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Review Article

Hyperglycemia and Degenerative Tendinopathy: A Role for Diet in Tendon Health

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Abstract

Tendinopathies are a common source of pain, poor mobility and decreased performance. The cause of tendinopathy is multi-factorial and systemic inputs play an underappreciated role. Metabolic syndrome is a growing problem in the developed world and usually involves varying degrees of insulin resistance and central obesity. Chronic hyperglycemia and central obesity are independent risk factors for degenerative tendon disease and the underlying mechanisms involve an accelerated accumulation of advanced glycation end-products (AGE's), collagen cross-linking, oxidative damage, and aberrant remodeling of the extracellular matrix. Consuming a diet that results in consistently optimal blood glucose levels and improvements in body composition may improve tendon health in the general population. Lifestyle interventions for preventing and treating tendinopathies should be considered given that evidence based treatment options are limited.

Keywords: Tendinopathy; Diabetic; Diabetes; Hyperglycemia; Metabolic Syndrome; Advanced Glycation End Products; Collagen;Cross Links; Mobility; Injury Prevention; Anti-Inflammatory Diet; Low Carbohydrate Diet; Sugar

Introduction

Tendinopathy is one of the most common problems managed by sports medicine practitioners. It causes pain, reduced mobility, functional deficits, and decreased performance. It presents in a wide variety of individuals from highly active athletes to the more sedentary population. Tendinopathy tends to be progressive and can lead to complete tendon ruptures resulting in significant disability. It can also involve tendons at nearly every major joint in the body. Treatment options are limited and providers should emphasize and implement prevention strategies. Much of the research on prevention focuses on mechanical variables, however, evidence suggests that dietary changes can significantly slow the underlying degenerative processes.

Obesity and insulin resistance are associated with unhealthy diets and are independent risk factors for tendinopathies [1-4]. Metabolic syndrome is reaching epidemic levels in the developed world and consists of abdominal obesity, dyslipidemia, hypertension and insulin resistance [5]. In metabolic syndrome central obesity and insulin resistance coincide, likely resulting in a damaging double hit to tendons and other connective tissues. When treating patients with insulin resistance, obesity, or both, nutrition is one of the most important variables to optimize [6]. In this review we will focus on how the excessive consumption of simple sugars and refined carbohydrates, common to the modern western diet, contributes to the development of tendinopathies in the general population.

Tendinopathy

The pathophysiological mechanisms contributing to the development of degenerative tendinopathies are poorly understood and are currently being researched. Tendinopathy has characteristic features. The extracellular matrix (ECM) becomes disorganized, there are changes in proteoglycan content, and there is an increased infiltration of blood vessels (neovascularization) with the presence of perivascular mast cells [7-9]. Though the idea is common that inflammation's role in tendinopathy is minimal, it is likely that elements

of the acute inflammatory response play a significant role in this degenerative process [10]. Tendinopathy is a chronic progressive condition, however, and its pathological changes will accumulate over time until clinically relevant to the patient.

A brief review of tendon structure

Tendon tissue consists primarily of tenocytes (tendon cells) and a large amount of the ECM. ECM is outside of the cell and is therefore continuously exposed to the body's extracellular fluids. Tendon ECM consists primarily of Type 1 collagen, proteoglycans (particularly decorin and versican), and glycosaminoglycans [11]. The ECM, which is synthesized by tenocytes, is the primary contributor to the tendon's biomechanical properties. The parallel structure of collagen fibrils facilitates the efficient transmission of energy from muscles to bones [11]. Proteoglycans (PG) constitute much of the tendon's ground substance and lie between the collagen fibrils [9]. They are important modulators of calcification in soft tissues and provide flexibility and smooth motion between the collagen [12,13].

The ECM is continuously remodeled maintaining equilibrium between synthesis and degradation [14]. Matrix metalloproteinases (MMP's) and their inhibitors largely mediate this complex remodeling process [4,15]. This is analogous to bone and its continuous state of flux between synthesis and resorption. Much like bone, mechanical forces are necessary for maintaining tendon homeostasis [16] and tendons that experience higher mechanical loads experience accelerated ECM turnover and increased type 1 collagen synthesis [14]. Though stem cells have been demonstrated in human and animal cultures [17], tendons lack the same degree of regenerative capacity that is present in many other tissues.

Tendinopathy and hyperglycemia

Advanced glycation end products (AGE's) are formed when a reducing sugar binds to an amino group altering a protein's structure and function. This occurs at an accelerated rate when there are more reducing sugars present in the body as occurs with chronic hyperglycemia. AGE's effect many structures in the ECM including collagen, laminin, elastin, vitronectin, and lipids [18]. Increased oxidative stress also accelerates the accumulation of AGE's independent of glycemic control. AGE's cause damage through their direct effects on the components of the ECM; as well as through their interaction with receptors for AGE's (RAGE's) which increases inflammation and oxidative damage [19]. Greater AGE accumulation leads to a local pro-inflammatory state, indicated by elevated expression of RAGE's, interleukin-6, and tumor necrosis factor-alpha, which then accelerates the development of collagen cross links [18,20].

AGE-mediated collagen cross links are associated with deterioration of tendon function over time [21]. Collagen cross linking appears to be mediated through the actions of transglutaminase which is up-regulated by higher levels of AGE-modified type 1 collagen and oxidative damage [22]. AGE-mediated collagen cross links also impact the biomechanical function of connective tissues [23-25] and tendon stiffness is increased in proportion to the amount of accumulated cross links [26-28]. Cross linking of collagen is thought to be one of the driving mechanisms behind altered tendon stiffness and elasticity [28, 29].

The ECM remodeling process is also altered in hyperglycemic environments [29]. Hyperglycemia appears to up-regulate certain MMP's that are involved in maintaining tendon homeostasis [30]. It is likely that this change pushes the equilibrium towards degradation and contributes to the development of a disordered and dysfunctional ECM. Aberrant ECM turnover, through altered MMP function, is also likely a major contributor to the development of degenerative tendon [31].

There are multiple other physiological processes that chronic hyperglycemia impacts in tendon. Inflammatory and growth mediator expression is altered following an injury to the Achilles tendons in rat models of diabetes [32] and the proliferative healing phase is impaired through altered MMP and collagen expression [33]. Hyperglycemia is also associated with significantly reduced tendon proteoglycan levels [34]. This may contribute to the disorganized ECM structure and altered mechanics [35]. Vascular hyperplasia is commonly observed in tendinopathy and is found to be increased in hyperglycemic environments as well [36].

Diabetes is a disorder of glucose metabolism resulting in chronic hyperglycemia and an accelerated accumulation of AGE's all throughout the body. It is well established that diabetes is an independent risk factor for chronic degenerative tendinopathies. Rotator cuff, long head of the biceps, and Achilles tendons of diabetic patients are shown to be significantly thicker, stiffer and tend to have more aberrant calcification [37-40] than non-diabetics. Ultrasound imaging [41] and electron microscopy [42] demonstrate disorganized collagen and increased thickness of the achilles tendons belonging to people with diabetes. Humans with diabetes and animal models of chronic hyperglycemia have demonstrated increased Achilles stiffness and decreased elasticity [29, 40, 43].

Accelerated AGE accumulation associated with hyperglycemia occurs in the general population as well [44] and these levels can be improved upon through lifestyle modifications [45]. Accelerated AGE accumulation is an important variable in the development of many other chronic diseases [46]. A recent study demonstrated that higher average blood glucose levels, still below the diabetic range, were associated with an increased the risk for dementia [47]. It is also established that

elevated serum levels of AGE's are predictive of both all-cause and cardiovascular mortality in the non-diabetic population. Additionally, serum AGE levels are predictive for the severity of coronary artery disease in patients without diabetes [48, 49].

The relationship between fasting blood glucose levels and rotator cuff tears has been examined in the non-diabetic population. Non-diabetic patients with tears in their rotator cuff tendons were found to have significantly higher fasting blood glucose levels than uninjured controls [50]. The average BMI in this study population was in the mildly-overweight range, which is highly representative of the general population.

Obesity

Obesity is reaching epidemic levels in the developed world and is strongly influenced by lifestyle and diet [6]. Elevated BMI is an independent risk factor for rotator cuff tendon pathology [3] and patellar tendinopathy in athletes is associated with central obesity [1, 2]. Central adiposity is also associated with chronic inflammation and coronary artery disease [15]. Increased body weight will alter the mechanical loads delivered to tendons, and this may further contribute to degenerative changes through accelerated ECM turnover [16]. Improving body composition requires dietary improvements which can reduce systemic inflammation and improve mechanical loading patterns on tendons.

Statin drugs, a brief consideration for future research

Statin use appears to alter MMP and ECM expression [51-53] and tendon pathology is a known side effect of this often used medication. This makes statin use a possible confounding variable and it is not always accounted for in human tendinopathy studies. This is a particularly important consideration in the presence of metabolic syndrome, because of how common these medications are prescribed in this population. Concomitant medication use is an important variable to take into account, both in the clinic, as well as for future studies examining tendinopathies.

Conclusion

Insulin resistance and central obesity are increasing in the general population and these are both independent, yet related, risk factors for tendinopathies. This relationship appears to be mediated primarily through inflammation and accelerated AGE accumulation. A diet that is low in highly refined carbohydrates and simple sugars, relative to the modern western diet, can reduce AGE accumulation, collagen cross links, inflammation levels, maintain ECM homeostasis, and improve body composition. These effects will likely provide significant benefits for long-term tendon health.

Human health is a system of dominos that can fall in the direction of better health if managed well, or toward chronic disease if managed poorly. For tendon health, like many other chronic diseases, diet should be considered one of the lead dominos.

More studies are needed to better characterize the relationship between blood sugar levels, AGEs, collagen cross links, body composition and tendon health. This concept, however, provides clinicians with another reason to initiate the increasingly important conversation about diet with their patients.

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