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BODY MASS INDEX AND THE ANTERIOR CRUCIATE LIGAMENT – INTEGRATING MECHANICAL AND INFLAMMATORY MECHANISMS

INDEKS TELESNE MASE I PREDNJI UKRŠTENI LIGAMENT – SPOJ MEHANIČKIH I INFLAMATORNIH MEHANIZAMA

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Abstract

Introduction. Obesity is a chronic metabolic disorder characterised by excess adiposity, persistent low-grade inflammation, and high frequency of musculoskeletal complications in both athletic and non-athletic populations. Body mass index and fat distribution, particularly visceral adiposity, are key determinants of metabolic and orthopaedic risk, including disorders of the knee tendons and ligaments. **From adiposity to ligament pathology.** In obesity, white adipose tissue undergoes phenotypic remodelling toward a pro-inflammatory state, marked by immune cell infiltration, increased secretion of cytokines and adipokines, and reduced adiponectin levels. These alternations promote lipotoxicity and ectopic fat deposition in skeletal muscle, ligaments, fat pads, and entheses, contributing to sarcopenic obesity, angiofibroblastic degeneration, and impaired ligament healing. **Clinical implications.** Elevated body mass index increases mechanical loading and alters lower-limb biomechanics, thereby promoting repetitive microtrauma, chronic inflammation, and higher incidence of tendinopathies, particularly of the extensor mechanism and pes anserinus. In individuals with body mass index above 25 kg/m², published studies report a higher prevalence of multiligament knee injuries, a greater proportion of trauma-related anterior cruciate ligament ruptures, increased postoperative complications, and delayed functional recovery. However, heterogeneity in study design limits precise quantification of effect sizes. **Conclusion.** Excess adiposity likely increases anterior cruciate ligament injury risk through the combined effects of mechanical overload and obesity-related inflammation and is associated with more extensive ligament damage and a less favourable postoperative course. Integrated interventions targeting fat-mass reduction, metabolic optimisation, and neuromuscular conditioning may enhance recovery, reduce re-injury risk, and support long-term knee joint health. This conceptual framework is applicable across age groups in both recreational and competitive sports populations.

Key words: Anterior Cruciate Ligament Injuries; Body Mass Index; Obesity; Adiposity; Inflammation; Sarcopenia; Metabolic Syndrome; Risk Factors

Sažetak

Uvod. Gojaznost je hronična metabolička bolest praćena porastom masne mase, perzistentnom niskogradusnom inflamacijom i čestim mišićno-koštanim komplikacijama kod sportista i opšte populacije. Indeks telesne mase i raspored masnog tkiva, naročito visceralna adipoznost, ključni su determinanti metaboličkog i ortopedskog rizika, uključujući patologiju tetiva i ligamenata kolena**. Od adipoznosti do patologije ligamenata.** U gojaznosti belo masno tkivo prelazi u proinflamatorni fenotip sa infiltracijom imunskih ćelija i pojačanom sekrecijom citokina i adipokina uz snižene nivoe adiponektina. Lipotoksičnost i ektopično deponovanje masti u skeletnim mišićima, ligamentima, masnim jastučićima i na entezama doprinose sarkopeničnoj gojaznosti, angiofibroblastičnoj degeneraciji i oslabljenoj reparaciji ligamenta. **Kliničke implikacije.** Povišen indeks telesne mase povećava mehaničko opterećenje i menja biomehaniku donjih ekstremiteta, što pogoduje ponavljanim mikrotraumama, hroničnoj inflamaciji i učestalijim tendinopatijama ekstenzornog mehanizma i *pes anserinus* sindromu. Kod osoba sa indeksom telesne mase iznad 25 kg/m², studije opisuju češće višeligamentne povrede kolena, veći udeo traumatskih ruptura prednjeg ukrštenog ligamenta, više postoperativnih komplikacija i sporiji funkcionalni oporavak, ali heterogenost dizajna ograničava preciznu procenu efekta. **Zaključak.** Gojaznost verovatno povećava rizik od povrede prednjeg ukrštenog ligamenta kombinacijom mehaničkih i inflamatornih mehanizama i povezana je sa težim obrascem povrede i nepovoljnijim postoperativnim tokom. Integrisane strategije koje kombinuju redukciju masne mase, metaboličku optimizaciju i neuromišićni trening mogu unaprediti oporavak, smanjiti rizik ponovne rupture i očuvati dugoročno zdravlje kolena. U planiranju lečenja i povratka sportu potrebno je uključiti savetovanje o ishrani i nadzor komorbiditeta tokom čitavog postoperativnog perioda.

Ključne reči: povrede prednjeg ukrštenog ligamenta; indeks telesne mase; gojaznost; masnoća; inflamacija; sarkopenija; metabolički sindrom; faktori rizika

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Abbreviations

ACL – anterior cruciate ligament
ADP – air-displacement plethysmography
BIA – bioelectrical impedance analysis
bFGF – basic fibroblast growth factor
BMI – body mass index
COX-1 – cyclooxygenase 1
COX-2 – cyclooxygenase 2
CT – computed tomography
DXA – dual-energy X-ray absorptiometry
EASO – European Association for the Study of Obesity
ESPEN – European Society for Clinical Nutrition and Metabolism
EWGSOP2 – European Working Group on Sarcopenia in Older People 2
FFA/FFAs – free fatty acid(s)
IgG – immunoglobulin G
IL-1β – interleukin 1 beta
IL-1Ra – interleukin 1 receptor antagonist
IL-4 – interleukin 4
IL-6 – interleukin 6
IL-8 – interleukin 8
IL-10 – interleukin 10
IL-13 – interleukin 13
IL-17 – interleukin 17
IL-21R – interleukin 21 receptor
IL-33 – interleukin 33
M1 – classically activated (pro-inflammatory) macrophage phenotype
MRI – magnetic resonance imaging
NK – natural killer (cells)
PCOS – polycystic ovary syndrome
SARC-F – Strength, Assistance in walking, Rise from a chair, Climb stairs, Falls
SPPB – Short Physical Performance Battery
TGF-β – transforming growth factor beta
Th17 – T helper 17
TNF-α – tumor necrosis factor alpha
TUG – Timed Up and Go
WAT – white adipose tissue
WHR – waist-hip ratio

Introduction

Obesity has long been recognized as a major public health problem with a high incidence and prevalence worldwide. As early as the time of Hippocrates, it was observed that individuals with excessive body weight experienced sudden death more frequently, highlighting the long-standing medical awareness of obesity-related risk. The conceptual understanding of obesity has evolved substantially over time, with the most significant advances occurring during the second half of the 20th century and the beginning of the 21st century. During this period, obesity-associated disorders were systematically identified, the critical role of fat distribution in the development of complications was established, key pathophysiological mechanisms were elucidated, diagnostic criteria were standardized, and increasingly precise methods for assessing body fat mass were developed. According to the World Health Organization, the fundamental parameter for defining nutritional status and diagnosing obesity is body mass index (BMI). Based on BMI (kg/m²) values, individuals are classified as underweight (BMI < 18.5), normal weight (18.5-24.9), overweight or pre-obesity (25.0-29.9), and obese (≥30). Obesity is further stratified into class I (30.0-34.9), class II (35.0-39.9), and class III (≥ 40). However, because total body mass does not necessarily reflect body fat content or distribution, more accurate assessment of obesity requires direct measurement of fat mass. Available methods include bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), computed tomography (CT), magnetic resonance imaging (MRI), hydrostatic weighing, air-displacement plethysmography (ADP), three-dimensional body scanning, and skinfold thickness measurement using calipers [1].

With respect to fat distribution – which largely determines the risk and type of obesity-related complications – obesity is commonly categorized as abdominal (central, visceral) or peripheral. Waist circumference and waist-hip ratio (WHR) are widely used for rapid characterization of obesity type.

Currently, obesity is defined as a chronic metabolic disease characterized by excessive accumulation of adipose tissue. Despite advances in diagnostic approaches and therapeutic strategies, obesity continues to present growing challenges, as it is associated with a wide spectrum of metabolic, cardiovascular, reproductive, psychological, and musculoskeletal disorders that significantly impair quality of life and increase overall mortality. Excess adipose tissue, particularly visceral fat, induces a state of chronic low-grade inflammation and is considered a central driver of obesity-related complications, including insulin resistance, type 2 diabetes mellitus, arterial hypertension, cardiovascular disease, dyslipidemia, gastrointestinal and urogenital disorders, polycystic ovary syndrome (PCOS), infertility, depression, malignancy, and musculoskeletal disorders [2–4].

From adiposity to ligament pathology: plausible biological pathways

White adipose tissue (WAT) functions not only as a lipid storage depot but also as an endocrine organ and immunological organ. It consists of mature adipocytes, preadipocytes, adipocyte precursors, and a diverse population of immune cells. WAT secretes more than 50 hormones and signaling molecules – collectively termed adipokines – that regulate metabolism and proper immune function. In individuals of normal body weight, adipose tissue synthesizes anti-inflammatory adipokines, including interleukin (IL)-4, IL-10,

IL-13, IL-1 receptor antagonist (IL-1Ra), transforming growth factor-beta (TGF-β), adiponectin, and apelin. In contrast, obesity is characterized by a shift toward a pro-inflammatory adipokine profile, with increased secretion of IL-1β, IL-6, TNF-α, resistin, visfatin, leptin, angiotensin II, and plasminogen activator inhibitor-1. This pro-inflammatory secretion pattern arises largely from immune–cell infiltration in adipose tissue, particularly macrophages, which accumulate in WAT and undergo polarization toward a pro-inflammatory M1-like phenotype. In addition to macrophages, adipose tissue contains B cells, T cells, dendritic cells, and neutrophils, all of which contribute to immune modulation. In obesity, B cells infiltrate WAT, secrete pro-inflammatory cytokines, and produce autoreactive IgG antibodies that amplify local inflammation and promote Th17 responses. Through antigen presentation, B cells also activate T cells, which in turn activate dendritic cells and macrophages, reinforcing the inflammatory cascade [5].

Beyond localized adipose tissue inflammation, excessive fat mass promotes a state of systemic chronic low-grade inflammation that underlines the development of obesity-related comorbidities. Increasing attention has recently been directed toward the musculoskeletal consequences of obesity. Conditions such as sarcopenic obesity, osteoporosis, osteoarthritis, and ligament disorders are increasingly recognized as integral components of metabolic syndrome and are closely linked to the chronic inflammatory milieu characteristic of obesity.

Clinical implications

Sarcopenia is defined as a loss of skeletal muscle mass, muscle quality, and strength. Although it most commonly develops with aging – at a rate of approximately 0.5-1% per year – it may also arise secondary to neurological disorders, mitochondrial dysfunction, hormonal imbalance, adverse lifestyle factors, and chronic low-grade inflammation. Clinically, the European Working Group on Sarcopenia in Older People (EWGSOP2) recommends a stepwise approach in which low muscle strength represents the primary criterion ("probable sarcopenia"), reduced muscle quantity or quality confirms the diagnosis, and impaired physical performance denotes severe sarcopenia. Case identification may be supported by screening instruments such as the SARC-F questionnaire, followed by objective assessment of muscle strength (e.g., handgrip strength or five-times chair stand test), evaluation of muscle quantity or quality using body-composition technique (dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA) in clinical practice), and measurement of physical performance using the tools such as gait speed, SPPB, TUG test, or the 400-m walk test.

When excess adiposity coexists with impaired muscle mass or function, sarcopenic obesity should be recognized as a distinct and clinically relevant entity. The ESPEN/EASO consensus defines sarcopenic obesity as the simultaneous presence of increased adiposity and reduced muscle mass and/or function and emphasizes a structured diagnostic approach based on validated, qualitative measures of both adiposity and muscle impairment, rather than reliance on a single fixed combination of historical cut-off values [6–9].

Skeletal muscle tissue exhibits high plasticity and continuous remodeling, rendering it particularly vulnerable to chronic low-grade inflammation. In the context of obesity, ectopic lipid deposition within non-adipose tissues – including skeletal muscle – leads to lipotoxicity, myosteatosis, and sarcopenic obesity **(Figure 1)** [3].

These functional alterations – characterized by compromised muscle integrity and persistent atrophy – are recognized risk factors for a range of musculoskeletal disorders, including tendinopathies, osteoporosis, osteoarthritis, and reduced preservation of range of motion in affected body segments, particularly the lower extremities [3].

A strong association has between described between sarcopenic obesity and metabolic syndrome. Because sarcopenic obesity is accompanied by disability, reduced physical activity, altered mechanical loading, and disrupted muscle biology due to lipid infiltration and lipotoxicity, together with chronic low-grade inflammation, it is likely to play a central role in the development of other musculoskeletal diseases [3,10].

Ligament disorders – including pain, inflammation, rupture, and impaired recovery following injury – have increasingly been linked to excess visceral adiposity and have become an important focus of investigation in both athletic and non-athletic populations. The mechanisms connecting adiposity to ligament pathology appear to be both mechanical and systemic in nature [10,11].

Mechanical mechanisms involve increased ligament loading and repetitive mechanical stress, particularly in the lower extremities, resulting from elevated BMI. Chronic overload promotes ligament inflammation, thereby predisposing to rupture. However, similar pathological ligament changes have also been observed in the upper extremities in individuals with obesity, suggesting that systemic inflammation plays a crucial etiological role [10,11].

The systemic effects of obesity on ligament health may be both direct and indirect [12]. Direct effects

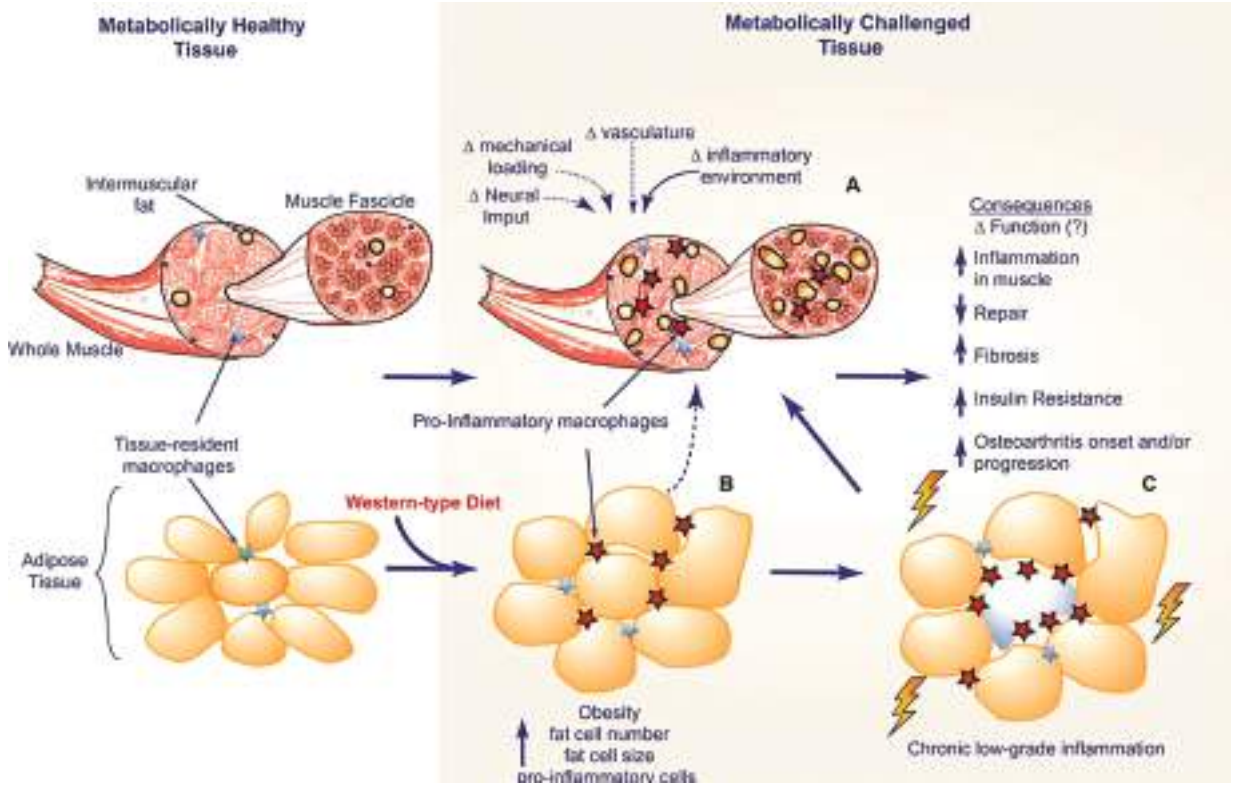

Figure 1. Structural and inflammatory alterations in muscle; (A) Factors compromising muscle structural integrity; (B) obesity-related changes in adipose tissue; (C) musculoskeletal consequences of chronic low-grade inflammation [3].

are mediated by bioactive peptides secreted by adipose tissue, while indirect effects arise from metabolic disturbances that negatively influence ligament structure [10,11]. Ligamentopathy was historically regarded as a degenerative, non-inflammatory condition. However, contemporary histopathological studies have demonstrated the presence of inflammatory cells and molecular markers within diseased ligament tissue, with earlier conclusions largely attributable to methodological limitations [13,14].

Histological analyses of chronically inflamed ligaments reveal an absence of acute inflammation; instead, tissue damage reflects failed cellular repair process associated with angiofibroblastic degeneration. Immune cells – including macrophages, mast cells, natural killer (NK) cells, and T cells – have been consistently identified in ligament biopsy specimens. Moreover, a broad spectrum of inflammatory cytokines has been detected, including IL-1β, IL-6, IL-8, IL-10, IL-17, IL-21 receptor, IL-33, COX-1, COX-2, TGF-β, TNF-α, and bFGF. In obesity, the balance between pro- and anti-inflammatory adipokines is markedly disrupted, resulting in sustained low-grade inflammation. Many of the cytokines overexpressed in obesity are also abundantly present in tendinopathies, providing a biological link between these conditions. Inflammatory cytokines (IL-6, IL-1β, TNF-α) are thought to drive the initiation and progression of chronic tendon inflammation by promoting cell proliferation, angiogenesis, extracellular matrix degeneration, tissue metaplasia, and secretion of pain mediators.

Hyperleptinemia and leptin resistance, characteristic features in obesity, have been associated with tenocyte degeneration, vascular proliferation, rupture at the tendon-bone interface, ectopic ossification following injury, and impaired healing. Reduced ligament healing capacity and a higher prevalence of chronic injury due to repetitive microtrauma in individuals with obesity have also been linked to decreased adiponectin levels and increased synthesis of free fatty acids (FFAs). FFAs exert lipotoxic effects through oxygen stress, lipid peroxidation, mitochondrial dysfunction, and induction of inflammatory cytokines. Although a direct causal relationship between FFAs and ligament disease has not been conclusively established, their lipotoxic effects have been documented in cartilage injury and osteoarthritis development [15–20].

Beyond intramuscular lipid accumulation, obesity is associated with increased fat deposition within ligaments themselves, as well as in the infrapatellar fat pad and at entheses – the sites of tendon and ligament insertion. These local fat depots are capable of producing inflammatory cytokines, thereby amplifying local inflammatory responses. Larger fat pads

correlate with higher cytokine production and may contribute to inflammation, pain, and rupture. Repetitive stress imposed on these fat pads by elevated BMI further promotes chronic low-grade inflammation, predisposing ligaments and tendons to inflammation. Collectively, the metabolic consequences of systemic obesity extend to local fat depots in adjacent muscles, ligament-bone insertions, adjacent fat pads, and even within ligament and tendon tissue itself, fostering inflammation, pain, and degeneration, and contributing to the development and progression of tissue damage [21–23].

Beyond inflammation, other obesity-associated comorbidities contribute to musculoskeletal pathology.

Elevated arterial blood pressure – commonly present in metabolic syndrome - induces local inflammation in tissue damage through vasoconstriction and impaired tissue perfusion. Dyslipidemia, including elevated cholesterol and triglyceride levels, has been directly linked to tendon and ligament pain and inflammation. Subendothelial lipoprotein deposition stimulates chemokine production and macrophage activation, leading to endothelial dysfunction and sustained inflammation [24, 25].

Increased BMI is also associated with reduced physical activity, while musculoskeletal disorders further limit exercise capacity, creating a self-perpetuating cycle of weight gain, mechanical overload, and inflammation. This cycle disproportionately affects the lower extremities and exacerbates tendon and ligament pathology.

Evidence indicates that a BMI >25 kg/m² (pre-obesity) is associated with reduced physical activity, increased comorbidity burden, and higher all-cause mortality [26,27]. Knee pathology, particularly osteoarthritis, is especially prevalent in individuals with obesity [28]. Knee tendinopathies may involve extensor mechanism – affecting quadriceps and patellar tendons – or the pes anserinus complex. Pes anserinus tendinopathy is common among obese women with valgus knee alignment and is characterized by pain during weight bearing activities, when standing, walking, or climbing stairs – at the insertion of the semimembranosus, semitendinosus, gracilis, and sartorius on the superomedial surface of the tibia. In these patients, repetitive friction of the hamstring tendons against the medial femoral condyle, often accompanied by inflammation of the anserine bursa, which is located between the tendon insertions and the posterior surface of the tibia, contributes to anserine bursitis as part of the tendinopathy complex [29,30].

Although clinical data on the relationship between elevated BMI and knee ligament pathology remain limited, available evidence suggests that individuals with obesity may be at increased risk of injury due to greater mechanical loading [30]. Rupture of the anterior cruciate ligament (ACL) is among the most common orthopedic injuries and is associated with reduced quality of life. While multiple modifiable and non-modifiable risk factors may contribute to ACL injury, increased BMI represents an important modifiable factor and has been associated with as many as 75% of non-contact ACL ruptures [27].

Existing studies report inconsistent findings regarding the association between BMI and ACL injury risk. However, higher BMI (pre-obesity and obesity) has been linked greater frequency of non-isolated (combined) ligament injuries, and, in some reports, higher re-rupture rates. Although obesity is more prevalent among women, ACL ruptures occur more frequently in men [4]. Other studies have reported a higher incidence of ACL injury in non-athletes and elevated BMI compared with athletes, with no clear association between BMI and re-rupture risk [31,32].

Regarding injury mechanism, no major differences have been observed between individuals with normal BMI and those with BMI >25 kg/m² in terms of contact versus non-contact injuries. However, a higher proportion of trauma-related injuries has been reported among pre-obese and obese individuals [27]. Chronic low-grade inflammation, metabolic dysregulation, increased mechanical loading, and reduced pre- and post-injury physical activity collectively contribute to impaired recovery, higher postoperative complications rates, and delayed functional restoration in this population [30,32].

Lifestyle modification – both dietary change and promotion of physical activity – is paramount for preventing complications of the musculoskeletal system [33]. Reducing body-fat mass significantly lowers the level of systemic chronic inflammation and mechanical loading, while increasing physical activity, all of which help prevent chronic disease.

Conclusion

Elevated body mass index appears to increase anterior cruciate ligament injury risk through the combined effects of mechanical overload and systemic inflammation and is associated with a greater burden of multi-ligament injury, a higher proportion of trauma-related mechanisms, and increased postoperative complication rates. Given that body mass index is a modifiable risk factor, integrated strategies combining neuromuscular training, weight reduction, and metabolic optimization represent a rational approach to reducing injury risk and improving outcomes through the anterior cruciate ligament care pathway.

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