FOOT & ANKLE INTERNATIONAL

Etiologic Factors Associated with Symptomatic Achilles Tendinopathy

George B. Holmes, M.D.; Johnny Lin, M.D.
Chicago, IL

ABSTRACT

Background: **The purpose of this study was to determine if a statistical association exists between Achilles tendinopathy (also referred to as tendinosis) and obesity, diabetes mellitus, hypertension, the supplemental use of estrogen, and exposure to local or systemic steroids.** ***Methods:*** **From July, 1997, to February, 2003, 82 patients with a diagnosis of Achilles tendinopathy were identified. The diagnosis of Achilles tendinopathy was confirmed by a review of medical records, radiographs, and MRI. There were 44 women and 38 men with an average age of 50 (range 27 to 77) years. For the parameters of obesity, hypertension, diabetes, steroid exposure, and the use of estrogen compounds, all patients were analyzed both cumulatively and stratified into subgroups by gender and age. Chi-square 2 x 2 tables were used to compare the observed prevalence of the parameters in patients with Achilles tendinopathy to the expected prevalence of these disorders and exposures in the population at large.** ***Results:*** **Cumulatively, 98% percent (43 of 44 women; 29 of 38 men) had hypertension, diabetes, obesity, and steroid or estrogen exposure. Seventy-six percent of men (29) had hypertension, diabetes, and obesity, or steroid exposure. Sixty-eight percent of women (15 of 22) had a history of hormone replacement therapy and 44% (8 of 15) had a positive history for use of oral contraceptives. When compared with published national data using Chi-square analysis, the association between tendinopathy and hormone replacement therapy and oral contraceptives was found to be statistically significant with *p*-values of 0.01 and 0.001, respectively. For both women and men, obesity was statistically associated with Achilles tendinopathy with *p*-values of 0.025 and. 001, respectively. Hypertension was statistically associated with Achilles tendinopathy only for women. Diabetes mellitus and Achilles tendinopathy were found to have a statistical association only for men younger than 44 years old** ***Conclusions:*** **Obesity, hypertension, and steroids have as their end-organ effect a diminution of local microvascularity. The significant correlation of these factors with Achilles tendinopathy suggests the importance of their effect on microvascularity in the development of Achilles tendinopathy.**

Key Words: Achilles Tendon; Haglund Deformity; Insertional Disorders

INTRODUCTION

Achilles tendinopathy has been classified as paratendinitis, paratendinitis with tendinosis, and tendinosis.[38] Paratendinitis was defined as an inflammation of the tissues surrounding the substance of the tendon. On the other hand, tendinosis and tendinopathy have been described as the chronic intratendinous degeneration of the tendon.[1,10,20] Histological studies have shown different findings for tendinitis compared to tendinosis.[17,18] In the former, specimens showed acute inflammatory features. However, with tendinosis and tendinopathy specimens revealed the presence of coalesced collagen fibers, cystic mucoid changes, calcifications, and vascular degenerative changes.[14]

The exact etiology and natural history of Achilles tendinopathy currently are unknown. The normal aging process may result in histologic tendinopathy, which predisposes patients to partial tears and the subsequent development of pain.[2,9,40] A diminution of local blood supply also may be a possible predisposing factor to the development of tendinosis.[1,48] The so-called "watershed" region of hypovascularity was found to occur between 2 and 6 cm proximal to the insertion of the Achilles tendon onto the calcaneus.[4,38] Other etiologic factors may include overuse, gait or biomechanical abnormalities, cortisone use, quinolone antibiotics use, and endocrine or metabolic factors.[37,43]

A previous study demonstrated an association between hypertension, diabetes, and obesity[25] with acute ruptures of the Achilles tendon.[12] A similar association has been determined to occur in patients with posterior tibial tendon ruptures.[11] The presence of the comorbid diseases of hypertension, diabetes mellitus, and obesity may cause altered and diminished vascularity in addition to decreased healing potential in other areas of the body.[7,27,45] The association of

Corresponding Author:
George B. Holmes, M.D.
Department of Orthopaedic Surgery
Rush University Medical School
800 South Wells, M30
Chicago, IL 60607
E-mail: george_holmes@rsh.net

these disorders with symptomatic Achilles tendinopathy was evaluated in this study.

The effect of female hormones on connective tissues has recently received new interest among researchers. Increased levels of estrogen have been shown to have a direct effect on tissue composition and tissue biomechanical properties.[5,47] For example, women with anterior cruciate ligament ruptures have been shown to have an increased incidence of ruptures associated with ovulation and elevated levels of estrogen.[46] Increased laxity of the anterior cruciate ligament also has been associated with pregnancy; this laxity reverses after childbirth.[5] Estrogen receptors have been localized within the substance of the anterior cruciate ligament, thereby establishing a direct physiologic link between the observed clinical effects and the levels of estrogen.[21] By studying the occurence of these possible etiologies in a large group of patients with the diagnosis of Achilles tendinosis, it was our goal to gain further insight into the role of estrogen as an etiologic factor in the development of degenerative changes that accompany Achilles tendinopathy.

MATERIALS AND METHODS

From July, 1997, to February, 2003, 82 patients were identified with a clinical diagnosis of Achilles tendinopathy. The clinical diagnosis was confirmed by a history of posterior Achilles tendon pain or posterior heel pain aggravated by weightbearing and walking activities and tenderness with direct palpation of the Achilles tendon. On examination, there was visual and textural confirmation of nodularity within the substance of the Achilles tendon or at its insertion onto the calcaneus. Radiographs and MRI were used to confirm the diagnosis and to exclude the diagnoses of Haglund deformity and Achilles tendinitis. Radiographs were useful in discerning the presence or absence of traction spurs, Haglund deformity, intrasubstance calcifications, and soft-tissue swelling within the Achilles tendon. The diagnosis of Achilles tendinopathy was further validated by MRI with the identification of intrasubstance signal change within the tendon on both T1 and T2-weighted images in the axial and sagittal planes (Figures 1 and 2). MRI scans were obtained in 76% of patients (63 of 82), and in each the diagnosis of Achilles tendinopathy was confirmed. Twenty-six patients had surgery for their Achilles tendinopathy. The procedures consisted of Achilles tendon debridement for relatively small lesions and Achilles tendon reconstruction for larger, more involved lesions.

Of the 82 patients, 44 were women and 38 were men. The average age was 50.5 (range 27 to 77) years. The average age of the men was 49.5 (range 27 to 77) years. For women the average age was 51.3 (range 34 to 72) years. Involvement of the right leg was predominant and occurred in 49 of the 82 patients.

Fig. 1: Sagittal view of Achilles tendinosis.

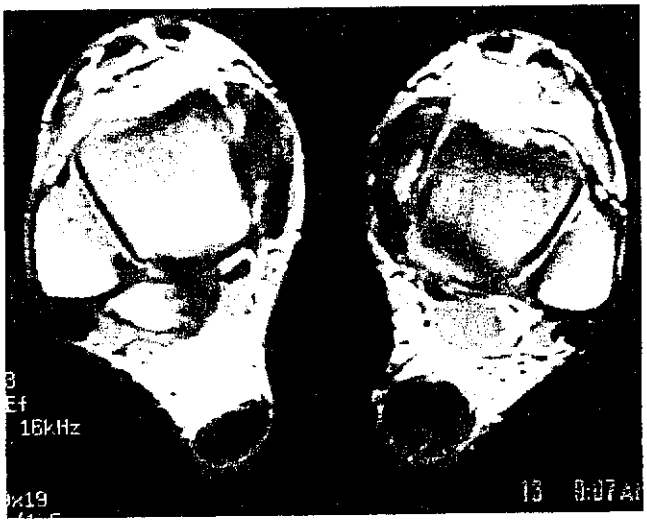

Fig. 2: Coronal view of Achilles tendinosis.

The charts were reviewed to determine the presence of obesity, hypertension, diabetes mellitus, steroid exposure, and estrogen exposure.

The height and weight of the patients also were recorded in the retrospective review of the charts. Obesity was considered to be present in patients with a body mass index (BMI) of more than 30.

The criterion for classifying patients as hypertensive was a systolic blood pressure of more than 140 mm Hg or a diastolic blood pressure of more than 90 mm Hg or both. Patients also were included in the hypertensive group if they were currently involved in a physician-directed treatment program for hypertension.

Patients were classified has having diabetes mellitus if they were under the treatment of their primary care physician or endocrinologist for a confirmed diagnosis of diabetes. The acceptable treatment modalities included a regimen of diet control, exercise, oral medications, or insulin. For the

purposes of data acquisition and data manipulation, there was no differentiation between insulin-dependent diabetes mellitus and noninsulin-dependent diabetes mellitus.

Previous or current use of systemic or local steroids, hormone replacement therapy, or oral contraceptive pills was obtained from the medical history completed by the nurse or physician or from the patient intake information sheet. The chart review was supplemented by telephone interviews using a standardized text for information not available in the patient's chart. The prevalences of steroid exposure, estrogen exposure, hypertension, and obesity were calculated and placed into groups stratified by age (Tables 1 and 2).

The prevalence data obtained from the control group were compared to two control groups. The first comprised an internal control group that consisted of a retrospective collection of 100 consecutive foot and ankle patients seen in the span of 1 month (2003) in the office of the senior author (GH). All patients were included regardless of the diagnosis. The age and prevalence of diabetes mellitus, hypertension, obesity, steroid, and estrogen exposure were obtained using a standard new patient intake form.

The second control group was a national control group, which consisted of the reported prevalence of specific chronic diseases.[28–31] Additionally, national controls were established for the reported prevalence of hormone replacement therapy and use of oral contraceptive pills in the general population.[16,32] Since there is no documented prevalence data for the use of steroids in the general population there were no values to compare for this study. The results for the association between steroids and Achilles tendinopathy are, therefore, limited to a descriptive and observational analysis.

For all parameters, the patients were analyzed cumulatively and in subgroups by gender and age. The national prevalence studies were used to determine the age groupings used in this study. Chi-square 2 × 2 tables were used to compare the observed prevalence in patients with Achilles tendinosis with the expected prevalence of these disorders and exposures in the population at large, as well as to the internal control patients. Statistical significance was determined as a p-value of less than 0.05.

RESULTS

The chi-squared results for the prevalence of obesity in patients with Achilles tendinopathy in men and women are reported in Table 3. There was a statistically higher than expected prevalence of obesity in men with Achilles

Table 1: Prevalence data for obesity, diabetes, and hypertension

Male				**Female**			
Age	OB	Total	Percent	**Age**	OB	Total	Percent
20–34	2	4	50.00	20–34	0	2	0
35–44	6	9	66.67	35–44	8	13	61.54
45–54	6	11	54.55	45–54	10	12	83.33
55–64	6	10	60.00	55–64	8	12	66.67
65–74	1	2	50.00	65–74	1	3	30.00
>74	1	1	100.00	>74	0	0	0
Total	22	37	59.46	**Total**	27	42	64.29
	DM	Total	Percent		DM	Total	Percent
27–44	1	13	7.69	27–44	0	15	0
45–64	1	22	4.55	45–64	3	24	12.5
65–74	0	2	0	65–74	1	5	20.00
>74	0	1	0	>74	0	0	0
Total	2	38	5.26	**Total**	4	44	9.09
	HTN	Total	Percent		HTN	Total	Percent
<20	0	0	0	<20	0	0	0
20–34	0	4	0	20–34	0	2	0
35–44	0	9	0	35–44	4	13	30.77
45–54	6	12	50.00	45–54	10	12	83.33
55–64	9	10	90.00	55–64	8	12	66.67
65–74	1	2	50.00	65–74	5	5	100.00
>74	0	1	0	>74	0	0	0
Total	16	38	42.11	**Total**	27	44	61.36

DM = diabetes mellitus; HTN = hypertension; OB = obesity.

tendinosis in comparison with the clinical control population for the age groups 45 to 54 years, 65 to 74 years, and older than 74 years. This increased prevalence also was noted when the Achilles tendinopathy group was compared with national norms in the age groups 35 to 44 years, 55 to 64 years, and older than 74 years and for the group as a whole. Among women, the significant groups in which obesity was associated with Achilles tendinopathy were the 35 to 44 year-old group, 45 to 54 year-old group, and the group as a whole when compared to both the clinical and national controls.

The only increased prevalence for diabetes and Achilles tendinosis was found to occur in men younger than 44 years old with Achilles tendinopathy compared to the clinical control group (Table 4).

The statistical data for hypertension are shown in Table 5. Hypertension was shown to be a statistically significant factor for men with Achilles tendinopathy in the 55 to 64-year-age group for both national controls and internal clinical controls. Statistical significance was found for women in the 35 to 44-year-age group and the 45 to 54-year-age group as well as the women grouped as a whole with respect to clinical controls in the 45 to 54-year-age group and when compared to national controls.

The statistical data for oral contraceptive pills are shown in Table 6. Statistical significance was noted for the 25 to 34-year-age group, 35 to 44-year-age group, and for the women in total from ages 15 to 44 years old when compared to national controls.

The Chi-squared results for the prevalence of hormone replacement therapy in women with Achilles tendinopathy also are summarized in Table 6. Hormone replacement therapy was statistically associated with Achilles tendinopathy in the 60 to 64-year-age group and for the group as a whole (50 to 74 years).

Table 2: Prevalence of oral contraceptive pills, hormone replacement therapy and steroids

Age	OCP	Total	Percent
15–19	0	0	0
20–24	0	0	0
25–34	2	2	100
35–44	6	13	46.15
Total			
Ages 15–35	8	15	53.33

*National norms only available for ages 15 to 35 years. Twenty-nine patients >35, three with inadequate information. OCP = oral contraceptive pills.

	HRT	Total	Percent
50–54	3	7	42.86
55–59	5	6	83.33
60–64	5	5	100.00
65–69	1	2	50.00
70–74	1	2	50.00
Total	15	22	68.18

*National norms only available for 50 to 74 years. Nineteen patients <50, three with inadequate information. HRT = hormone replacement therapy.

	Steroid	Total	Percent
Injection	15	82	18.29 (Heel injections)
Injection	14	82	17.07 (None heel injections)
Oral	13	82	15.84
Other	32	82	39.02

DISCUSSION

Disorders of the Achilles tendon include bursitis, Haglund deformity and Achilles tendinitis, tendinopathy, and tendinosis. The effect of systemic disease on the development of ruptures of the Achilles tendon has been demonstrated.[12] An association between various systemic diseases and degenerative tendinopathy of the Achilles tendon has yet to be quantified by epidemiologic studies. The purpose of this study was to identify risk factors that may contribute to the development of Achilles tendinosis by comparing the presence of specific epidemiologic risk factors in patients with Achilles tendinopathy with national and internal control patient populations.

The results of the comparison of hypertension, diabetes, obesity, oral contraceptive pills, and hormone replacement therapy between patients with Achilles tendinopathy and controls indicated that there is an increased aggregate association between these conditions and the development of symptomatic Achilles tendinopathy.

Hypertension has been cited as a common and important risk factor for nearly all vascular disorders.[8] An animal study showed that the presence of hypertension results in alterations in the composition and biomechanical properties of arterial vessels causing them to be less distensible.[42] The cumulative result of hypertension affects all three limbs of Virchow's triad which includes 1) endothelial damage,[18] 2) stasis or turbulence of flow,[39,42] and 3) hypercoagulability.[36] This promotes a prothrombotic state in which small thrombi, occlusive arterial disease, and decreased blood flow may alter circulation to the Achilles tendon.

Obesity has been found to be an independent epidemiologic risk factor for atherosclerotic disease.[9] Obesity also has been shown to cause an insulin-resistant state that

Table 3: Statistical analysis for obesity

Male					
Age	**Study group**	**Office Control**		**National control**	
20–34	50	57.14	($p < 1$)	24.1	($p < 1$)
35–44	66.67	75.00	($p < 1$)	25.2	**($p < 0.01$)**
45–54	54.54	14.29	**($p < 0.001$)**	30.1	($p < 0.10$)
55–64	60	42.86	($p < 1$)	23.9	**($p < 0.01$)**
65–74	50.00	0	**($p < 0.001$)**	33.4	($p < 1$)
>74	100	0	**($p < 0.001$)**	20.4	**($p < 0.05$)**
Total	59.46	44.68	($p < 0.2$)	27.7	**($p < 0.001$)**
Female					
Age	**Study group**	**Office Control**		**National control**	
20–34	0	0	($p < 1$)	25.8	($p < 1$)
35–44	61.54	25.00	**($p < 0.01$)**	33.9	**($p < 0.05$)**
45–54	83.33	47.06	**($p < 0.025$)**	38.1	**($p < 0.01$)**
55–64	66.67	60.0	($p < 1$)	43.1	($p < 0.20$)
65–74	33.33	42.86	($p < 1$)	38.8	($p < 1$)
>74	0	75.00	($p < 1$)	25.1	($p < 1$)
Total	64.29	41.51	**($p < 0.025$)**	34.0	**($p < 0.001$)**

Bold type = statistical significance.

Table 4: Statistical analysis for diabetes mellitus

Male					
Age	**Study group**	**Office Control**		**National control**	
0–44	7.7	4.35	($p < 1$)	0.61	**($p < 0.05$)**
45–64	4.55	33.33	($p < 1$)	5.92	($p < 1$)
65–74	0	0	($p < 1$)	12.6	($p < 1$)
>74	0	0	($p < 1$)	11.76	($p < 1$)
Total	5.26	17.02	($p < 1$)	2.92	($p < 1$)
Female					
Age	**Study group**	**Office Control**		**National control**	
0–44	0	0	($p < 1$)	0.93	($p < 1$)
45–64	12.5	7.41	($p < 1$)	6.24	($p < 1$)
65–74	20.0	28.57	($p < 1$)	10.94	($p < 1$)
>74	0	25.0	($p < 1$)	10.4	($p < 1$)
Total	9.1	9.43	($p < 1$)	3.46	($p < 0.2$)

Bold type = statistical significance.

Table 5: Statistical analysis for hypertension

Male					
Age	**Study group**	**Office Control**		**National control**	
20–34	0	14.29	($p < 1$)	11.8	($p < 1$)
35–44	0	18.75	($p < 1$)	19.2	($p < 1$)
45–54	50.00	28.57	($p < 0.2$)	36.9	($p < 1$)
55–64	90.00	42.9	**($p < 0.025$)**	50.7	**($p < 0.025$)**
65–74	50.00	100	($p < 1$)	68.3	($p < 1$)
>74	0	0	($p < 1$)	70.7	($p < 1$)
Total	42.11	29.79	($p < 0.2$)	29.8	($p < 0.2$)
Female					
Age	**Study group**	**Office Control**		**National control**	
20–34	0	14.29	($p < 1$)	3.10	($p < 1$)
35–44	30.77	0	**($p < 0.001$)**	18.6	($p < 1$)
45–54	83.33	29.41	**($p < 0.001$)**	33.4	**($p < 0.001$)**
55–64	66.67	60.0	($p < 1$)	57.9	($p < 1$)
65–74	100	50.0	($p < 1$)	84.9	($p < 1$)
>74	0				
Total	61.36	32.08	**($p < 0.01$)**	27.5	**($p < 0.001$)**

Bold type = statistical significance.

Table 6: Statistical analysis for oral contraceptive pills and hormone replacement therapy

OCP			
Age	**Study group**	**National control**	
15–19	0	43.8	($p < 1$)
20–24	0	52.1	($p < 1$)
25–34	100	33.3	**($p < 0.05$)**
35–44	46.15	8.7	**($p < 0.001$)**
Total	53.33	26.9	**($p < 0.025$)**
HRT			
Age	**Study group**	**National control**	
50–54	42.86	49.43	($p < 1$)
55–59	83.33	45.31	($p < 0.1$)
60–64	100.00	35.35	**($p < 0.01$)**
65–69	50.00	32.58	($p < 1$)
70–74	50.00	22.89	($p < 1$)
Total	68.18	37.86	**($p < 0.01$)**

Bold type = statistical significance.

results in decreased endothelial cell nitric oxide levels.[35] A similar decrease in nitric oxide levels also is caused by hypertension.[45] These factors both lead to decreased blood flow, which would compromise the normal metabolism and reparative maintenance of the Achilles tendon.

Diabetes mellitus also may contribute to the progression of arterial disease.[8] However, except for men up to 44 years of age, an increased prevalence of diabetes mellitus in patients with Achilles tendinopathy was not noted. This finding differs somewhat from previous epidemiologic data, which indicated an increased prevalence of diabetes in patients with Achilles tendon ruptures.[12] Studies have shown an increased tendency to have type II and type III collagen in diabetic patients. A study using a rat model demonstrated increased glycation of the Achilles tendon, which results in an alteration of several biomechanical properties.[35] This process leads to an increase in the general stiffness of the tendon. Further investigations are necessary to determine if and why diabetes mellitus may be more prevalent in patients with Achilles tendon ruptures than in patients with Achilles tendinopathy.

Female hormones have been shown to play a significant role in the composition and biomechanical properties of connective tissues.[21,46,47] For example, within the anterior cruciate ligament, physiologic levels of estrogen reduces collagen synthesis by more than 40% in isolated ligament

cells. There is an associated decrease in the proliferation of collagen as well.[21] Approximately 70% of the dry weight of a tendon is collagen, with about 95% of this being type I collagen.[20] Type I pro-collagen and cellular proliferation have been shown to decrease in a dose-dependent manner with increasing levels of estrogen in human in-vitro anterior cruciate ligament fibroblasts.[47] Type I collagen imparts greater mechanical strength to connective tissues. Type III collagen contributes to decreased elasticity and increased weakness to tensile stress.[20] Therefore, a decrease in the type I to type III ratio would have the overall effect of weakening collagen tissues. This theoretical increased susceptibility to ligament or tendon failure is supported by the observed increased rate of rupture of the anterior cruciate ligament in females during the ovulation phase of the menstrual cycle when estrogen is at its highest level and type I to type III collagen ratio would be at its lowest level.[47] These findings are further supported by the discovery of actual estrogen receptors within the fibroblasts of human anterior cruciate ligament tissue.[21]

The results of this study demonstrated a significantly increased prevalence in the use of hormone replacement therapy and oral contraceptive pills in women with Achilles tendinopathy relative to control populations. The higher prevalence of patients with exposure to estrogen seen relative to national rates of hormone use may demonstrate the effects of estrogen on the biomechanical properties of the Achilles tendon. A decrease in type I collagen induced by an increased exposure to estrogen could subsequently weaken the tendon or disrupt the normal reparative processes. This in turn could promote the creation of microtears along with inadequate healing, thereby leading to degenerative changes and ultimately tendinopathy.

Steroid use has been linked to rupture of the Achilles tendon through studies using animal models and human case reports.[10,41] Some human studies have suggested that weakening of the Achilles tendon can occur with both local and systemic steroid exposure.[12,23] Recent work by Wiggins et al.[44] showed a decrease in failure loads and greater histologic disorganization of collagen in injured medial collateral ligaments in rabbits after a one-time steroid injection. The steroid injection not only delayed healing but also resulted in weakening of the ligaments exposed to the injection for a long as 12 weeks after the injection. Other studies confirm the deleterious effects of steroids.[15,22,24,33]

We were unable to provide a statistical assessment of the prevalence of steroid exposure in patients with Achilles tendinopathy in comparison with national prevalence because there is no such published data. From an observational standpoint, 39% of patients (32 of 82) with Achilles tendinosis were exposed to local or systemic steroids. Further studies are necessary to determine if our observed rates of steroid exposure conclusively demonstrate an increased statistical prevalence.

The goal of delineating risk factors of Achilles tendinopathy was hampered by our overall population size and the lack of assessment of many of the other potential contributory factors, such as the mechanical axis of the Achilles tendon, patient occupation, history of trauma, and activity level. The overall higher prevalence of hypertension, diabetes, obesity, and exposure to both hormone replacement therapy and steroids in our foot and ankle control population compared to the population at large further suggests the possibility that there also may be a higher incidence of these factors in patients with foot and ankle problems, albeit at considerably lower levels than in patients with Achilles tendinopathy.

This study heightens our awareness of the possible role of systemic diseases and medications in the development of Achilles tendinopathy and possibly other tendinopathy in the foot and ankle, such as that involving the posterior tibial tendon. This study supports a previous study that suggested an association between primary tendinopathy and hypertension, obesity, diabetes, and steroids.[11]

REFERENCES

1. **Ahmed, IM; Lagopoulos, M; McConnell, P; et al.:** Blood supply of the Achilles tendon. J. Orthop. Res. **16**:591–596, 1998.
2. **Alfredson, H:** Chronic midportion Achilles tendinopathy: an update on research and treatment. Clin. Sports med. **22**:727–741, 2003.
3. **Astrom, M; Rausing, A:** Chronic Achilles tendinopathy. A survey of surgical and histopathologic findings. Clin. Orthop. **316**:151–164, 1995.
4. **Carr, A; Norris, S:** The blood supply of the calcaneal tendon. J. Bone Joint Surg. **71-B**:100–101, 1989.
5. **Charlton, W; Coslett-Charlton, LM; Ciccotti, M:** Correlation of estradiol in pregnancy and anterior cruciate ligament laxity. Clin. Orthop. **387**:165–170, 2001.
6. **Clain, M; Baxter, D:** Achilles tendinitis. Foot Ankle Int. **13**:482–487, 1992.
7. **Falanga, V:** Wound healing and its impairment in the diabetic foot. Lancet **366**:1736–1743, 2005.
8. **Fowkes, F; Housley, E; Riemersa, RA, et al.:** Smoking, lipids, glucose intolerance and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh artery study. Am. J. Epidemiol. **135**:331–140, 1992.
9. **Galloway, MT; Jokl, P; Dayton, OW:** Achilles tendon overuse injuries. Clin. Sports Med. **11**:771–782, 1992.
10. **Gottlieb, N; Riskin, W:** Complications of local corticosteroid injections. J. Am. Med. Assoc.**310**:1547–1548, 1980.
11. **Holmes, GB; Mann, RA:** Possible epidemiological factors associated with rupture of the posterior tibial tendon. Foot Ankle. **13**:70–79, 1992.
12. **Holmes, GB; Mann, RA; Wells, L.:** Epidemiological factors associated with rupture of the Achilles tendon. Contemp. Orthop. **23**:327–331, 1991.
13. **Hubert, H; Feinleib, M; McNamara, PM; Castelli, WP:** Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation. **67**:968–977, 1983.
14. **Kannus, P; Jozsa, L:** Histopathological changes preceding spontaneous rupture of a tendon. A controlled study of 891 patients. J. Bone Joint Surg. **73-A**:1507–1525, 1991.
15. **Kapetanos, G:** The effect of the local corticosteroids on the healing and biomechanical properties of the partially injured tendons. Clin. Orthop. **163**:170–79, 1982.

16. **Keating, N; Cleary PD; Rossi, AS:** Use of hormone replacement therapy by postmenopausal women in the United States. Ann. Intern. Med.**130**:545–553, 1999.
17. **Khan, KM; Cook, JL; Bonar, F; et al.:** Histopathology of common tendinopathies. Implications for clinical management. Sports Med. **27**:393–408, 1999.
18. **Leach, RE; James, S; Wasilewski, S:** Achilles tendinitis. Am. J. Sports Med. **9**:93–98, 1981.
19. **Lip, G; Blann, A:** Von Willebrand factor: a marker of endothelial dysfunction in vascular disorders? Cardiovasc. Res. **34**:255–265, 1997.
20. **Liu, S; Yang, R; al-Shaikh, R; Lane, J:** Collagen in tendon, ligament, and bone healing: A current review. Clin. Orthop. **318**:265–278, 1995.
21. **Liu, S; al-Shaikh, R; Panossian, V:** Primary immunolocalization of estrogen and progesterone target cells in the human anterior cruciate ligament. J. Orthop. Res. **14**:526–533, 1996.
22. **Mackie, J; Goldin, B; Foss, ML; Cockrell, J:** Mechanical properties of rabbit tendons after repeated anti-inflammatory steroid injections. Med. Sci. Sports. **6**:198–202, 1974.
23. **Mahler, F; Fritschy, D:** Partial and complete ruptures of the Achilles tendon and local corticosteroid injections. Br. J. Sports Med. **26**:7–14, 1992.
24. **McWhorter, JW; Franeis, RS; Heckmann, RA:** Influence of local steroid injections on traumatized tendon properties: a biomechanical and histological study. Am. J. Sports Med. **19**:435–439, 1991.
25. **Mokdad, A; Ford, ES; Bowman, BA:** Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. J. Am. Med. Assoc. **289**:76–79, 2003.
26. **Movin, T; Gad, A; Reinholt, FP; Rolf, C:** Tendon pathology in long standing Achillodynia. Biopsy findings in 40 patients. Acta. Orthop. Scand. **68**:170–175, 1997.
27. **Naschitz, JE; Wolfson, V; Tsikonova, I; et al.:** Pulsatile venous insufficiency in severe tricuspid regurgitation: does pulsatility protect against complications of venous disease? Angiology **51**:231–239, 2000.
28. **National Center for Chronic Disease Prevention and Health Promotion:** Diabetes surveillance system: prevalence of diagnosed diabetes per 1000 population, females, by age, United States, 1980–1996. www.cdc.gov/diabetes/statistics.
29. **National Center for Chronic Disease Prevention and Health Promotion:** Diabetes surveillance system: prevalence of diagnosed diabetes per 1000 population, males, by age, United States, 1980–1996. www.cdc.gov/diabetes/statistics.
30. **National Center for Chronic Disease Prevention and Health Promotion:** Healthy weight, overweight, and obesity among persons 20 years of age and over, according to sex, age, race, and Hispanic origin: United States, 1960–62, 1971–74, 1976–80, 1988–94 and 1999–2000. www.cdc.gov/nchs/
31. **National Center for Chronic Disease Prevention and Health Promotion:** Hypertension among persons 20 years of age and over, according to sex, age, race, and Hispanic origin: United States, 1960–62, 1971–74, 1976–80, 1988–94, 1999–2000. www.cdc.gov/nchs/
32. **National Center for Chronic Disease Prevention and Health Promotion:** Methods of contraception for women 15–44 years of age, according to race and age: United States, 1982, 1988, and 1995. www.ncbi.nlm.nih/gov/books/bv.fcgi?rid=healthus04.table.295.
33. **Phelps, D; Sonstegard, D; Matthews, L:** Corticosteroid injection effects on the biomechanical properties of rabbit patellar tendons. Clin. Orthop. **100**:345–348, 1974.
34. **Puddu, G; Ippolito, E; Postacchini, F:** A classification of Achilles tendon disease. Am. J. Sports Med. **4**:145–150, 1976.
35. **Reddy, K; Stehno-Bittel, L; Enwemeka, C:** Glycation-induced matrix stability in the rabbit Achilles tendon. Arch. Biochem. Biophys. **399**:174–180, 2002.
36. **Riondino, S; Pignatelli, P; Pulcinelli, F; et al.:** Platelet hyperactivity in hypertensive older patients is controlled by lowering blood pressure. J. Am. Geriatr. Soc. **47**:943–947, 1999.
37. **Schepsis, AA; Jones, H; Haas, AL:** Achilles tendon disorders in athletes. Am J. Sports Med. **30**:287–305, 2002.
38. **Schmidt-Rohlfing, B; Graf, J; Schneider, U; Niethard, F:** The blood supply of the Achilles tendon. Int. Orthop. **16**:29–31, 1992.
39. **Schwartzkopff, B; Mundhenke, M; Strauer, BE:** Remodeling of intramyocardial arterioles and extracellular matrix in patients with arterial hypertension and impaired coronary reserve. Eur. Heart J. **16(Suppl 1)**:82–86, 1995.
40. **Strocchi, R; DePasquale, V; Guizzadi, S, et al.:** Human Achilles tendon: morphological and morphometric variations as a function of age. Foot Ankle **12**:100–104, 1991.
41. **Unverfirth, I; Olix, ML:** The effect of local steroid injections on tendon. J. Bone Joint Surg. **55-A**:1315, 1973.
42. **Van Gorp, W; Schenau, DS; Hoeks, A; et al.:** In spontaneously hypertensive rats alteration in aortic wall properties precede development of hypertension. Am. J. Physiol. Heart Circ. Physiol. **278**:H1241–H1247, 2000.
43. **Vora, AM; Myerson, MS; Oliva, F; Maffulli, N:** Tendinopathy of the main body of the Achilles tendon. Foot Ankle Clin. **10**:293–308, 2005.
44. **Wiggins, M:** Effects of local injection of corticosteroids on the healing of ligaments. J. Bone Joint Surg. **77-A**:1682–1691, 1995.
45. **Williams, IL; Wheatcroft, SB; Shah, AM; Kearney, MT:** Obesity, atherosclerosis and the vascular endothelium: mechanisms of reduced nitric oxide bioavailability in obese humans. Int. J. Obesity **26**:754–764, 2002.
46. **Wojtys, E; Huston, L; Lindenfeld, T; et al.:** Association between the menstrual cycle and anterior cruciate ligament injuries in female athletes. Am. J. Sports Med. **26**:614–619, 1998.
47. **Yu, W; Panossin, V; Hatch, JO:** Combined effects of estrogen and progesterone on the anterior cruciate ligament. Clin. Orthop. **383**:268–281, 2001.
48. **Zantop, T; Tillman, B; Peterson, W:** Quantitative assessment of blood vessels of the human Achilles tendon: an immunohistochemical cadaver study. Arch. Orthop. Trauma Surg. **123**:501–504, 2003.