairing the hoof's ability to bear weight and maintain normal function [19].

4.6. Comparison of Pathophysiological Mechanisms

Table 1: A comparison of the pathophysiological mechanisms associated with the causes of laminitis

Cause	Primary Mechanisms	Secondary Effects
Endocrinopathic	Hyperinsulinemia, vascular dysregulation, altered glucose metabolism	Prolonged vasodilation, laminar cell dysfunction, ECM degradation
Inflammatory	Endotoxemia, systemic inflammation, cytokine release, MMP activation	Laminar oedema, ischemia, reperfusion injury, oxidative stress
Mechanical	Prolonged weight-bearing, ischemia from vascular compression	Laminar hypoxia, structural fatigue, secondary inflammation
Carbohydrate Overload	Gut dysbiosis, endotoxemia, lactic acidosis	Systemic inflammation, MMP activation, microthrombi formation
Trauma/Direct Injury	Physical disruption of laminar tissues	Localized inflammation, mechanical weakening, secondary infection

Equine laminitis has a diverse range of causes that all lead to the disruption of the laminar tissue of the foot, either through vascular compromise, inflammatory cascades, metabolic dysregulation, or mechanical overload. Early identification of the underlying cause and targeted intervention is essential to prevent the progression of the condition and minimize long-term damage.

5. Diagnosis of Equine Laminitis

The diagnosis of equine laminitis relies on a combination of clinical examination, diagnostic imaging, and laboratory tests. Early detection is imperative to prevent irreversible damage to the laminae and improve the prognosis. Understanding the physiology of metabolic and inflammatory pathways that lead to laminitis can aid in the identification of specific biomarkers and improve diagnostic accuracy.

5.1 Clinical Examination

Clinical evaluation remains the gold standard for diagnosing laminitis, with specific signs providing critical insights into the severity and progression of the condition. Lameness is a key feature and is commonly graded using the Obel Lameness Scale. This scale ranges from mild weight-shifting behaviour (grade 1) to complete refusal to bear weight on the affected limbs (grade 4), offering a standardized approach to assess severity [35]. Lameness often reflects the underlying inflammation, structural damage, and mechanical dysfunction of the hoof.

Another common finding during clinical examination is hoof sensitivity, particularly when hoof testers are applied over the toe region. Increased sensitivity in this area is indicative of laminar inflammation and mechanical stress, which are characteristic of laminitis. Postural changes are also frequently observed in affected horses. The characteristic "laminitic stance," where the horse shifts its weight to the hind limbs, is an adaptive mechanism to relieve pressure on the more painful front hooves. This posture not only highlights the severity of the condition but also serves as a diagnostic purpose [36].

Bounding digital pulses in the digital arteries are another key diagnostic sign, reflecting inflammation and vascular dysregulation within the hoof. These palpable pulses indicate increased blood flow and vascular activity, which often accompany the inflammatory processes in laminitic horses [6]. Together, these clinical signs form a comprehensive framework for the diagnosis of laminitis, emphasizing the importance of thorough physical examination and the application of standardized diagnostic scales.

5.2. Diagnostic Imaging

Imaging technologies are invaluable in the evaluation of structural and functional changes in the hoof associated with laminitis. Radiography remains the primary diagnostic tool, providing critical information about bone and hoof alignment. Standard radiographs can detect key pathological changes, such as coffin bone rotation, where the coffin bone becomes displaced relative to the hoof wall, and sinking (or "founder"), characterized by vertical displacement of the coffin bone within the hoof capsule. Quantitative radiographic measurements, including the Founder Distance, the distance between the dorsal hoof wall and the dorsal aspect of the coffin bone, are particularly valuable for assessing the severity of laminitis. Ideally, the dorsal hoof wall should remain parallel to the dorsal aspect of the coffin bone, and deviations from this alignment indicate progressive structural failure [2].

Thermography is another valuable imaging modality, particularly in early or subclinical cases of laminitis. This technique detects abnormal heat patterns in the hoof, which are indicative of inflammatory changes. Thermography can provide early warning of laminar inflammation before lameness becomes clinically apparent, making it a useful tool for monitoring horses at risk of developing laminitis [6].

Advanced imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), offer detailed three-dimensional visualization of internal hoof structures. These imaging tools are particularly useful for assessing soft tissue and vascular damage, including laminar separation, oedema, and other subtle changes that may not be visible on standard radiographs. By providing a comprehensive view of both the bony and soft tissue components of the hoof, CT and MRI allow for a more thorough understanding of the extent of laminar damage and therefore more targeted therapeutic interventions [1].

5.3. Laboratory Testing

Advances in understanding the metabolic and inflammatory pathways underlying laminitis have facilitated the development of laboratory-based diagnostic tools. Endocrine testing plays a pivotal role in diagnosing endocrinopathic laminitis, particularly in identifying hyperinsulinemia, a key feature of this condition. Insulin testing involves measuring insulin concentrations through various methods, including the assessment of resting insulin levels and dynamic testing such as the Oral Sugar Test (OST). The OST evaluates the insulin response to dietary carbohydrates, providing a more sensitive measure of insulin dysregulation, which is central to the pathogenesis of endocrinopathic laminitis [4]. Additionally, the measurement of adrenocorticotropic hormone (ACTH) levels is essential for diagnosing Pituitary Pars Intermedia Dysfunction (PPID), another common endocrine disorder associated with laminitis. Elevated ACTH levels indicate dysfunction of the pituitary gland, which contributes to the development of laminitis in affected horses.

The role of inflammation in laminitis, particularly in sepsis-associated forms, highlights the importance of inflammatory markers in diagnostic evaluations. Increased levels of cytokines, such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), in plasma or laminar tissue are indicative of systemic inflammation and local inflammatory responses within the hoof. These markers provide insights into the severity of the inflammatory processes involved in causing laminar damage [3].

In addition to inflammatory mediators, oxidative stress biomarkers are emerging as significant indicators of laminitis. Elevated levels of reactive oxygen species (ROS) and a concurrent decrease in antioxidant enzyme activity have been linked to oxidative stress in laminitic horses. These changes reflect the imbalance between pro-oxidants and antioxidants, contributing to cellular damage and weakening of the laminar bond [8]. Together, these laboratory-based diagnostics complement clinical and imaging evaluations, enhancing the early detection, monitoring, and management of laminitis.

5.4. Emerging Biomarkers

Recent advances in molecular biology have led to the identification of potential biomarkers that may facilitate the early detection of laminitis. Among these, matrix metalloproteinases (MMPs) have emerged as critical indicators of laminar degradation. Specifically, increased activity of MMP-2 and MMP-9 has been linked to the breakdown of the extracellular matrix within the laminae during the development of laminitis. These enzymes are upregulated in response to inflammatory mediators and metabolic dysregulation, contributing to the weakening of the laminar bond and the progression of structural damage in the hoof [5].

Another promising biomarker is plasma lactate levels, which reflect systemic inflammation and tissue ischemia, both of which are central to laminitis development. Elevated lactate concentrations indicate impaired oxygen delivery to tissues, a key component of ischemic processes, and are associated with the metabolic stress observed in laminitic horses. Monitoring lactate levels may offer a valuable tool for assessing the severity of laminitis and guiding early therapeutic interventions.

The identification and validation of these biomarkers represent significant advancements in the understanding of laminitis at a molecular level. These advancements in diagnostics tools suggest further improvements in early diagnosis, monitoring, and management of this often disease.

5.5. Challenges in Diagnosis

Subclinical laminitis presents a significant diagnostic challenge, as horses with mild or intermittent symptoms may go undiagnosed until substantial laminar damage has already occurred. Early detection is often hindered by the subtlety of clinical signs, which may not prompt immediate veterinary attention. Furthermore, the overlap of clinical signs with other hoof-related conditions, such as abscesses or sole bruising, complicates the diagnostic process. These similarities provide the grounds for a thorough and systematic approach to accurately differentiate laminitis from other potential causes of lameness.

The diagnosis of laminitis requires a multidisciplinary approach, integrating clinical examination, imaging techniques, and laboratory testing. Advances in understanding the physiological disruptions associated with metabolic and inflammatory pathways have significantly enhanced diagnostic capabilities. These developments are particularly valuable in identifying subclinical or early-stage laminitis, where intervention may prevent progression to more severe stages. Imaging modalities such as radiography, thermography, and MRI, along with the assessment of biomarkers like MMP activity or inflammatory cytokines, provide valuable tools for diagnosing laminitis at the early stages [2].

Future advancements in research hold promise for further improving diagnostic accuracy. The continued development of biomarkers and advanced imaging technologies offers potential for earlier detection and more precise characterization of laminitis. These developments, combined with a comprehensive diagnostic framework, could enable more targeted and effective treatment plans for cases, ultimately improving outcomes for affected horses.

6. Treatment Methods of Equine Laminitis Based on the Pathophysiology

Effective treatment and prevention of equine laminitis are based on addressing the underlying causes and interrupting the pathophysiological mechanisms, such as inflammation, vascular dysregulation, metabolic dysfunction, and mechanical stress. Below are the recommended treatment options currently available.

6.1. Treatment Methods

6.1.1. Early Detection and Intervention

Early identification of clinical signs is crucial for the prompt diagnosis and management of equine laminitis. Key indicators include reluctance to move, weight-shifting behaviour, increased heat in the hooves, and bounding digital pulses. These signs reflect the underlying inflammatory and vascular changes occurring within the hoof and serve as critical early markers of laminar compromise [1, 15]. Recognizing these clinical manifestations allows for prompt intervention, potentially mitigating further progression of the condition.

Objective diagnostic tools play a pivotal role in confirming laminitis and monitoring its progression. Hoof testers can be employed to detect localized pain or sensitivity within the hoof capsule. Advanced diagnostic modalities, such as thermography, provide non-invasive means to assess increased vascular activity and localized inflammation. Radiographic imaging remains the gold standard for visualizing laminar damage, enabling the identification of critical changes such as coffin bone rotation or sinking and structural compromise within the hoof's suspensory apparatus [2, 6]. Together, these tools provide a comprehensive framework for the diagnosis, assessment, and management of laminitis in equine patients.

6.1.2. Inflammatory Control

The management of equine laminitis often incorporates the use of non-steroidal anti-inflammatory drugs (NSAIDs) to alleviate pain and inflammation. Commonly used NSAIDs, such as phenylbutazone and flunixin meglumine, function by inhibiting cyclooxygenase enzymes (COX-1 and COX-2). This inhibition reduces the synthesis of inflammatory prostaglandins, thereby diminishing both the inflammatory response and associated discomfort. These drugs are a leading treatment of laminitis, targeting the underlying inflammatory mechanisms while improving the animal's comfort and mobility [3].

Cryotherapy, or ice therapy, is another widely used intervention, particularly during the developmental and early acute phases of laminitis. This approach involves submerging the affected hoof in ice water or various other methods of cooling the foot, effectively reducing inflammation and enzymatic activity within the hoof capsule. The therapeutic benefits of cryotherapy are attributed to its ability to lower tissue temperature, thereby inhibiting the activity of matrix metalloproteinases (MMPs) and decreasing vascular permeability. By combating these pathological processes, cryotherapy can limit the progression of laminar damage and preserve hoof integrity [22, 28]. Together, NSAIDs and cryotherapy represent key strategies in the complex management of laminitis, offering both symptomatic relief and the potential to minimize structural compromise.

6.1.3. Vascular Support

Vascular support is a critical component in the management of equine laminitis, as compromised blood flow to the laminae exacerbates tissue damage and inflammation. Vasodilators, such as acepromazine, are given to enhance blood flow by dilating blood vessels, thereby improving perfusion to the affected laminar tissues. This mechanism helps counteract ischemia and supports the delivery of nutrients and oxygen essential for tissue repair and recovery [14].

In addition to vasodilation, anticoagulant therapies may play a role in reducing laminar damage. Low-dose aspirin and heparin are frequently used to prevent microthrombosis within the laminar capillaries. These agents act by inhibiting platelet aggregation or enhancing anticoagulant pathways, reducing the risk of capillary obstruction, and maintaining microvascular integrity [1].

Hydration management is another key strategy in promoting adequate vascular function. Ensuring systemic hydration optimizes the blood volume and supports consistent perfusion to the laminae. This approach complements pharmacological interventions by addressing the systemic factors influencing vascular health and hoof perfusion [19]. Together, these measures form a comprehensive vascular support strategy aimed at minimizing ischemic damage and facilitating recovery in horses with laminitis.

6.1.4. Mechanical Support

Hoof trimming and therapeutic shoeing are essential mechanical interventions in the management of equine laminitis. Corrective trimming aims to redistribute weight away from the compromised laminae, thereby alleviating mechanical pressure and promoting a more balanced load distribution across the hoof. Specialized shoes, such as heart-bar or wedge shoes, are often utilized in conjunction with trimming. These shoes provide additional structural support to the hoof, stabilize the coffin bone, and enhance the overall biomechanics of the limb. By addressing mechanical stressors, these interventions contribute to pain relief and facilitate recovery [2].

In addition to trimming and shoeing, proper padding and bedding are vital for reducing mechanical stress on the hooves. Providing soft, supportive bedding—such as sand, foam, or rubber mats—can cushion the affected limbs and minimize pressure on the sole. Foam or rubber pads placed directly on the hoof offer further shock absorption, enhancing comfort for the horse while protecting the integrity of the laminar structures. These measures, when combined with other therapeutic strategies, help mitigate the mechanical challenges posed by laminitis and support the recovery process [16].

6.1.5. Metabolic Management

Dietary adjustments are a major factor in the management of equine laminitis, particularly in cases linked to metabolic disorders. Reducing the intake of high-carbohydrate feeds and sugar-rich forage, such as lush grass, is essential for stabilizing glucose and insulin levels. Diets low in sugar and high in fibre are recommended, as they promote metabolic stability and minimize the risk of exacerbating laminar inflammation or structural damage. These nutritional strategies are particularly relevant in horses with insulin dysregulation, where strict dietary control can significantly reduce the risk of laminitis recurrence [4].

Endocrine treatments play a crucial role in managing laminitis associated with underlying metabolic disorders such as Equine Metabolic Syndrome (EMS) and Pituitary Pars Intermedia Dysfunction (PPID). For EMS, weight loss programs combined with pharmacological interventions, such as Metformin, are employed to enhance insulin sensitivity and regulate metabolic function. In cases of PPID, Pergolide Mesylate remains the treatment of choice, effectively managing hormonal dysregulation and reducing the associated risk of laminitis. These endocrine therapies, when integrated with dietary management and other supportive measures, address the root causes of metabolic imbalances, and improve clinical outcomes in affected horses [1, 29].

6.1.6. Pain Management

Effective pain management is a critical aspect of laminitis treatment, aiming to improve both the welfare and functionality of the affected horse. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line therapy, offering significant pain relief through their anti-inflammatory effects. However, in severe cases where NSAIDs alone are insufficient, additional analgesic measures may be required. These can include the use of Opioids for pain control or the administration of Nerve blocks to provide temporary localized relief. Such interventions are critical for maintaining the horse's comfort while minimizing stress and further damage to the laminar structures [3].

Physical activity is another important aspect of laminitis management, emphasizing controlled and limited movement. Encouraging gentle, limited activity helps to reduce stiffness and maintains joint flexibility while improving circulation to the hooves. Increased blood flow supports healing by delivering oxygen and nutrients to the damaged laminae. Careful monitoring during physical therapy ensures that movement does not exacerbate the condition, striking a balance between promoting circulation and avoiding mechanical stress on the hoof [15]. Together, these approaches contribute to a comprehensive strategy for managing pain and supporting recovery in horses with laminitis.

6.1.7. Surgical Interventions

Innovative therapies are being explored to address the underlying pathophysiological mechanisms of laminitis. Gene therapy targeting inflammatory cytokine pathways, such as tumor necrosis factor-alpha (TNF-α) inhibitors, is under investigation as a potential strategy to prevent laminar degradation by interrupting the inflammatory cascade [10]. Similarly, stem cell therapy, particularly the use of mesenchymal stem cells, shows promise in regenerating damaged laminar tissue. These cells promote angiogenesis, reduce inflammation, and support tissue repair, offering a novel approach to laminitis treatment [8].

7. Preventative Measures of Equine Laminitis

7.1. Prevention Methods

7.1.1. Managing Risk Factors

Prevention of laminitis begins with managing dietary and metabolic risk factors. Controlling carbohydrate intake by limiting grain consumption and access to lush pastures, especially during high-risk periods such as spring and fall, is essential to prevent carbohydrate overload and insulin dysregulation [4, 28]. Weight management is equally critical, as maintaining a healthy body condition score reduces mechanical stress on the hooves and decreases the risk of insulin resistance, a key factor in endocrinopathic laminitis [29]. Regular exercise also supports metabolic health by improving insulin sensitivity and preventing obesity in predisposed horses [4].

7.1.2. Monitoring Metabolic Health

Routine metabolic health assessments play a crucial role in early detection and management of conditions associated with laminitis. Regular blood tests to monitor glucose and insulin levels are recommended for horses at risk of Equine Metabolic Syndrome (EMS) or Pituitary Pars Intermedia Dysfunction (PPID) [1, 30]. Proactive treatment of these disorders, including the use of pergolide for PPID and dietary management for EMS, helps mitigate the risk of laminitis development [4, 29].

7.1.3. Hoof Care

Consistent hoof care is essential for reducing mechanical stress and maintaining hoof integrity. Routine trimming ensures proper hoof alignment, minimizing abnormal forces on the laminae and decreasing the risk of mechanical laminitis [2]. In horses with a history of laminitis, preventative shoeing with therapeutic options such as heart-bar shoes provides additional support and reduces the likelihood of recurrence [16].

7.1.4. Managing Environmental and Systemic Risks

Environmental and systemic factors also play a role in laminitis prevention. Limiting prolonged confinement and encouraging movement help maintain circulation and reduce the risk of vascular dysfunction [15]. Careful management of weight-bearing in injured horses, including the use of therapeutic shoeing or hoof pads, can prevent support-limb laminitis by alleviating stress on the unaffected limbs [14]. Prompt treatment of systemic infections, such as those caused by retained placenta, colitis, or sepsis, is essential to prevent systemic inflammation and subsequent laminar damage [3, 10].

7.1.5. Stress Management

Minimizing stress is an important preventative strategy, as stress can exacerbate metabolic and vascular dysfunction, increasing the risk of laminitis. Providing a calm environment and consistent routines helps mitigate stress-related risks [1]. Effective pain control for concurrent conditions also reduces compensatory weight-bearing issues that could lead to secondary laminitis [19].

7.1.6. Integration of Pathophysiological Insights

Prevention strategies informed by the pathophysiology of laminitis offer targeted approaches to reduce the risk of disease progression. Vascular compromise can be addressed through the use of cryotherapy and vasodilators, such as acepromazine, to mitigate ischemia and edema [22, 34]. Inflammatory processes can be controlled with NSAIDs and cytokine inhibitors, such as TNF-α inhibitors, to protect laminar tissues [3, 10]. Cryotherapy also inhibits matrix metalloproteinases (MMPs), preventing enzymatic degradation of the extracellular matrix and preserving the laminar bond [22, 28]. Finally, stabilizing metabolic dysregulation through endocrine treatments, such as pergolide, and dietary management helps maintain glucose and insulin homeostasis, thereby protecting laminar cell function [4, 29].

The treatment and prevention of equine laminitis require a multifaceted approach bases on a thorough understanding of its pathophysiology. Early interventions targeting vascular, inflammatory, and metabolic pathways are critical to minimizing laminar damage and preventing long-term complications. Preventative measures focusing on diet, metabolic health, hoof care, and environmental management are equally important for maintaining hoof integrity and reducing the risk of recurrence. Advances in therapeutic and preventative strategies offer hope for improving outcomes in horses affected by this debilitating condition.

7.1.7 Economic impact of Equine Laminitis

The economic impact of the various factors associated with equine laminitis, highlighting the financial burden on horse owners and caretakers is illustrated below in **(Figure 4).**

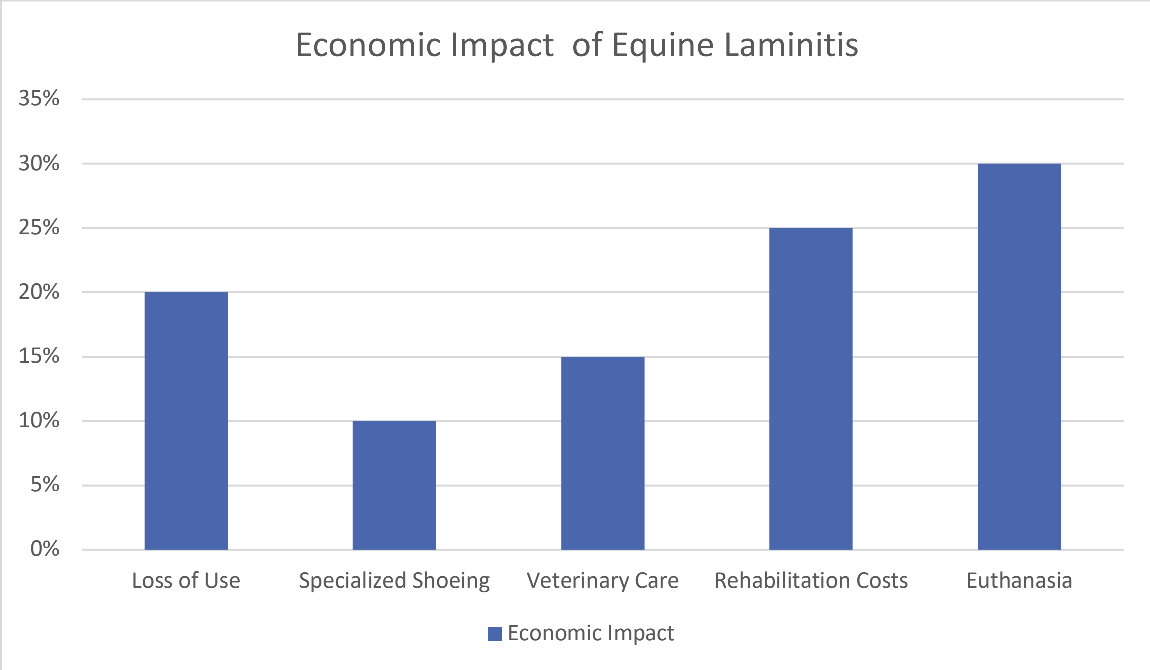

Figure 4: The economic impact of laminitis [15].

Laminitis imposes substantial economic burdens on horse owners, arising from the multifaceted nature of its management and consequences. In severe cases where treatment is no longer viable, euthanasia may become the only humane option. This not only incurs direct costs such as veterinary fees and disposal expenses but also causes significant emotional toll on owners. Euthanasia-related expenses account for approximately 30% of the financial burden associated with laminitis, highlighting the devastating impact of the condition in its most severe forms [1].

Chronic laminitis cases contribute significantly to long-term costs through rehabilitation efforts, which account for an estimated 25% of expenses. Prolonged management often involves physical therapy, specialized dietary regimens, and ongoing farrier care to stabilize the affected hooves and maintain quality of life. These cumulative costs stresses the importance of effective long-term care strategies for horses with chronic laminitis [17].

Loss of use represents another substantial financial challenge, contributing to approximately 20% of the total economic impact. Horses affected by laminitis frequently lose their ability to perform in work, competition, or breeding, resulting in significant economic losses for their owners. This loss of utility underscores the critical need for early diagnosis and effective treatment to preserve the horse's functional capabilities [13].

Veterinary care for acute cases accounts for an additional 15% of costs, encompassing diagnostic evaluations, medications, and supportive therapies. These expenses are often incurred early in the disease course, reflecting the urgent need for immediate intervention to mitigate further damage [15].

Specialized shoeing, including corrective and therapeutic hoof care, is an essential component of laminitis management. This contributes approximately 10% to the overall economic burden and involves recurring costs to stabilize hoof structures and alleviate pain in affected horses [14].

These findings align with previous research highlighting the significant economic and emotional toll of laminitis. They emphasize the importance of early diagnosis and preventative measures to reduce long-term costs. By targeting the underlying pathophysiology and intervening promptly, owners can alleviate financial burdens while improving equine welfare and preserving the horse’s functionality [10].

8. Conclusion

Equine laminitis is a complex and multifactorial condition that represents a critical challenge in equine medicine due to its devastating impact on equine welfare and its economic implications. This thesis has explored the physiological disturbances in inflammatory and metabolic regulatory pathways that underpin the development of this debilitating disease, emphasizing the intricate interplay of vascular compromise, inflammation, enzymatic activity, and metabolic dysfunction.

The findings reveal that the pathophysiology of laminitis is driven by dysregulated inflammatory signalling, with key mediators such as cytokines and matrix metalloproteinases (MMPs) contributing to laminar degradation [5, 21]. Simultaneously, metabolic disturbances—most notably insulin dysregulation in conditions like Equine Metabolic Syndrome (EMS) and Pituitary Pars Intermedia Dysfunction (PPID)—exacerbate laminar stress by disrupting vascular tone, glucose metabolism, and cellular energy supply [4, 29, 30]. These interconnected pathways ultimately compromise the integrity of the suspensory apparatus of the hoof, leading to clinical manifestations such as pain, lameness, and, in severe cases, mechanical failure of the hoof's structural framework [14, 15].

From a clinical perspective, understanding these physiological disruptions has been instrumental in advancing diagnostic and therapeutic approaches. Cryotherapy has proven effective in the early stages by reducing inflammation and enzymatic activity [22]. NSAIDs, such as flunixin meglumine, have also demonstrated efficacy in controlling inflammation by targeting the prostaglandin pathway [3]. However, significant gaps remain in early detection, effective intervention, and long-term management. Tools such as thermography and biomarkers, including MMP-9 and cytokine levels, are emerging as valuable aids for early diagnosis [6, 10].

While treatments targeting inflammation, vascular dysfunction, and metabolic stability show promise, prevention remains the most reliable strategy in combating laminitis [1]. Proactive management of risk factors—such as dietary regulation, endocrine health, and hoof care—combined with emerging technologies in molecular diagnostics and biomechanical analysis, offers hope for mitigating the impact of this disease [2, 12, 16].

In conclusion, the insights gained from this exploration of inflammatory and metabolic regulatory disturbances not only deepen our understanding of equine laminitis but also highlight the need for a multidisciplinary approach in addressing this condition. Future research focusing on molecular pathways and translational therapies, such as gene therapy targeting TNF-α or stem cell therapy for tissue regeneration, has the potential to revolutionize the prevention and management of laminitis, ultimately improving the welfare of horses worldwide [8, 28].

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