

The Basic Science of Lateral Epicondylitis: Update for the Future

Shariff K. Bishai, D.O., M.S.,*‡ and Kevin D. Plancher, M.D., M.S.†‡

Summary: Lateral sided elbow pain affects 1% to 3% of the general population. It is clear that lateral epicondylitis is not an inflammatory based disease and more appropriately should be named lateral epicondylitis. Significant contributions in the field of basic science has led us to a better understanding of the cause of this disease. This article reviews a most up to date understanding of this complex disease process.

Key Words: Lateral epicondylitis—Lateral epicondylitis—Tennis elbow—Lateral sided elbow pain—Basic science—Tendonitis—Tendinosis—Immunohistochemistry.

Many have been credited as being the first to describe lateral epicondylitis such as Morris¹ in 1882 and Major² in 1883 as “lawn tennis elbow,” Runge in 1873 as “writer’s cramp,” or Bernhardt in 1896 who thought modern day lateral epicondylitis was neuralgia.^{1,18,20,27} The irony of this disease is that only 5% to 10% of those with “tennis elbow” actually play tennis.³ The orthopaedic surgeon is often confronted by a patient with a myriad of elbow type symptoms; which in the past were all grouped under the heading of lateral epicondylitis. Today lateral epicondylitis affects 1% to 3% of the general population and as many as 19% of men by the 5th decade of life, with the average age of the classic patient with lateral epicondylitis of 42 years (range, 30–50 years).¹² Lateral sided elbow pain occurs much more frequently than medial-sided elbow pain, with ratios reportedly ranging from 4:1 to 7:1.³² We have also learned that lateral epicondylitis should be labeled lateral epicondylitis as no infection exists in this disease. The definition of lateral epicondylitis for this article is an overuse injury affecting the extensor carpi radialis brevis (ECRB) origin with resultant angiofibrotic dysplasia to the proximal end of this same tendon.

ANATOMY

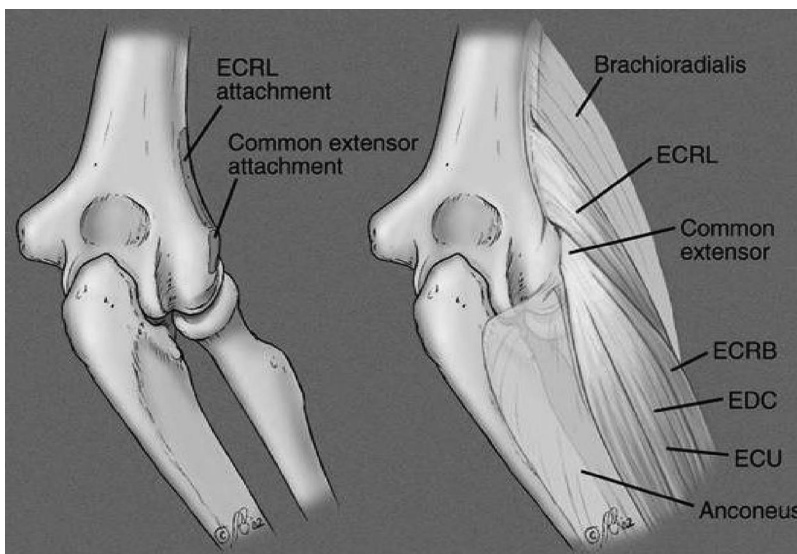
The lateral epicondyle gives rise to the musculotendinous structures of the ECRB, which is most commonly the origin of this muscle, the primary pathologic tissue of lateral epicondylitis according to histopathologic studies as has been shown in multiple studies. The extensor carpi radialis longus (ECRL), extensor digitorum communis (EDC), and the extensor carpi ulnaris (ECU) also have their origin from the lateral epicondyle. The ECRB is deep to the origin of the ECRL and deep to the EDC, with often a poor definition of the border between the ECRB and EDC (Fig. 1).

Newer studies have tried to explain why lateral sided epicondylitis occurs in many nonactive individuals. Normal vascular supply to tendons is from capillaries and nerves that penetrate the epitendon and endotenon but not the parietal paratenon that surrounds individual tendon fascicles.²⁴ The ECRB is a vascular tendon and does not receive any nutrition via its synovial sheath. Utilizing 12 cadaveric specimens, Schneeberger and Masquelet in 2002 described the vascular supply to the entire proximal ECRB. By injecting colored latex solution through the cadaver extremities, the vasculature to the area was investigated. They found that the radial recurrent artery nourishes the ECRB and the medial and lateral border of ECRB the tendon forms a network of small vessels on its surface. Important contributions from the posterior branch of the radial collateral artery and minor contributions are also provided by the interosseous recurrent artery. The undersurface of the

From the *Beth Israel Medical Center, New York, New York; †Albert Einstein College of Medicine, New York, New York; and ‡Plancher Orthopaedics and Sports Medicine, Orthopaedic Foundation for Active Lifestyles, Cos Cob, Connecticut.

Address correspondence and reprint requests to Kevin D. Plancher, MD, MS, Orthopaedic Foundation for Active Lifestyles, 31 River Rd., Cos Cob, CT 06807. E-mail: kplancher@plancherortho.com

FIG. 1. Muscular anatomy of the elbow (Copyright Kevin D. Plancher, M.D.).



ECRB tendon was almost avascular. These authors used these findings to hypothesize the potential hypovascular zones; located at the undersurface of the ECRB tendon causing degeneration and partial tears of the ECRB tendon. This they felt was the etiologic factor in the pathogenesis of lateral epicondylitis (Fig. 2).²⁸

Kaplan best described the neural anatomy about the elbow in 1959. He dissected the arm and elbow in

formalin specimens and found that branches of the radial nerve supply the periosteum and fibrous structures of the lateral distal end of the humerus. His description details the course of the radial nerve trunk to its terminal branches about the elbow. He also noted that an anastomosis was found occasionally between a branch of the musculocutaneous nerve and the radial articular branches supplying the lateral epicondylar region.¹¹

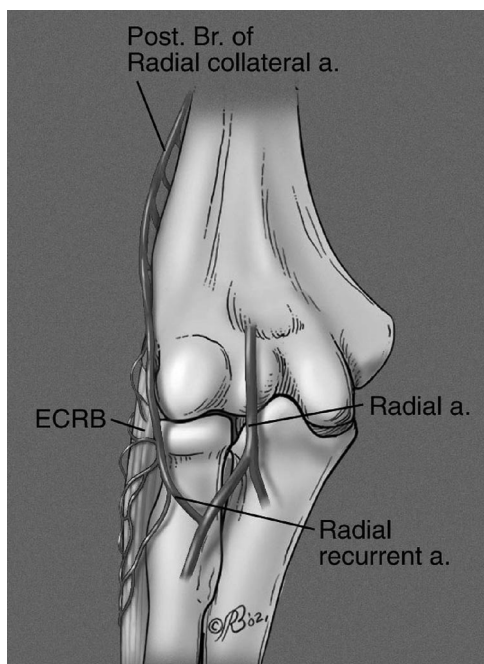


FIG. 2. Vascular anatomy of the elbow (Copyright Kevin D. Plancher, M.D.).

PATHOPHYSIOLOGY

Carp described lateral epicondylitis as “radial humeral bursitis in 1932.”⁴ Theories swarmed after his that an inflamed synovial fringe or fibrosis of the annular ligament as a result of trauma was responsible for the symptoms describes as lateral sided elbow pain.^{2,30} With more recent studies, Nirschl and Pettrone as well as Regan have confirmed that lateral epicondylitis is a neovascular problem caused by a degenerative process and is not an inflammatory process. This neovascular theory helps explain the patient’s refractory symptoms after intervention with anti-inflammatory modalities.^{24,26} Nirschl²² was the first to describe the prime etiological factor, which he described, is a force overload at the extensor aponeurosis leading to the following steps:

1. A mechanical predisposition of the elbow to stress overload on the basis of a disadvantaged leverage force system
2. Inadequate forearm extensor power and endurance to withstand moments of force placed against the forearm (intrinsic overload)

3. Inadequate forearm extensor flexibility (extrinsic overload)
4. Overwhelming moments of force or repetition in the face of reasonable muscle power, endurance, and flexibility (intrinsic and extrinsic overload)

Histologically, Ciccotti and others helped to show that the normal parallel orientation of collagen fibers are disrupted by the invasion of fibroblasts and vascular granulation-type tissue, with a paucity of acute and chronic inflammatory process. Microtearing of the ECRB tendon origin, with subsequent failed healing response alters the normal musculotendinous biomechanics leading to the onset of lateral sided elbow pain known to vary wrongly so as lateral epicondylitis.⁵

PATHOPHYSIOLOGY OF THE HEALING RESPONSE

Understanding the pathophysiology of a normal healing response to an injured tendon helps clarify why lateral epicondylitis often persists. After disruption of normally homeostatic structures occurs, the cells of the body are activated to mobilize necessary materials for repair and reconstruction of damaged tissues. As for tendons, structural disruption, bleeding, and a healing cascade that occurs over a period of months will be followed by a laceration of a tendon. Macrophages, endotenon-based fibroblasts and surrounding tissues contribute to the healing process. Blood-borne cellular and chemical systems form an extrinsic response lead to a clotting cascade in conjunction to the macrophage-based inflammatory and immune-response systems.¹⁰

The healing of a lacerated tendon is not comparable with chronic inflammatory conditions, such as rheumatoid arthritis, which are characterized by lymphocyte and neutrophil reactions. In tendon repair it is the presence of macrophages that are seen. This being true for acute, full-thickness tears of the ECRB, a common repetitive, overuse injury can be considered actually a chronic microtraumatic event. With sudden onset of pain to the lateral side of the elbow, it is likely that an acute worsening of an accumulated series of microscopic injuries of a tendon. Eccentric contractures are theorized to be the primary cause of these internal microtears.¹⁰ Józsa showed that a tendon could tear with as little as a net increase of 8% of its total length.⁹

TENDINOSIS VERSUS TENDONITIS

The term tendinosis has been used in recent studies to describe lateral sided elbow pain, as it has become more clear that the work of Nirschl and his description of the



FIG. 3. MRI: T2 image of rupture of the ECRB with lateral epicondylitis (Copyright Kevin D. Plancher, M.D.).

angiofibroblastic hyperplasia plays a role in lateral epicondylitis. Tendinosis appears to be a degenerative process that is characterized by the presence of dense populations of fibroblasts, vascular hyperplasia, and disorganized collagen.¹⁰ Tendinosis more accurately defines the histopathological presentation of this degenerative process. The term “tendonitis” in the past had been used to describe the theoretical chronic inflammatory changes in the overused tendon. Histologic evaluation of pathologic tendons has failed to show the presence of inflammatory cells. If chronic inflammatory cells are evident in the tendon, they are those of traumatic repair, and include granulation tissue and scar.^{23,24} Because the term “tendonitis” is a misnomer of, the term “tendinosis” should be used instead.

PATHOGENESIS OF TENDINOSIS

Lateral epicondylitis is a tendinosis caused by a cellular response to internal microtears. Nirschl staged his tendinosis into four stages. In stage 1 injury, occurs an inflammatory response is likely to start the cascade of events. With stage 2, angiofibrotic changes occurring leading to tendinosis and eventual angiofibrotic degeneration of the origin of the ECRB tendon. Stage 3 occurs when pathologic changes to a structural failure and rupture along with a tear of the ECRB tendon. Finally, stage 4 exhibits the features of stages 2 or 3 and is associated with other changes such as fibrosis, soft matrix calcifications, and hard osseous calcification.¹⁰ Nirschl staged the pathologic stages of tendinosis as shown in Table 1.

Regan et al. believed that the vascular hyperplasia seen in lateral epicondylitis was evidence of an immature repair process.²⁶ Kraushaar and Nirschl noticed under light microscopy of sections of pathologic ECRB

TABLE 1. Stages of Lateral Epicondylitis including MRI and Histologic Changes

Pathologic Stages of Tendinosis ¹³		MRI ²²	Findings
Stage 1	Temporary irritation (? chemical inflammation)	T1&T2 increased signal	Usually at the origin of the ECRB
Stage 2	Permanent tendinosis—less than 50% tendon cross section	T2—increased signal	Corresponds with area of mucoid degeneration and neovascularization
Stage 3	Permanent tendinosis—greater than 50% tendon cross section	T2—increased signal	Corresponds with area of significant disruption of collagen fibers and tear of tendon
Stage 4	Partial or total rupture of tendon (Fig. 3)	T2—increased signal	Disruption of the tendon and edema

tendons stained with hematoxylin and eosin revealed vascular hyperplasia within regions of tendinosis. They also noted that immunohistochemical studies with smooth muscle antigen (SMA) enhanced the more mature vascular elements regardless of whether the vessels in the area of tendinosis were caused by extrinsic capillary ingrowth or were the product of an intrinsic mesenchymal reaction proving that this hyperplasia was not entirely an immature process. It was also, noted by Nirschl that the vascularity of tendinosis was abnormal when visualized with the electron microscope. The collagen matrix in the regions surrounding the vascular hyperplasia was of poor quality, which including the vessels commonly seen in the most abnormal appearing areas of collagen. This proved that the vascular hyperplasia in tendinosis was not associated with improved healing of the tendon but rather a pathologic state.¹⁰

Microfibrils form subfibrils, fibrils, and fascicles, in increasing order of size. With normal collagen, ribosomes in the fibroblast assemble amino acids, mostly glycine, proline, and hydroxyproline, into a primary structure of tropocollagen. Their linear structure is formed into a left-handed configuration whereas the tertiary structure of collagen is made of tropocollagens that are formed into a right-handed helix. Five collagen molecules make up a single microfibril of tendon. The tendon collagen is approximately 64 nm wide, triple helical, with a quarter-stagger arrangement. They are internally bound by a matrix of proteoglycans and glycosaminoglycans.¹⁰

The collagen in lateral sided tendinosis is abnormal. It can be appreciated by gross examination by light or by electron microscopic examination. Grossly, the collagen has a dull, gray, and soft appearance compared with the shiny, white, firm, normal appearing fibers. The presence of fibrocartilage alone should not be misdiagnosed as tendinosis. Milz et al. studied 12 cadaveric specimens, 6 with a mean age of 47 and 6 with a mean age of 84. Chondrocytic clusters and signs of fibrocartilage cell proliferation were also a striking features found in the elderly patients without any symptoms of lateral sided pain. Fibrocartilage is now felt to be a normal feature of epicondylar tendonopathy that should not merely be equated with pathologic changes.¹⁹

HISTOPATHOLOGIC FEATURES OF TENDINOSIS

Goldie⁸ was the first to describe the histopathologic changes of tendinosis. Later work by Nirschl and Pettrone³ crystallized many modern theories of this disease process. Angiofibroblastic tendinosis, is a distinctly noninflammatory, degenerative, avascular process associated with the formation of disorganized collagen. Goldie as well as Nirschl and Pettrone have studied immature collagen as well as immature fibroblastic and vascular elements. Tendinosis is known to be a result of failed tendon healing.^{3,8}

In normal tendons, type I collagen bundles are oriented along the long axis of the tendon in a tightly packed, highly ordered fiber matrix that is ideal for transmitting load (Fig. 4).³³ Between these rows are a sparse number of spindle-shaped, long, thin tendon fibroblast cells with dark cytoplasm, which are arranged longitudinally, parallel to the long axis of the tendon. The collagen fibrils are embedded in a matrix of proteoglycans, glycosaminoglycans, and water with few cells.³³

The predominant type of cell in tendinosis is a mesenchyme-derived tendon fibroblast (tenocyte), which has plump fibroblasts and a decreased nucleus-to-cytoplasm ratio compared with normal tenocytes.²⁶ In the article by Kraushaar and Nirschl in 1999, the authors stained the



FIG. 4. Histologic slide of lateral epicondylitis (Copyright Kevin D. Plancher, M.D.).

tendons with hematoxylin and eosin, which demonstrated fibroblastic hyperplasia. Sections were stained for elastin with modified Verhoeffvan Gieson stain revealing well defined fibroblasts. Areas stained with Masson trichrome and vimentin stain showed permeative fibroblastic hyperplasia throughout regions that had appeared nearly normal on the sections that had been stained with hematoxylin and eosin.¹⁰ Doran et al. examined histologic specimens from surgical releases of the ECRB finding evidence of a repair response of variable degree at the bone-tendon junction. The most frequent features being mucopolysaccharide infiltration and bone formation. Fibrofatty degenerative changes were also present in some of the specimens retrieved from the operating room.⁷ These findings represent the structural changes caused by lateral epicondylitis.

When Kraushaar and Nirschl viewed these specimens by electron microscopy, the fibroblasts revealed many vacuoles, open nuclear chromatin, abundant production of collagen along the periphery of the cells, and contractile elements within some of the fibroblasts as seen with myofibroblasts. The authors identified two populations of fibroblasts, those with intracellular contractile elements and those without.¹⁰

Multiple authors have written about the histopathologic changes of the ECRB tendon in lateral sided elbow pain. Regan et al. spoke of an immature reparative process set in a background of focal hyaline degeneration.²⁶ Leadbetter reported disorganization of the collagen fibers with microtears and signs of repair and hyaline degeneration. Nirschl and Pettrone noted the formation of disorganized and immature collagen and suspected a mesenchymal cell-derived failure of collagen cross-linkage.²⁴ Teitz et al. has written about the matrix in areas of tendinosis as disorganized lacking the usual axial, tightly woven bundles.²⁹

At high power magnification with vimentin staining, the abnormal tendon shows a blend of abnormal and more normal-appearing collagen. When stained with elastin, though, nests of tendinosis are insinuated between fibers of normal collagen showing the heterogeneous pattern of tendinosis. The collagen fibers in areas of tendinosis are integrated into the surrounding matrix and appear as a separate mass of unremodeled collagen and matrix production.¹⁰

With electron microscopy, abnormal collagen with tendinosis is composed of individual strands, which are of normal width and had a normal periodicity of banding pattern. Fibrils, though, do not form fascicles and often are highly fragmented into very short segments that are mixed among longer pieces. Looking at their cross section, colla-

gen fibers from the tendinotic area have a variable diameter, with an uneven mixture of thick and thin fibrils.¹⁰

IMMUNOHISTOCHEMISTRY OF LATERAL EPICONDYLITIS

Uchio et al. (2002) purposed that neuropeptides and cytokines such as substance P, calcitonin gene-related peptide, interleukin 1 α , and transforming growth factor β 1 are found at the origin of the ECRB muscle affected the pathogenesis of lateral epicondylitis. Utilizing immunohistochemistry on biopsies of 10 elbows (9 patients) they found nerve fibers around small vessels for substance P-like immunoreactivity or CGRP-like immunoreactivity as well as IL-1 α and TGF- β 1. Their findings suggested such a link that might promote inflammation and stimulate proliferation and matrix synthesis of fibroblasts, contributing to the pathology of tennis elbow.³¹

Ljung and associates conducted a similar study, but they also looked at patients suffering from medial epicondylalgia. As with the previous study, by using immunohistochemistry and antibodies to neurokinin 1-receptors, the distribution of this receptor was studied at the ECRB insertion to the lateral epicondyle. Specific immunoreactions were seen as varicose fibers occurring as single fibers or grouped into bundles indicating that substance P has effects in the nerves of this region. Their results give further evidence for a possible neurogenic involvement in the pathophysiology of tennis elbow and in medial epicondylalgia.¹⁵ In another study by Ljung et al., no inflammatory-cell infiltrates and few mast cells were seen in a 6 patients with lateral epicondylitis and in 6 controls taken from patients at their symptomatic ECRB origin. This recent study gives further evidence to previous suggestions that lateral epicondylitis is not an inflammatory process. These studies would substantiate that frequent mechanical involvement affects sensory innervation, substance-P and calcitonin gene-related peptide; which may have various important efferent effects including microvascular leakage and local edema formation at the lateral side of the elbow at the ECRB attachment.¹⁶ Further studies to assess immunohistochemical links to lateral epicondylitis are needed.

In an alternate study by Ljung et al., they used immunohistochemistry and antibodies to protein gene product (PGP) 9.5 to assess the innervation of the ECRB muscle origin. Neuropeptide Y (NPY), tyrosine hydroxylase (TH), and vasoactive intestinal peptide (VIP) antibodies were used as markers to analyze the pain source to the ECRB. PGP 9.5 immunoreactions were detected in association with small blood vessels and arteries and within nerve bundles. The interesting finding was het-

erogenicity in the perivascular nerve fiber distribution since some blood vessels exhibited a high degree of PGP 9.5 and others did not. In the arteries there was a marked TH/NPY innervation of the walls but basically no VIP-containing nerves, and sensory innervation restricted to the small blood vessels. These findings show that the ECRB muscle origin is supplied with heterogeneously distributed sympathetic and sensory innervations and therefore there appears to be an imbalance between the vasoconstrictor and vasodilator innervations along the vascular tree in this region.¹⁶ Zeisig and associates used ultrasound and color Doppler to examine the common extensor origin. In 21 of 22 patients with diagnosed Lateral Epicondylitis, increased vascularity was demonstrated whereas only 2 of 22 in the pain-free control group were seen to have increased vascularity.³⁴ These studies add merit to our strong beliefs that plausibility of vascularity plays a major role in the pain process of lateral epicondylitis.

SUMMARY

Lateral epicondylitis is an extremely common problem. Many studies have been done to describe the pathologic process. What was first thought to be an inflammatory process has been proven not to be the case. Nirschl and Pettrone's finding of disruption of the normal collagen architecture with ingrowth of fibroblastic and granulation tissue help show that there is a paucity of an inflammatory process. The angiofibroblastic process that is noted as well as the immunohistochemical changes present with lateral epicondylitis has now given credence to a pain pathway that leads us to understand the pathologic process at a microscopic level leading to the considerable pain too many patients have when noting their lateral sided elbow pain. Further studies are underway to help us as clinicians understand the basic science of lateral epicondylitis so that we may treat our patients more efficiently and effectively.

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