Cushing, acromegaly, GH deficiency and tendons

Mariano Galdiero[1]
Renata S. Auriemma[2]
Rosario Pivonello[1]
Annamaria Colao[1]

[1] Department of Clinical Medicine and Surgery, Endocrinology Section, University "Federico II", Naples, Italy
[2] Ios & Coleman Medicina Futura Medical Center, Naples, Italy

Corresponding author:
Annamaria Colao
Department of Clinical Medicine and Surgery,
Endocrinology Section
University "Federico II"
Via S. Pansini 5
80131 Naples, Italy
E-mail: colao@unina.it

Summary

Cushing's syndrome, induced by an endogenous or exogenous cortisol excess, and acromegaly, the clinical syndrome caused by growth hormone (GH) excess in adulthood, as well as the disease induced by GH deficiency (GHD), represent perfect models for the evaluation of the effects induced by chronic exposure *in vivo*, respectively, to cortisol and GH/IGF-1 excess or deficiency on the complex structure of the tendons as well as on the related post-traumatic repair mechanism. Although the literature is still scant, here in main scientific evidence on this topic is summarized in order to provide suggestions about the management of the above mentioned illnesses, to translate such information in the field of sports medicine and/or traumatology, and to increase and to disseminate knowledge on this misunderstood theme.

KEY WORDS: Cushing's syndrome, acromegaly, GH deficiency, cortisol, GH, IGF-I, tendons, tendinopathy.

Introduction

Tendons are composed by fibroblast-like cells of mesenchymal derived cells (tenocytes) embedded in a three dimensional network of extra-cellular matrix (ECM) consisting of collagenous structures, predominantly composed by collagen type I (CICP; > 95%) and other types of collagens (type III and V), proteoglycans (PG), fibronectin (FBN) and elastin[1]. Tenocytes are responsible for the synthesis of all these components that provide tendon its biomechanical properties and maintain its structure, especially collagen fibres[2]. Moreover, tenocytes play an important role in regenerative response following traumatic injury or spontaneous degeneration[3]. CICP mediates cell adhesion and stimulates cell migration and differentiation in injured tendons repair processes, whereas PG provides viscoelastic properties thanks to trapping of water and give tendon a resistance to compressive forces and FBN play a role in cells adhesion and migration[4,5]. All these cellular and extra-cellular components are targeted by cortisol and/or GH and IGF-1.
According to Padulo et al.,[6] the study meets the ethical standards of the journal.

Cushing's Syndrome and tendons

Cushing's Syndrome (CS) results from chronic exposure to excessive circulating levels of glucocorticoids[7,8]. The commonest cause of CS, seen in general clinical practice, is the exogenous iatrogenic CS, induced by prolonged treatment with synthetic steroids that have glucocorticoid activity for chronic conditions such as respiratory or rheumatological diseases[7]. The endogenous form of CS could be ACTH dependent or ACTH independent. ACTH-dependent forms are characterized by ACTH overproduction, which stimulates adrenal gland increasing circulating glucocorticoids levels[7,8]. ACTH-independent forms are due to spontaneous adrenal glucocorticoid hypersecretion. Pituitary-dependent CS, known as Cushing's disease, is the most common cause of endogenous CS, accounting for 60-80% of all cases with an incidence of between 0.7 and 2.4 per million per year while ectopic ACTH or CRH tumors are rare causes of ACTH dependent CS[7,8].
The clinical features in CS are variable, showing a wide spectrum of abnormalities, from mild, subclinical disease to florid manifestations. The classical pictures of CS includes central obesity, wasting of the limbs, proximal muscle weakness, wide purple striae, facial rounding and plethora, hirsutism with frontal balding, osteoporosis with possible vertebral frac-

tures, hypertension and diabetes mellitus[7,8]. Nevertheless, the clinical diagnosis may be frequently equivocal because many signs and symptoms of CS, including lethargy, depression, obesity, hypertension, hirsutism, and menstrual irregularity, are also associated to other diseases and are very common in the general population[7,8]. Cortisol exerts a wide spectrum of effects on many physiologic processes, including the 'catabolic' action on protein metabolism[9-15]. Cortisol or glucocorticoids effect on collagen metabolism is not fully elucidated, and effects of glucocorticoids on tendons structures were a hot topic in sport medicine and traumatology for many years and continued to be hardly debated. A number of studies have demonstrated many effects of glucocorticoids at the cellular level. Glucocorticoids have been found to decrease the amount of mRNA coding procollagen chains[9]. Post-translational modifications including hydroxylation of proline and lysine residues and glycosylation of hydroxylysine residues in procollagen are depressed by glucocorticoids[9]. This is caused by reduced activity of the specific enzymes of intracellular stages of collagen biosynthesis[9] . Extracellular maturation of collagen is affected by glucocorticoids but changes depend upon the rate of collagen turnover[9]. The effect of glucocorticoids on collagen degradation is a subject of controversy, and some evidence has shown that glucocorticoids decrease activity of collagenolytic enzymes[9]. Dexamethasone, a potent synthetic glucocorticoid, has been shown to inhibit type I collagen mediated upregulation of matrix metalloproteinases (MMP) type 2 and 9 by canine flexor digitorum profundus tendon tenocytes[10], rat Achilles tendon tenocyte migration[11], rat Achilles tendon proliferation[12] and patellar tendon tenocytes[13], as well as collagen synthesis and gene expression by embryonic chick tendon[14,15]. Furthermore, dexamethasone has been shown to inhibit human tenocyte proliferation and collagen synthesis[16] in a concentration-dependent manner directly by effects on both tenocyte proliferation and collagen accumulation, and also indirectly by modulating the recruitment of tendon progenitor cells[17]. Although these data suggested a negative effects of glucocorticoids on tendons structure and repair mechanisms, corticosteroids injections are nowadays still commonly used to treat tendon lesion even though it is clear that inflammation is not the base for tendon lesions. Noteworthy, studies on animal models have shown that intratendinous corticosteroid adversely affects the biomechanical properties of tendons[18,19]. Corticosteroids can inhibit formation of adhesions, granulation, and connective tissue, can reduce tendon mass and can decrease biomechanical integrity, also reducing the amount of load that can be taken before failure[20,21]. The biomechanical effects of peritendinous corticosteroid treatment on human tendons are not well established. However, some case reports have documented rupture of tendons shortly after glucocorticoid injections[20,21]. Moreover, the increased incidence of the spontaneous rupture of the Achilles tendon has been described in patients receiving long-term glucocorticoid treatment[22-25]. The incidence of spontaneous rupture of tendons in noniatrogenic CS is unknown but some clinical case reports have suggested this traumatic lesion as a first clinical sign of CS[26-28]. It has been argued that chronic over-exposure to hypercortisolism, as occurs in some chronic rheumatic diseases requiring corticosteroids use, could amplify deleterious effect of this hormones/drugs on tendons structures and cellular activity[26].

Acromegaly, GH-deficiency and tendons

Acromegaly is a rare endocrine syndrome with an estimated annual incidence of 3 to 4 cases per 1 million and a current estimated prevalence of 40 cases per 1 million[29]. In more than 95% of cases, it is due to a GH-secreting pituitary adenoma. Acromegaly may also be rarely associated with a hypothalamic or an ectopic GH-releasing hormone-producing tumor[29]. Clinical features usually develops over many years because of chronic exposure to elevated levels of GH and IGF-I[29]. The elevated GH and IGF-I levels lead to a wide range of cardiovascular, respiratory, endocrine, metabolic, musculoskeletal and tendinous diseases also[29]. Acromegaly may be associated to a wide range of sign and symptoms[29] as coarsened, enlarged facial features, enlarged tongue, oily and thickened skin, excessive sweating, skin tags, fatigue and muscle weakness, a deepened voice severe snoring due to obstruction of the upper airway, headaches, pain and limited joint mobility as well as menstrual cycle irregularities in women and hypogonadism or sexual dysfunction in man[29]. Furthermore symptoms from an expanding tumor, such as visual-field defects and headache, might worsen the clinical presentation of acromegaly[29]. On the other side GHD is an endocrine disease with different clinical pictures according to age of onset. Idiopathic and genetic forms, as well as GH deficiency due to congenital structural malformation, tumors, irradiation, inflammation or autoimmunity, infection and traumatic brain injury could be diagnosed[30,31]. In childhood it is rare with an incidence of 1 per 4,000. Children with severe growth hormone deficiency often have midface hypoplasia and increased truncal adiposity, but the major clinical feature of this condition is growth failure[30]. Adult GHD has an estimated prevalence of 2 to 3 per 10,000 population[30,31]. This is characterised by decreased mood and general well-being, decreased exercise tolerance, reduced bone remodelling activity, changing in body fat distribution with increased central adiposity, hyperlipidaemia and increased predisposition to cardiovascular diseases[30,31]. GH is well known for its anabolic action in a direct or indirect, *via* IGF-I, manner. It enhances the proliferation of cells and maturation of several tissues including bone, cartilage, and skeletal muscle. GH/IGF-I axis has been demonstrated to exert an increase in whole body protein synthesis with no effects or decrease of proteoly-

sis[32,33], as well as an important role in collagen synthesis[34]. Nevertheless information about the direct effect of GH/IGF-I on tendon growth and maturation is far from a fully comprehension. GH stimulates procollagen synthesis in humans[35]. While a short GH treatment in rats has been shown to increase new collagen production with a concomitant reduction of maturation of tendon structures, investigated by hydroxylysylpyridinoline collagen cross link contents, of about 20% during new collagen accumulation[36].

It has been shown that IGF-I is present in human Achilles tendon, and a detectable interstitial concentration has been demonstrated in human tendons[37]. IGF-I is known to induce collagen synthesis in tendon cells[37,38], and both IGF-I protein and mRNA have been localized in tendon tissue from humans and several animal species[38,39].

In the Achilles tendon, the expression of IGF-I result in increased response to strength training without difference in contraction types (lengthening *vs* shortening contractions), suggesting a possible IGF-I up-regulation by exercise or mechanical loading[40,41]. IGF-I, in fact, could mediate the increase in collagen synthesis observed in response to exercise/training[42,43].

Furthermore GH/IGF-I axis could be potentially involved in the recovery of tendon structure after tendon injury considering that some data suggested an acceleration of tendons repair when IGF-I was administered in rat[44].

Existing data on chronic alterations in GH/IGF-I and the muscle-tendon unit come from a study in patients with acromegaly and GHD[45]. A trend towards smaller mean collagen fibril diameter in the patellar tendon of acromegalic patients compared to the GHD patients has been discovered[45]. Furthermore, collagen mRNA expression was altered according to GH levels, but the collagen synthesis rates in tendon were not significantly different between the two patient groups[45]. Although these data indicated a link between chronic changes in the GH/IGF-I axis and tendon ultra-structure, these human patients were not optimal to study this system, since all patients were medically treated and showed almost normalized GH and IGF-I levels[45].

A recent study demonstrate that mice knockout for GH receptor (GHR$^{-/-}$ mice), a model of GHD, had significantly lower collagen fibril volume fraction in Achilles tendon compared to control mice[46]. In contrast, the mRNA expression of IGF-I and collagens in mice over expressing GH was generally high in both tendons compared to control[46]. Mean collagen fibril diameter was significantly decreased with both high and low GH/IGF-I signaling, but the GHR$^{-/-}$ mouse tendons were most severely affected with a total loss of the normal bimodal diameter distribution[46]. These findings suggested that whereas only moderate structural changes were observed with up-regulation of GH/IGF-I axis, disruption of the GH receptor had pronounced effects upon tendon ultra-structure[46].

From a clinical point of view these latest data cannot be confirmed. In fact the majority of acromegalic patients have joint manifestation leading to increased morbidity and disability and the reversibility of these manifestation after GH normalization seems to be not fully achievable[29]. Quality of life of acromegalic and GHD patients could be reduced by bone, joint and muscle alterations but by tendons diseases also.

A significant increased thickness of right and left heel tendons measured by ultrasound scans were found in acromegalic compared to healthy controls. Short term treatment by lanreotide (1-2 months)[47] or octreotide (6 months)[48] has been demonstrated to not modify the size of heel tendons, while a significant reduction of both heel tendons was observed after suppression of GH and IGF-1 after 12 months of lanreotide treatment[47].

Acromegalic patient could also suffer from a trigger fingers, characterized by thickening and constriction of the proximal part of the flexor tendon sheath at the base of the finger or thumb. It seems related to the pulley system rather than to tendon alteration itself and is reversible by normalizing GH/IGF-1 excess[49].

Conclusions

Cushing, acromegaly and GHD patients, affected by highly disabling disease with systemic involvement, can have major alterations in the structure and/or tendons function. The peculiar effects of cortisol, GH and IGF-I at exclusively tendon level are difficult to study, given the interaction of the tendons with the muscle-tendon unit. Further efforts are necessary, therefore, to fully understand the physiological effects of these hormones on tendon. Moreover, the study of the relative changes in special conditions such as sports and injuries can be useful to hypothesize a possible therapeutic use in the field of traumatology.

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