Review

The effect of relaxin on the musculoskeletal system

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Relaxin is a hormone structurally related to insulin and insulin-like growth factor, which exerts its regulatory effect on the musculoskeletal and other systems through binding to its receptor in various tissues, mediated by different signaling pathways. Relaxin alters the properties of cartilage and tendon by activating collagenase.

Relaxin, the mammalian 6-kDa heterodimeric polypeptide hormone, is a member of the insulin-like superfamily (Hisaw, 1926) and consists of seven peptides of high structural but low sequence similarity. Relaxin plays an essential role in the biological processes such as metabolism, growth, pregnancy, and parturition in different species including humans and rodents. Relaxin circulates in these species during pregnancy emanating from the corpus luteum (Conrad & Baker, 2013) and placenta (Goh et al., 2013); however, temporal pattern of change and serum concentrations of this hormone are different. In rodents, circulating relaxin peak concentrations at the end of pregnancy reach 100 ng/mL, two times greater than in human (Sherwood, 1994). While relaxin plays important role in collagen catabolism of the pubic symphysis during gestation in lower mammals such as mice and rats (Samuel et al., 1998), the role of this hormone on pubic symphysis of human is however unknown (Hashem et al., 2006; Wang et al., 2009). Several studies have highlighted the therapeutic potential of relaxin for ectopic pregnancy, male infertility, and heart failure, cardiovascular and musculoskeletal diseases. Currently, there are seven known relaxin family peptides (RXFP) that are structurally related to insulin which include relaxin (RLN)1, RLN2, RLN3, and insulin-like peptide (INSL)3, INSL4, INSL5, and INSL6 (Bathgate et al., 2013). RLN1 and RLN2 are strong regulators of collagen expression and metabolism in fibroblasts, and are differentially expressed in the corpus luteum, decidua, and endometrium, as well as prostate tissue, while RLN3 is specific to the brain (Sherwood, 2005). Relaxin1 and 2 reconcile the hemodynamic changes occurring during pregnancy such as cardiac output, renal blood flow, and arterial compliance (Conrad, 2011), as well as weakening the pelvic ligaments for parturition in species such as guinea pigs and mice (Sherwood et al., 1993). RLN3 is a highly conserved neuropeptide in vertebrates, and is involved in a wide range of neuroactivities such as response to stress and cognition, as well as in neurological disease (Smith et al., 2011).

Relaxin binds to RXFP receptors and exerts its action through a ligand-receptor system in multiple pathways. The relaxin receptor is involved in signal transduction between extracellular/intracellular domains. Relaxin1–4 hormones are ligands for the RXFP1, RXFP2, RXFP3, and RXFP4, respectively (Fig. 1). This family peptides act on four G-protein-coupled receptors (GPCRs; formerly LGR7, LGR8, GPCR135, and GPCR142) (Kong et al., 2010). RXFP1 and RXFP2 are composed of large extracellular domains which encompass of leucine-rich repeats. On the other hand, RXFP3 and RXFP4 proteins are more similar to small peptide ligands. Recently, it has been shown that there is a difference in the ligand binding mode between RXFP1 and RXFP2 (Scott et al., 2012). RXFP1 and RXFP2 exist in uterus, cervix, vagina, brain, and heart of a number of animal species. However, production of these...
proteins differs among tissues of various species. For example, RXFP1 is expressed in rats and mice myometrium (Vodstrcil et al., 2010), whereas in human, this receptor is mainly localized to the endometrium (Campitiello et al., 2011). Moreover, RXFP1 is expressed in the rats and mice heart localized to the atria where it mediates positive inotropic and chronotropic responses (Piedras-Renteria et al., 1997), while there is currently no report of this receptor binding or function in the human heart.

Evidence also suggests that the functional domains of RXFP1, the cell type in which it is expressed, and the ligand used to activate the receptor all have important roles in the musculoskeletal system (Fig. 2). Relaxin alters cartilage and tendon stiffness by activating collagenase (Hashem et al., 2006; Pearson et al., 2011). Relaxin is also involved in bone remodeling process and in healing of injured ligaments and skeletal muscles (Li et al., 2005; Dragoo et al., 2009). The soft tissue healing cascade is composed of three phases, inflammation, regeneration, and fibrosis, and relaxin is a regulator of both inflammation and fibrosis (Mu et al., 2010).

Fig. 1. Interaction of RLN1, RLN2, and RLN3 proteins with their receptors RXFP1, RXFP2, and RXFP3, respectively, as well as with insulin-like growth factor (INSL3) and rearranged L-myc fusion (RFL) in the network (http://www.genecards.org/).

Fig. 2. A summary of relaxin role in the locomotor system.
Relaxin also acts as an antifibrotic agent, and favors muscle regeneration and against muscle fibrosis to promote regrowth of myofibers in skeletal muscle healing. In this review, our aim is to summarize and critically investigate the available data, strictly related to relaxin and its regulatory effect on the musculoskeletal system.

**Relaxin function in the musculoskeletal system**

The musculoskeletal system is composed of bone, synovium, ligament, muscle, tendon, articular cartilage, and the related connective tissues that support the body’s ability to move (Farley et al., 2012). Relaxin plays an integral role in the remodeling of multiple tissues of the musculoskeletal system.

**Bone**

Relaxin along with hormones such as estrogen and growth factors such as transforming growth factor-beta (TGF-β) helps orchestrate the bone remodeling process. These factors regulate a cytokine system containing three fundamental molecules: the receptor activator of nuclear factor κB ligand (RANKL), RANK, and osteoprotegerin (OPG). In the RANKL/RANK/OPG system, RANKL on the preosteoblastic/stromal cells binds to its receptor (RANK) on the osteoclastic precursor cells and induces expression of a variety of genes to provide the crucial signal to drive osteoclast recruitment and development (Faccioli et al., 2009). OPG regulates the system through blocking the effects of RANKL and interfering with RANK signaling. Relaxin facilitates differentiation of peripheral blood mononuclear cells into mature osteoclasts during osteoclastogenesis by stimulating osteoblastic/stromal cell production, while estrogen inhibits this process through increasing OPG production (Faccioli et al., 2009). Therefore, relaxin is one of the osteoclast-activating factors that increase bone resorption. It is also overexpressed in tumors that promote growth, differentiation, and invasiveness, which lead to osteolytic metastases (Clezzardin & Teti, 2007). Together, these data indicate a possible role of relaxin in osteoclastogenesis (Faccioli et al., 2009; Ferlin et al., 2010). Relaxin 2 (RLX2) regulates bone metabolism and proliferation in human osteoblasts. Stimulation of osteoblasts with RLX2 activates adenylyl cyclase (AC) and increases cAMP production by G-proteins and thereby increases cell proliferation (Ferlin et al., 2009). Previous studies have identified an inactivating mutation in the RXFP2 gene (T222P), which caused idiopathic osteoporosis in young men through functional osteoblast impairment and reduced bone density (Ferlin et al., 2009). A similar result was also observed in knockout mouse model (Ferlin et al., 2008, 2011). There is also some evidence to suggest that higher levels of estrogen and relaxin in pregnant women correlated with an increased prevalence of congenital dysplasia of the hip in neonates (Uden & Lindhagen, 1988; Saugstad, 1991; Steinetz et al., 2008). In view that relaxin affects both osteoclast and osteoblast, therefore this hormone is involved in bone remodeling process, and stimulation of osteoblast by RLX2 suggests that this hormone is potentially useful in the treatment of bone condition such as osteoporosis.

**Synovium**

Relaxin in combination with estrogens may also have therapeutic value in the treatment of rheumatoid arthritis (RA) (Santora et al., 2005; Ho et al., 2011). RA is a chronic and systemic inflammatory disorder that may affect many tissues and organs, but also causes bone destruction through synovial hypertrophy. However, the incidence and severity of this disease during pregnancy is lower than normal. During pregnancy, relaxin and estrogen levels in the serum are elevated leading to decrease in inflammation in RA patients (D’elia et al., 2003; Ho et al., 2011). Relaxin exerts its anti-inflammatory effect through down-regulation of neutrophil function (Bani et al., 1998) and stimulates leukocyte adhesion and migration in human mononuclear cells (Figueiredo et al., 2006). A combined treatment using relaxin and estrogen appears to reduce circulating tumor necrosis factor-α level in rat adjuvant-induced arthritis model of RA and increased the anti-inflammatory cytokine IL-10 in human cells. (Santora et al., 2005; Figueiredo et al., 2006). In view of this, relaxin has a potential beneficial effect in the treatment of synovial diseases.

**Ligament**

Relaxin hormone alters ligament mechanics due to its collagenolytic effect mediated by discharge of matrix metalloproteinases (MMPs) (Qin et al., 1997), collagenase (Wiqvist et al., 1984; Granstrom et al., 1992), and plasminogen activator (Koay et al., 1983). Relaxin treatment in pregnant cattle increased pelvic width and height (Perezgrovas & Anderson, 1982; Musah et al., 1986), but not in other joints such as wrist and knee (Weinberg, 1956; Marnach et al., 2003). Increase in serum relaxin concentration may also correlate with joint laxity (Lubahn et al., 2006; Dragoo et al., 2011a, b), but this effect during pregnancy is controversial (Forst et al., 1997). Some studies have reported higher relaxin levels in pregnant women with pelvic joint instability or hip joint laxity as compared with controls (Saugstad, 1991; Steinetz et al., 2008), while other studies did not (Ohtera et al., 2002). Two studies on the relationship between serum relaxin levels and joint laxity reported no significant association between this hormone level and knee and generalized joint laxity (Arnold et al., 2002; Wolf et al., 2013). Studies have also suggested a relationship between higher relaxin and progesterone serum levels in pregnant females with pelvic girdle pain syndrome (Maclennan...
et al., 1986; Wreje et al., 1995; Kristiansson et al., 1999) and pelvic floor dysfunction (Harvey et al., 2008), whereas other studies have not found such a relationship (Crelin & Brightman, 1957; Petersen et al., 1994; Vollestad et al., 2012). Study design and methodological differences may account for some of the conflicting data.

Relaxin appears to play a role in anterior cruciate ligament (ACL) injury (Faryniarz et al., 2006; Dragoo et al., 2009). Estrogen and relaxin receptors have been found in the human female ACL (Faryniarz et al., 2006). Studies on the mechanical properties of human ACLs illustrate that those treated with relaxin have reduced ligament integrity and may be at higher risk of injury (Toth & Cascas, 2001; Dragoo et al., 2011a). This finding was also replicated in an animal model, where rabbits treated with relaxin had significantly weaker ACLs compared with controls. Additionally, there was increased anterior tibial displacement on radiographic assessment, indicating ACL laxity, in animals treated with relaxin (Dragoo et al., 2009).

There may also be an association between ACL injuries and stages of menstrual cycle. Occurrence of ACL injuries during the ovulatory phase (midcycle) is more frequent than the luteal phase (Wojtyś et al., 2002). During this period, estrogen and relaxin levels are high; therefore, activation of the estrogen and relaxin receptors may be increased (Min & Sherwood, 1996; Slauterbeck et al., 2002). Relaxin activates collagenolytic system which increases collagenase synthesis and finally degrades the extracellular matrix composition (Garibay-Tupas et al., 2004; Guttridge, 2004).

A prospective study of elite female athletes illustrated that players with increased serum relaxin levels had an increased risk of an ACL tear compared with females with lower relaxin levels (Dragoo et al., 2011a). Players having a relaxin concentration of greater than 6.0 pg/mL had more than four times greater risk of ACL injury. Other studies have collaborated these findings (Schauberger et al., 1996; Wojtyś et al., 2002; Beynon et al., 2006; Dragoo et al., 2011a). Relaxin appears to affect other ligaments such as volar oblique in perimenopausal women via a receptor-mediated process. In this ligament, relaxin particularly binds and probably reveals in presence of cellular or extracellular matrix receptors (Lubahn et al., 2006). Taken together, these findings indicate that while relaxin effects are beneficial to the lower animals especially during pregnancy, its proposed effect on the peripheral ligament laxity in humans and animals may predispose the joint to a non-traumatic injury.

**Muscle**

Relaxin helps regulate normal skeletal muscle through two principle signaling pathways: AC and nitric oxide (NO). Relaxin activates the AC signaling pathway in skeletal muscles through the following signal chain:

relaxin receptor tyrosine kinase → Gi protein (βγ-dimer) → phosphatidylinositol 3-kinase (PI3K) → protein kinase Cz (PKCζ) → heterotrimeric Gs protein → AC → protein kinase A (Kuznetsova et al., 1999; Shpakov et al., 2004, 2006a, b, 2007a, b; Pertseva et al., 2006; Plesneva et al., 2008). Relaxin also activates the NO pathway in skeletal muscle via relaxin-mediated activation of receptor tyrosine kinase → Gi protein → PI3K → protein kinase D1 → protein kinase B → NO (Plesneva et al., 2008). NO regulates various biological processes, and is produced by NO synthase (Stamler & Meissner, 2001). There are data that indicate relaxin stimulates NO synthase signaling in the skeletal muscles of type 2 diabetic rats, leading to NO dysfunction (Kuznetsova et al., 2010).

Relaxin may be implicated in the skeletal muscle healing process by regulating inflammation, tissue remodeling, and fibrosis (Formigli et al., 2005; Sherwood, 2005). The degree of fibrotic response varies with the level of inflammation and injury. Relaxin may improve spontaneous regeneration of injured skeletal muscle as illustrated in an injured muscle mouse model (Fukushima et al., 2001; Sato et al., 2003). During this process, skeletal muscle cells regenerate and repair to reduce the size of a damaged or necrotic area and replace it with new living tissue. Degeneration/inflammation is a retrogressive change in cells and tissues characterized by abnormal structural changes and decreased functions (Li et al., 2005; Merchav et al., 2005; Negishi et al., 2005; Mu et al., 2010). Relaxin has been reported to regulate several steps during inflammation which include inhibition of platelet aggregation (Bani et al., 2007), inhibits activation and recruitment of neutrophils to the site of inflammation (Emanuela et al., 2004), and promotes migration of mononuclear leucocytes through RXFP1-dependent mechanism (Figueiredo et al., 2006).

In regeneration phase, immature granulation tissue containing active fibroblasts produces abundant type III collagen, which fills the defect left by an open wound (Volk et al., 2011). Granulation tissue moves, as a wave, from the border of the injury toward the center. As granulation tissue matures, fibroblasts produce less collagen and become more spindly in appearance, which then begin to produce a much stronger type I collagen (Syed et al., 2011). Some of the fibroblasts mature into myofibroblasts containing similar actin to the smooth muscle, which enables them to contract and reduce the size of the wound (Sarrazzy et al., 2011). Fibrosis is the last phase of healing where a non-functional scar tissue is formed caused by excessive accumulation of connective tissue following damage. Fibrosis often delays and impairs the recovery of damaged tissue (Diegelmann & Evans, 2004). Relaxin has been shown to inhibit fibrosis formation through several mechanisms that include neutralization of the effect of TGFβ1 and activation of the collagenolytic system, which increases collagenase synthesis (Garibay-Tupas et al., 2004; Guttridge, 2004;
Mendias et al., 2004, 2012; Mu et al., 2010; Vinall et al., 2011). Through these mechanisms, relaxin reduces the formation of fibrous scar tissue (Fig. 3). Relaxin administration to the injured skeletal muscle promotes activation of satellite cells, induces angiogenesis and revascularization, as well as represses the extended inflammatory reaction (Mu et al., 2010). Recently, relaxin administration to diabetic wound in mice has been shown to up-regulate the mRNA expression of vascular endothelial growth factor, epithelial NO, and stromal-cell-derived factor 1-α, stimulates angiogenesis and vasculogenesis, enhances MMP-11 expression, and increases wound-breaking strength (Bitto et al., 2013). In view that relaxin plays important role in the healing process, it can potentially be used as a therapeutic agent to treat damaged skeletal muscle (Negishi et al., 2005).

**Tendon**

Relaxin has been reported to effect tendon metabolism by controlling the length of tendon growth (Maclellan et al., 1986; Wood et al., 2003) and reduce tendon stiffness by increasing tendon laxity through activation of collagenase (Pearson et al., 2011). An in vivo study investigating the growth of rat tails and human patellar tendons showed that relaxin levels correlate with tendon length (Wood et al., 2003; Pearson et al., 2011). Rat tail tendons treated with relaxin exhibited alterations in collagen through interfering with fibril association and collagen sliding (Wood et al., 2003). Another study in women with normal menstrual cycle, who did not take any contraception pills, demonstrated a significant link between serum relaxin levels and patellar tendon stiffness (Pearson et al., 2011). Besides the reported effects of relaxin on the tendon, potential benefits of relaxin on tendon repair and remodeling are largely unknown.

**Cartilage**

Relaxin appears to decrease knee articular cartilage stiffness (Bonaventure et al., 1988; Hellio Le Graverand et al., 1998) through induction of collagenase-1, MMP-1, and MMP-3, which reduces collagen content and expression in fibrocartilaginous cells. Modulation of MMPs to loss of collagen by hormones may contribute selectively to degeneration of specific joints fibrocartilaginous explants facilitated by proteinases (Naqvi et al., 2005; Hashem et al., 2006). The degradation of extracellular matrix in fibrocartilage is synergized by β-estradiol. Relaxin exerts its effect through binding to RXFP1 and RXFP2 receptors (Hellio Le Graverand et al., 1998; Wang et al., 2009). The ratio of RXFP2 in knee meniscus of pregnant rabbits was shown to be more than RXFP1, which may indicate differential role of these receptors in the remodeling of fibrocartilage (Hellio Le Graverand et al., 1998; Wang et al., 2009). Comparison of collagen content in articular cartilage of nonpregnant and pregnant rabbits showed that the total RNA levels and chondrocyte metabolism decreased during pregnancy. Depending on the level of skeletal maturity, pregnancy can exert both general and specific effects on the RNA levels in articular cartilage of the rabbit knee (Hellio Le Graverand et al., 1998). Thus, relaxin may play a role in women’s susceptibility to musculoskeletal disease (Naqvi et al., 2005). Taken together, these findings suggested that in female, increased relaxin level may result in undesirable effects on the articular cartilage.

**Perspective**

Relaxin plays a vital role in biological processes including metabolism, growth, and reproduction. Among the four relaxin types, RLN1 and RLN2 regulate the musculoskeletal system via multiple pathways through a ligand-receptor system, depending on cell type and ligand (Table 1). Our investigation of relaxin’s role in the musculoskeletal system showed some limitations in the literature. For example, most of the reports did not delineate the relaxin isoform or its specific receptor. Additionally, despite relaxin’s accepted role in the regulation of AC and NO pathways, few studies have focused on the regulatory effect of these pathways in the
<table>
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<th>Organ</th>
<th>Author (year)</th>
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<th>Role of relaxin</th>
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<td></td>
<td>Naqvi et al. (2005)</td>
<td>Joint fibrocartilaginous cells</td>
<td>Rb/vitro</td>
<td>Human relaxin, β-estradiol</td>
<td>NI</td>
<td>No increase collagenase1 and MMP3 expression</td>
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<td>Knee meniscus fibrocartilage and articular cartilage</td>
<td>Rb/vitro</td>
<td>Human relaxin, β-estradiol, progesterone</td>
<td>NI</td>
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<td>Joint fibrocartilaginous cells</td>
<td>M/vitro</td>
<td>NI</td>
<td>1,2</td>
<td>Expression of RXFP2 &gt; RXFP1</td>
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<td>Santora et al. (2005)</td>
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<td>R/vivo</td>
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<td>Bone resorption by mediators</td>
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<td>Osteoclast cell</td>
<td>H/vitro</td>
<td>Relaxin</td>
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<td>Relaxin is a potent stimulator of osteoclastogenesis</td>
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<td>H/vitro</td>
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<td>Joint</td>
<td>Weinberg (1956)</td>
<td>Four nonpregnant and 11 pregnant Pelvic joints</td>
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<td>Relaxin as releasin</td>
<td>NI</td>
<td>No change in pelvic measurement</td>
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<td>Crelin and Brightman (1957)</td>
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<td>Relaxin, estrogen</td>
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<td>NI</td>
<td>Expansion of the pelvic area (p)</td>
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<td>H/vivo</td>
<td>NI</td>
<td>NI</td>
<td>High relaxin link between pelvic pain and joint laxity during late pregnancy</td>
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<td>Musah et al. (1986)</td>
<td>Pelvic joint</td>
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<td>Induction of pelvic expansion, highly significant interaction (p)</td>
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<td>Udén and Lindhagen (1988)</td>
<td>CDH patients</td>
<td>H/vivo</td>
<td>NI</td>
<td>NI</td>
<td>Increased sensitivity of the receptors of the fibroblasts</td>
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<td>Saugstad (1991)</td>
<td>153 pregnant women</td>
<td>H/vivo</td>
<td>NI</td>
<td>NI</td>
<td>Congenital hip dysplasia rate, consistent with estrogen and relaxin levels</td>
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<td>Schauberger et al. (1996)</td>
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<td>H/vivo</td>
<td>NI</td>
<td>2</td>
<td>No correlation with serum relaxin and joint laxity</td>
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<td></td>
<td>Forst et al. (1997)</td>
<td>90 newborn children</td>
<td>H/vivo</td>
<td>NI</td>
<td>NI</td>
<td>NI lower relaxin in newborns with pelvic presentation hip instability</td>
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<td>Vogel et al. (1998)</td>
<td>12 girls, three boys newborn 200 pregnant women</td>
<td>H/vivo</td>
<td>NI</td>
<td>2</td>
<td>Reduction of relaxin concentration with increasing sonographic hip</td>
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<td>Kristiansson et al. (1999)</td>
<td>Knee joint of nonpregnant and pregnant Athlete eumenorrheic women and men Pregnant women</td>
<td>R/vivo</td>
<td>NI</td>
<td>NI</td>
<td>Relaxin related with pelvic pain in early pregnancy</td>
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<td>NI</td>
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<td>Higher relaxin and fall significantly faster in women with PFD</td>
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<td>Volledstad et al. (2012)</td>
<td>212 women pelvic joints</td>
<td>H/vivo</td>
<td>NI</td>
<td>NI</td>
<td>Contribution with pelvic joint laxity but no responses to pain and disability</td>
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<td>Wolf et al. (2013)</td>
<td>289 healthy human</td>
<td>H/vivo</td>
<td>NI</td>
<td>2</td>
<td>No link between serum relaxin and generalized joint laxity</td>
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musculoskeletal organs. Although relaxin may affect many ligaments and tendons of the musculoskeletal system, previous studies have mostly concentrated on the anterior cruciate and wrist ligaments. Future studies are warranted to gain a better understanding of relaxin’s role in the musculoskeletal system.

**Key words:** relaxin, motor organs, skeletal muscle, tendon, ligament.

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