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Pathological changes and clinical use of the measurement of serum/plasma concentrations of insulin-like growth factor type 1 (IGF-1) in horses, dogs and cats

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Abstract. The biological effects of the growth hormone are in part mediated by the release of insulin-like growth factor type 1 (IGF-1) by the liver but also from other non-hepatic tissues. As opposite as GH, IGF-1 is not release in an episodic manner, is stable in the bloodstream and has a long biological half-life. As a consequence, the measurement of serum IGF-1 is an indirect way to measure GH. The present article reviews the alterations in serum IGF-1 concentrations in veterinary medicine, focused mainly in the diagnosis and prognosis of liver, heart, musculoskeletal, endocrine diseases and tumors. Some applications of the measurements of serum IGF-1 concentrations in sport horses are also provided.
Key Words: cats, dogs, growth hormone, horses, insulin-like growth factor, veterinary medicine.

Resumen. Los efectos biológicos de la hormona del crecimiento vienen determinados en parte por la liberación del factor de crecimiento tipo 1 (IGF-1) fundamentalmente por el hígado, pero también por otros tejidos no hepáticos. Al contrario de lo que ocurre con la hormona GH, el IGF-1 no se libera de forma pulsátil, es estable en circulación periférica y tiene una vida media prolongada. Por ello, la medición de las concentraciones de IGF-1 es una forma indirecta de determinar los niveles de GH. El presente artículo revisa las alteraciones en las concentraciones séricas de IGF-1 en medicina veterinaria, centrándose sobre todo en el diagnóstico y pronóstico de enfermedades hepáticas, cardiacas, músculo-esqueléticas, endocrinas y oncológicas. Finalmente, se describen algunas aplicaciones de la medición de IGF-1 en caballos de deporte.
Palabras clave: gato, perro, hormona del crecimiento, factor de crecimiento similar a la insulina, medicina veterinaria.

Introduction. Growth hormone (GH) or somatotropin (ST) is a protein synthesized in the anterior pituitary gland and secreted in an episodic manner in different animal species, including horses (Stewart et al 1993; Thompson et al 1994), dogs (Lee et al 2003) and ruminants (Breier & Sauerwein 1995). The action of GH on tissues is mediated in part by insulin-like growth factor I (IGF-1), which is secreted primarily from the liver but also from other non-hepatic tissues to act in an endocrine-autocrine-paracrine fashion (LeRoith & Robers 1991). Serum/plasma concentrations of IGF-1 in man and domestic animals are relatively stable due to its long biological half-life with no obvious diurnal rhythm (Breier & Sauerwein 1995). Additionally, IGF-1 measurements are performed in more veterinary laboratories than GH. Therefore, the measurement of serum IGF-1 concentrations is very useful in determining the level of activity of the somatotrophic axis, as GH measurement provides very little information due to its pulsatile secretion.

The measurements of the serum IGF-1 concentrations might have substantial clinical applications. Their circulating levels may increase or decrease in response to different diseases and they can serve as useful biomarkers in the diagnosis of these diseases, as well as in the monitoring of their course. It is already known that that serum IGF-1 concentrations are affected by many physiological factors, such as animal species,

body weight and body size, breed (Eigenmann et al 1983ab; Ozawa et al 1995; Riber et al 2009; Muñoz et al 2010), age (Malinowski et al 1996; Champion et al 2002; Fortier et al 2005; Noble et al 2007; Riber et al 2009), sex (Stewart et al 1993; Thompson et al 1994), circadian rhythms and environmental conditions (Noble et al 2007), diet (Treiber et al 2005; Staniar et al 2007), exercise and training (Jackson et al 2003; Noble et al 2007).

The following article reviews the most recent findings on the changes on IGF-1 concentrations in different clinical situations in dogs, cats and horses. This information is summarized in tables 1, 2 and 3. It is pursued to summarize our current knowledge of the use of the measurements of serum IGF-1 in equine and small animal medicine. However, unfortunately, scientific information regarding the effect of diseases on IGF-1 in veterinary medicine is scare in comparison to human medicine.

Serum IGF-1 Concentrations in Liver Diseases. IGF-1 is mainly produced in the liver and therefore, any factor that impairs liver parenchyma and resultant in hepatocyte dysfunction may lead to altered components of the somatotrophic axis (GH-IGF-1). In dogs with congenital portosystemic shunts, it has been found that serum IGF-1 concentrations were reduced, with a marked increase noted post-surgery (Maxwell et al 2000). Serum IGF-1 concentrations were measured in 36 dogs with various liver diseases and compared with 22 healthy controls and 20 dogs with non-hepatic diseases (Neumann et al 2007). The results showed that dogs with liver diseases had significantly lower serum IGF-1 concentrations than clinically healthy dogs or dogs with non-hepatic diseases. However, Neumann et al (2007) also indicated that the etiology of liver disease has no influence on serum IGF-1 concentrations.

Data provided for dogs are in agreement with those presented for human patients. Different liver diseases, such as liver neoplasm, metastasic liver disease, echinococcosis, hepatitis C virus infection and liver cirrhosis, have been associated with a reduction in serum IGF-1 concentrations (Vyzantiadis et al 2003; Elsammak et al 2006; Colakogen et al 2007; Cujic et al 2010).

Serum IGF-1 Concentrations in Heart Diseases. IGF-I has substantial effects on the cardiovascular system. In addition to the inotropic and trophic effects, IGF-1 appears to play an important role in the regulation of vascular tone (Saccá et al 1999; Colao et al 2001). Endothelial cells has high-affinity IGF-1 receptors and release nitric oxide when stimulated by IGF-1. Thus, IGF-1 seems to be an important stimulus for endothelium-dependent vasodilation (Böger 1999). In human patients with heart failure, an inverse relationship between the degree of heart failure and circulating IGF-1 concentrations has been reported in some studies (Giustina et al 1999; Osterziel et al 2000b; Al-Obaidi et al 2001), but not all studies (Broglio et al 1999; Answar et al 2002). In severe heart failure, GH resistance with high GH and low IGF-1 concentrations often appears, especially if body mass index is decreased (Hambrecht et al 2002). Treatment that stabilizes the patient's condition often normalizes serum concentrations of IGF-1 (Corbalan et al 1998).

Only a few studies have focused on IGF-1 concentrations in animals with heart failure. A study in conscious dogs during the development of congestive heart failure, induced by rapid ventricular pacing, showed that plasma IGF-1 concentrations were not related with left ventricular performance (Shen et al 1998). On the other hand, it has been investigated how IGF-1 modulates cardiovascular function in a canine model of dilated cardiomyopathy. The dogs treated with IGF-1 had better cardiac output, stroke volume, left ventricular end-systolic and end-diastolic pressures. Additionally, pulmonary wedge pressure and systemic vascular resistance decreased in the IGF-1 treated group and this treatment was associated with less thinning of the ventricular wall (Lee et al 1999).

More recently, Pedersen et al (2005) examined the concentrations of serum IGF-1 in dogs with mitral regurgitation caused by myxomatous mitral valve disease. They found that circulating IGF-1 concentrations were not altered before development of congestive heart failure in dogs with naturally occurring mitral regurgitation. However, serum IGF-1 concentrations decrease by approximately 20% with the development of decompensated

and untreated heart failure and return to within the reference range in dogs with treated stable heart failure (Pedersen et al 2005).

The role of GH or IGF-1 treatment in congestive heart failure is unclear. Several studies of spontaneous heart failure in human beings and some cases of experimentally induced heart failure in animals (Giustina et al 1999; Tivesten et al 2001; Kahn et al 2002) have demonstrated beneficial effects. However, other studies have demonstrated that human with heart failure experience little or no benefit from treatment with GH (Isgaard et al 1998; Osterziel et al 2000a). In dogs with heart failure, little is known about the therapeutic potential of GH and IGF-1. In one study, daily injections of porcine GH for 4 weeks during development of pacing-induced heart failure in dogs was found to have no effect on the left ventricular performance or systemic vascular dynamics (Shen et al 1998). In other study, IGF-1 injections twice daily for the final 2 weeks of a 4-week pacing period had marked positive effects on cardiovascular function (Lee et al 1999).

Although GH and IGF-1 activate several mechanisms that protect against the development of heart failure, chronic excess can causes pathological cardiac hypertrophy and, if not corrected, eventually leads to heart failure (Wickman et al 1999; Von Lewinski et al 2003; Saccá et al 2003). Most human beings with acromegaly (i.e chronic GH excess) develop biventricular concentric hypertrophy and subsequent diastolic dysfunction due to myocardial hypertrophy with interstitial fibrosis (Colao et al 2001). At a late stage, this has been reported to progress to systolic dysfunction, decompensated eccentric hypertrophy, and heart failure (Saccá et al 2003). GH and IGF-1 also promote the formation of cardiac collagen tissue (Bruel & Oxlund 1991). Collagen is the major structural component determining the architecture and functional integrity of the myocardium. Since the contractibility of the myocardium relies on the supporting collagen framework alterations in this matrix have a strong influence on the function of the heart (Gübert et al 2000). Vegter et al (2009) induced elevated serum GH and IGF-1 concentrations in dogs by daily administration of supraphysiological doses of GH. These authors reported that the hearts of the treated dogs had larger atria, thicker left ventricular wall, and their cardiomyocytes were longer, thicker and with great volume than those or control dogs. This research demonstrated that excess of GH and/or IGF-1 in dogs result in myocardial hypertrophy, findings that were consistent with observations performed in acromegalic human patients.

To the authors' knowledge, there is only a report concerning the concentrations of serum IGF-1 in cats with heart diseases. Yang et al (2008) compared IGF-1 concentrations in cats with and without hypertrophic cardiomyopathy in order to assess the hypothesis that cats with this heart disease would have higher serum IGF-1 concentrations than healthy cats. This research showed that mean serum concentrations of IGF-1 were not significantly different between groups (Yang et al 2008).

It is clear that additional studies are warranted to clarify the importance of IGF-1 in the pathophysiology and treatment of heart failure in veterinary medicine.

Serum IGF-1 Concentrations in Tumors. The GH/IGF-1 axis plays an important role in mammalian mammary tumourigenesis. IGF-1 is a potent mitogenic and anti-apoptotic agent, which is also involved in the angiogenesis stimulation (Chong et al 2007). These features are the bases for their involvement in the maintenance and progression of the neoplasias (Rosfjord & Dickson 1999; Grimberg & Cohen 2000; Holdaway et al 2003). In fact, in human patients with acromegalia, breast cancer incidence is increased (Yakar et al 2005). Further, the GH mRNA and the GH receptor expression in normal and neoplastic mammary cells have been established in dogs (Mol et al 1995a; Van Garderen et al 1999) and humans (Mol et al 1995b). It has been shown an elevated IGF-1 mRNA expression in vitro and in vivo (Manni et al 1992), and the IGF-1 breast mitogenic capacity has been confirmed in in vitro studies, in humans (Karey & Sirbasku 1988) and in dogs (Oosterlaken-Dijksterhuis et al 1999).

Queiroga et al (2010) performed a prospective study including 32 female dogs with mammary tumors, in comparison with a control group. It was observed that serum IGF-1 concentrations in female dogs with malignant tumors were significantly higher than in healthy controls. It was suggested that some of the autocrine GH and IGF-1 produced

locally by the neoplastic cells might enter the circulation and contribute to increase the serum concentrations. However, malignant mammary tumors cannot be distinguished from benign mammary lesions by systemic serum IGF-1 concentrations, as it was previously observed in human breast cancer (Singer et al 2004).

IGF-1 concentrations have been also analyzed in cats affected by fibroadenomatous changes or feline mammary hypertrophy, a non-neoplastic condition characterized by a rapid proliferation of mammary stroma and duct epithelium in one or more glands (Ordás et al 2004). These lesions occur in progestin-treated, pregnant and very young cats and are associated with endogenous and exogenous progesterone (Misdorp et al 1999). In the dog, treatment with progestins resulted in increases in plasma levels of GH and IGF-1 (Selman et al 1994), stimulating the local proliferation of epithelial cells (Mol et al 1995a; Van Garderen et al 1997). Ordás et al (2004) studied 22 cases of feline fibroadenomatous changes. They detected IGF-1 in 77% of the cases at the site of ductal budding. Their results indicated that progesterone receptors may induce the local synthesis of GH, which in turn may exert its proliferative action directly and also indirectly through the production of other growth factors, such as IGF-1 (Ordás et al 2004).

The research of the potential prognostic value of IGF-1 in veterinary oncology is of current interest. It was demonstrated that administration of IGF-1 in human beings may rescue breast cancer cell lines from chemotherapy-induced cell death, by induction of proliferation and inhibition of apoptosis (Gooch et al 1999), which may indicate that inhibition of IGF-1 action could be an important adjuvant to cytotoxic chemotherapy in breast cancer. Moreover, the use of GH antagonists as antineoplastic agents seems to be very promising and it is under investigation in human patients (Van der Lely & Kopchich 2006).

Serum IGF-1 Concentrations in Endocrine Diseases. Insulin (INS) is a major anabolic effector in the body, and is also an important regulator of the GH-IGF axis (Bereket et al 1999). In veterinary medicine, there are different endocrine diseases associated with alterations in INS release, such as obesity, diabetes mellitus, Cushing's disease and peripheric Cushing's disease or peripheric metabolic syndrome, laminitis, acromegaly and myopathies.

Serum IGF-1 Concentrations in Endocrine Diseases in Dogs. It has been considered that obesity is associated with multiple endocrine alterations and changes in serum concentrations of circulating hormones. Obesity in humans and rodents is associated with disturbances of the main hormonal axes, including GH/IGF-1 axis. In human beings an increase in body fat seems to be associated with an increase of cortisol, INS, IGF-1 secretion and a decrease of GH secretion (Smith 1996).

In dogs, it is still unclear if the changes in the activity of the GH/IGF-1 axis in obesity are alterations or adaptations and which cases of obesity lead to increased serum IGF-1 concentrations. Gayet et al (2004) reported that serum IGF-1 was significantly elevated in obese dogs. These authors also have shown a correlation between IGF-1 and postprandial hyperinsulinemia, suggesting that elevated IGF-1 concentrations in these cases may be caused by INS resistance. Therefore, a possible relationship between IGF-1 and high energy intake and a link to INS resistance can exist in obese dogs. However, Martin et al (2006) studied 31 adult dogs with long-standing obesity and they found that serum IGF-1 concentrations were increased in only six of these 31 dogs (<20%) and they failed to find a correlation between IGF-1 and overweight.

Serum IGF-1 Concentrations in Endocrine Diseases in Cats. Acromegaly in cats is caused by a functional somatotrophic adenoma in the pars distalis of the anterior pituitary gland resulting in excessive GH secretion (Feldman & Nelson 2004). Clinical signs are the result of the catabolic and diabetogenic effects of GH, the anabolic effects of IGF-1, and the space-occupying effect of the pituitary macro-adenoma. GH-induced catabolic effects include INS resistance, carbohydrate intolerance, hyperglycemia, and diabetes mellitus (Rosenfeld et al 1982; Hansen et al 1986). As a consequence of these

actions, most cats are diabetic at the time acromegaly is diagnosed and most are poorly controlled because of GH-mediated INS resistance (Peterson et al 1990). The anabolic effects of IGF-1 are responsible for many of the abnormalities identified on physical examination in acromegalic diabetic cats, including large body size and head, prognathia inferior, renomegaly, arthropathy, and respiratory difficulties caused by thickening of pharyngeal tissues (Alt et al 2007; Berg et al 2007; Niessen et al 2007).

Although the diagnosis of acromegaly traditionally has relied on measuring increased serum GH concentrations, unfortunately, a validated assay for measuring GH in cats is not always available. An alternative screening test for acromegaly, therefore, is the measurement of serum IGF-1 concentrations. In humans, serum IGF-1 concentrations are increased in acromegaly and correlates closely with the severity of the clinical signs (Clemmons et al 1979; Chang & Jackson 1992). In the same way, increased serum IGF-1 concentrations have been documented in diabetic cats with acromegaly (Middleton et al 1985; Norman & Mooney 2000), suggesting that serum IGF-1 may be a useful diagnostic test for feline acromegaly. However, recent studies identified increased serum IGF-1 concentrations in diabetic cats without acromegaly (Lewitt et al 2000) as well as in diabetic cats treated with INS for more than 14 months (Starkey et al 2004). A research assessed the serum IGF-1 concentrations in cats with diabetes mellitus and acromegaly (Berg et al 2007). It was found that serum IGF-1 was significantly increased in acromegalic diabetic cats compared with well-controlled and poorly controlled diabetic cats. Sensitivity and specificity for serum IGF-1 concentrations were 84% and 92% respectively. They did not observe a significant correlation between serum IGF-1 concentrations and between duration of INS treatment, INS dosage.

Therefore, it is concluded that measurement of serum IGF-1 concentrations is an accurate screening test for acromegaly in diabetic cats. However, interpretation of serum IGF-1 test results should always take into consideration the status of control of the diabetic state, the presence and severity of INS resistance and the index of suspicion for acromegaly based on review of the history, physical examination, and complementary diagnostic tests. An increased serum IGF-1 concentration does not, by itself, confirm the diagnosis of acromegaly nor does a normal serum IGF-1 concentration result rule out acromegaly (Berg et al 2007).

Serum IGF-1 Concentrations in Endocrine Diseases in Horses. INS resistance is defined as a lower than normal response of peripheral tissues to a normal serum concentration of INS. It can occur prior to INS receptor binding, at the level of the INS receptor due to down regulation of the receptor, or subsequent to INS binding resulting in interruption of the intracellular INS-signaling pathways (Kronfeld et al 2005; Treiber et al 2006). As a consequence, higher INS concentrations are required to achieve the same biological effect. Thus, initially there is a compensation characterized by increased pancreatic INS secretion, resulting in hyperinsulinemia and normoglycemia.

INS resistance is though to be involved in the pathogenesis of some metabolic diseases, such as pars intermedia dysfunction (Cushing's syndrome), equine metabolic syndrome, hyperlipemia, pasture-associated laminitis, osteochondrosis and endotoxemia, whereas polysaccharide storage myopathy and equine motor neuron disease have been associated with increased INS sensitivity (Johnson 2002; Schott 2002; Firshman & Valberg 2007; Bailey et al 2008). It has been indicated that both increased cortisolemia and increased GH and/or IGF-1 concentrations are responsible for INS resistance in horses.

Although primarily associated with growth, IGF-1 also has metabolic effects. It can mimic the effects of INS increasing glucose uptake, decreasing hepatic glucose production and decreasing lipid mobilization (Froesch et al 1996). The commonality between INS resistance and increased serum IGF-1 concentrations could be a high-energy intake. Diets rich in hydrolysable carbohydrates contribute to increased INS secretion, a primary factor in the development of tissue resistance to INS (Kopp 2003). Constant hyperinsulinemia resulting from a high-carbohydrate diet contributes to pancreas β-cell-dysfunction associated with type II diabetes possible through amyloid deposits on the islet cells. In fact, weanlings adapted to a supplement rich in

hydrolysable carbohydrates have higher circulating serum IGF-1 concentrations than weanlings adapted to a forage-like diet (Treiber et al 2005).

Serum IGF-1 Concentrations in Musculoskeletal Diseases. The health status of the musculoskeletal system in a horse is of paramount importance to determine the durability, usability and suitability for sport competitions. In fact, the main reasons involved in lack of performance, loss of training days and early finish of a sport career are musculoskeletal injuries.

Several in vitro and in vivo studies have demonstrated the role of IGF-1 in cartilage growth and development (Nixon et al 2000; Fortier et al 2002; Dart et al 2003), IGF-1 appears to function as an inducing signal for chondrogenesis and an anabolic growth factor in cartilage homeostasis. In the context of joint biology, IGF-1 is considered to be an essential anabolic growth factor in the regulation of cartilage metabolism and exerts its effects by binding to the IGF-1 type 1 receptor on the chondrocyte membrane. Mechanisms for controlling the effects of IGF-1 include alterations in the level of this growth factor, its receptor and/or the IGF-1 affinity or availability to its receptor. Disturbances of any one of the above elements may induce a disregulation of the mechanisms involved in the local control of joint tissue integrity.

Osteochondrosis can be defined as a disturbance of the process of endochondral ossification of the articular-epiphyseal complex. The ensuing irregularities of the ossification front lead to thick cartilage plugs, the deeper parts of which may become necrotic. In the final state, osteochondral fragments may detach and become loose or semiloose intraarticular bodies or joint mice. The cause of osteochondrosis in horses is unknown, although it is considered a multifactorial disease in which genetic influences (accounting for about 25% of the phenotype), nutritional factors, biomechanical influences, and conformation plays a role (Van Weeren 2006). It has been demonstrated that osteochondrosis-positive foals showed significantly lower serum IGF-1 concentrations that osteochondrosis-negative foals (Sloet van Oldruitenborgh-Oosterbaan et al 1999).

Lejeune et al (2007) determined the serum IGF-1 concentrations in horses affected by juvenile digital osteoarthropathy. They found significant lower serum IGF-1 concentrations in horses affected by this disease compared to healthy horses. However, the role of the reduction of IGF-1 production in the pathogenesis of this joint disease was not demonstrated.

Similarly, Verwilghen et al (2009) investigated the relationship between the radiological status of horses with joint diseases and the levels of biochemical markers of cartilage degradation and synovial inflammation, including IGF-1. These authors found that, when comparing IGF-1 levels from horses with low scores (minimal or absence of radiographic changes) with those horses with higher radiological scores (from mild to moderate radiographic changes to severe radiographic changes responsible for lameness and impairing future sport career), the higher radiological scores showed significantly lower IGF-1 concentrations. These results support the data presented previously in foals with osteochondrosis (Sloet Van Oldruitenborgh-Oosterbaan et al 1999) and in Ardenner horses suffering from juvenile digital degenerative osteoarthropathy (Lejeune et al 2007). These data suggested a relationship between IGF-1 and the osteoarticular status of the animal.

Other Applications of Serum IGF-1 Concentrations in Sport Horses. There are other potential uses of the measurements of serum IGF-1 concentrations in sport horses: detection of fraudulent administration of GH in sport horses, design of training programs which minimize the risk of locomotor injuries, enhancement of healing after musculoskeletal injuries and improvement of welfare in geriatric horses.

Detection of Administration of GH in Sport Horses. Recognition of the potential for GH to exert anabolic effects has led to its use by human athletes (Myhal & Lamb 2002). However, studies of highly conditioned athletes demonstrated that GH administration does not increase fat-free mass, skeletal muscle protein synthesis or strength (Deyssig et

al 1993; Yarasheski et al 1993). However, GH could be effective in the treatment of individuals with a documented deficiency of this hormone, but currently is considered ineffective as an anabolic agent in clinically normal human athletes (Myhal & Lamb 2002).

It has been suggested that administration of GH may be detected by measurement of serum IGF-1 concentrations (Noble & Sillence 2000; De Kock et al 2001; Popot et al 2001). Serum IGF-1 concentrations are increased for hours to days after administration of GH, whereas GH has a very short half-life and detection of increased concentration is therefore difficult (Popot et al 2001).

In order to investigate the influence of factors, such as acute exercise, fitness, training, time of day, sex, and age on serum IGF-1 concentrations in normal, healthy horses, Noble et al (2007) studied 1,880 horses from 3 different countries, aged from 1 to 29 years. The greatest serum IGF-1 concentration observed in the entire population in this study was 709 ng/ml. Because exogenous GH treatment can increase IGF-1 concentrations in horses to levels over 1000 ng/ml (Noble & Sillence 2000), IGF-1 could be a useful marker to detect GH abuse, at least as a preliminary screening test. This would require the setting of a threshold value for normal IGF-1 concentrations in the horse, which it was suggested to be about 800 ng/ml. This value is about 5 standard deviation greater than the mean obtained by Noble et al (2007) in the whole population (310 ng/ml), and it is 100 ng/ml greater than the preliminary threshold suggested by Popot et al (2001) based on a smaller sample size. According to Noble et al (2007), in the case of a normal distribution, the probability of finding an untreated horse with high serum IGF-1 concentration (false positive), would be less than 1 in 1,000,000. A horse that exhibits suspiciously high IGF-1 concentrations should be sampled several days. It has been previously described that serum IGF-1 concentrations decrease markedly within 5 to 10 days after the withdrawal of GH treatment (Noble & Sillence 2000). In a horse with naturally high IGF-1 levels, this decrease would not be seen.

Design of Safe Training Programs. Failure of the adaptive response to change bone architecture appropriately to withstand loads generated by physical activity can lead to damage. In sport horses, injuries to the skeleton remain a major cause of illness, lack of performance and loss of days of training. One factor involved in this may be a rigorous training program, mainly in young Thoroughbred horses, when still they are skeletally immature.

Because the training of young racing Thoroughbreds remains largely empirical, the development of safe and effective training programs can be reached if further studies are undertaken to identify those training regimes that stimulate fracture-resistant bone, compared with those that may have detrimental effects. The means by which effects of the exercise on the skeleton are mediated is still not completely understood, although there is evidence that GH/IGF-1 axis is involved. Serum IGF-1 concentrations are associated with changes in bone formation following exercise (Yeh et al 1994) and loading regulates the synthesis of mRNAs for IGF-1 by osteoblasts. Studies in humans have shown that serum concentration of biochemical markers (that provide a measurement of the activity of osteoclasts and osteoblasts) may provide a means by which changes that occur in bone in response to physical loading can be studied (Price 1999). Although this use of the measurement of IGF-1 concentrations is very promising in equine sport medicine, to the authors' knowledge, the changes in IGF-1 in response to different training programs and in relation to the incidence of musculoskeletal injuries have not been studied yet in horses.

Enhancement of Healing after Musculoskeletal Injuries. During and/or after a musculoskeletal injury, as well as during the recovery from a disease, an equine athlete undergoes detraining of the different systems implied in exercise (Mukai et al 2006). The start of training is a critical moment in order to avoid new injuries or an increase of the old injuries. It has been suggested that the administration of IGF-1 could potentate the effects of the training in these initial phases. However, this hypothesis has not been demonstrated yet (Noble et al 2007).

Improvement of Welfare in Geriatric Horses. Like humans, the mean age of the population of horses is increasing (Paradis 2002). A large portion of horses is over 20 years and they are still used for athletic activities. Aging results in many physiological changes in the horse including decreases in cardiopulmonary function, decreased aerobic capacity, decreased immune function, impaired nutrient utilization, decreased nitrogen retention and decreased lean body mass (Malinowski et al 1997; McKeever et al 1998). Similar changes have been observed in other species and comparative data from rats, dogs, and humans have shown that there is a relationship between plasma concentration of GH and what has been called the 'aging phenotype' (Nelson 1995; Holloszy & Kohrt 1995).

The importance of GH in maintenance of normal physiological functions and its possible role in slowing or even reversing the effects of aging can be seen in some younger adult humans, where GH deficiency results in changes in appearance, decreased lean body mass, decreased immune function and other sequelae of aging (Nelson 1995). For that reasons, the administration of GH in old horses has been investigated.

Champion et al (2000) analyzed the effects of intramuscularly administered GH on IGF-1 concentrations and the hematopoietic system in Thoroughbred geldings aged 6-9 years. It was found that white blood cells and hemoglobin concentration significantly increased after treatment. These effects have been previously reported in aged humans and rodents. GH administration stimulated lymphocyte production, stimulated differentiation of stem cells into granulocytes, and stimulated erythropoiesis (Li et al 1992; Wit et al 1993; Kelly et al 1996). These actions could be used therapeutically, as advancing age in horses, is eventually associated with an increase in susceptibility to infections caused by an overall decline in immune function (Fermaglich & Horohov 2002).

Table 1

Changes in serum/plasma IGF-1 concentrations in dogs with several naturally ocurring diseases

Disease	*IGF-1 changes*	*Observations*	*References*
Congenital portosystemic shunts	↓	Increased IGF-1 after surgery	Maxwell et al 2000
Different liver diseases	↓	Differentes in IGF-1 between etiologies not found	Neumann et al 2007
Mitral regurgitation associated with myxomatous mitral valve disease	↓	Decreased IGF-1 with decompensated heart failure. Recovery of IGF-1 concentrations after treatment	Pedersen et al 2005
Obesity	↑	Correlation between IGF-1 and hyperinsulinemia	Gayet et al 2004
Obesity	↑	Increased IGF-1 only in less than 20% of the dogs No correlation with overweight	Martin et al 2006

Table 2

Changes in serum/plasma IGF-1 concentrations in cats with several naturally occurring diseases

Disease	*IGF-1 changes*	*Observations*	*References*
Hypertrophic cardiomyopathy	No differences with control group		Yang et al 2008
Acromegaly	↑	Acromegaly is common in feline diabetes	Middleton et al 1985 Norman & Mooney 2000 Berg et al 2007

Table 3

Changes in serum/plasma IGF-1 concentrations in horses with several naturally occurring diseases

Disease	*IGF-1 changes*	*Observations*	*References*
Cushing's syndrome Equine metabolic syndrome Hyperlipidemia Pasture-associated laminitis Osteochondrosis Endotoxemia	↑	Relationship between high energy intake, IGF-1 and insulin resistance	Johnson, 2002 Schott, 2002 Firsman & Valberg 2007 Bailey et al 2008
Osteochondrosis	↓		Sloet van Oldruitenborgh-Oosterbaan et al 1999
Juvenile digital osteoartropathy	↓	In Ardennes horses	Lejeune et al 2007
Several joint diseases	↓	Lower IGF-1 in horses with joint with worse radiological signs	Verwilghen et al 2009

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