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Investigating IGFBP3 as a biomarker for early detection and a therapeutic target in tenosynovitis

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Abstract. Tenosynovitis is a prevalent and debilitating musculoskeletal disorder with a rising incidence linked to metabolic diseases, an aging population, and modern lifestyle factors such as prolonged digital device use. Current diagnostic methods are limited by operator dependency and high costs, while pharmacological treatments are associated with adverse effects and limited long-term efficacy. To address these gaps, this study integrated Genome-Wide Association Studies (GWAS), published literature, and GEO RNA-seq data (GSE93698) to identify novel biomarkers and therapeutic targets. Differential expression analysis revealed that while most GWAS-derived genes showed no significant changes, IL6 and IGFBP3 were significantly upregulated, and CREB5 was downregulated in tenosynovitis. IGFBP3 emerged as a promising candidate given its role in regulating IGF-mediated cellular processes and its interaction with inflammatory pathways. Molecular dynamics simulations further demonstrated that Salvianolic Acid B (SAB) binds to the active pocket of IGFBP3, and structure-based chemical modification of the SAB catechol ring significantly enhanced binding affinity. These findings identify IGFBP3 as a potential early detection biomarker and a novel drug target for tenosynovitis, providing a foundation for the development of targeted, mechanism-based therapies.

Keywords: tenosynovitis, IGFBP3, biomarker, molecular dynamics, Salvianolic Acid B

1. Introduction

Tenosynovitis, characterized by inflammation of the synovial sheath surrounding tendons, is a clinically significant musculoskeletal disorder that imposes considerable morbidity. The condition presents in both infectious and noninfectious inflammatory forms, commonly involving the hands, wrists, feet, and other synovial joints. Epidemiological evidence indicates a substantial and increasing burden. In the general population, the lifetime risk of stenosing tenosynovitis (trigger finger) ranges from 1.7% to 2.6%, whereas the prevalence rises markedly to 10–20% among individuals with diabetes mellitus [1, 2]. Infectious (pyogenic) flexor tenosynovitis accounts for approximately 2.5%–9.4% of all hand infections [3]. Among patients with Rheumatoid Arthritis (RA), ultrasound and MRI studies demonstrate that up to 50–55% exhibit tenosynovitis, often involving multiple tendons [4, 5]. Broader contributing factors include population aging and occupational biomechanical exposures, with women demonstrating a 3–10 fold higher risk compared with men in certain studies [6]. The growing importance of tenosynovitis research is reinforced by contemporary lifestyle changes and demographic transitions. Repetitive strain associated with smartphone use, prolonged

computer work, and video gaming has been increasingly implicated in upper-extremity overuse syndromes, particularly during the COVID-19 pandemic when sedentary behaviors intensified [7]. In young adults aged 18–25 years, excessive mobile phone use has been associated with increased prevalence of De Quervain's tenosynovitis and related wrist disorders [8]. In a study of Saudi Arabian teenagers, the prevalence of positive Finkelstein signs indicative of De Quervain's tenosynovitis was 67.5%, with longer durations of smartphone use (> 5 hours daily) significantly linked to symptom development [9, 10]. Similarly, among college-aged populations, higher daily smartphone usage (≥ 8 h/day) and engagement in phone gaming and social media activities were independently associated with significantly increased odds of tenosynovitis (ORs up to ~4.5) [11]. Therefore, there is an urgent need to discover novel treatment solutions for tenosynovitis.

Clinically, tenosynovitis leads to chronic pain, joint stiffness, restricted mobility, and impaired hand function, substantially affecting activities of daily living. Tenosynovitis patients were reported with physical functional limitations and significant work productivity loss [12]. Severe infectious cases may result in complications including tendon adhesions, necrosis, rupture, or even amputation if diagnosis and treatment are delayed [3]. Economically, Tenosynovitis, mean annual healthcare costs increased from $8,943 pre-diagnosis to $14,880 post-diagnosis, largely driven by surgical interventions and outpatient care [13]. In high-risk occupational populations, prevalence estimates for work-related tenosynovitis range from 3.1% to 5.5% [14] Collectively, these trends underscore the urgent need for improved mechanistic understanding and therapeutic innovation.

Current diagnosis primarily relies on clinical assessment, including medical history, physical examination, and provocative maneuvers such as the Finkelstein test for De Quervain's tenosynovitis, which elicits pain with ulnar deviation of the wrist while the thumb is flexed [11, 15]. Ultrasound is widely regarded as the preferred first-line imaging modality because it allows dynamic, radiation-free visualization of tendon sheath thickening, peritendinous effusion, and hypervascularity [4]. However, ultrasound is highly operator-dependent, potentially limiting interobserver reproducibility. Magnetic Resonance Imaging (MRI) provides superior soft tissue contrast and can detect subtle synovitis, tendon sheath inflammation, and peritendinous edema [5]. Nevertheless, its high cost and limited accessibility constrain routine application. Conventional radiography is useful for identifying bony erosions or structural abnormalities but lacks sensitivity for soft tissue pathology. In infectious tenosynovitis, synovial fluid aspiration and laboratory evaluation of inflammatory markers are essential but may delay definitive diagnosis if not promptly performed [3]. Thus, while effective, current diagnostic strategies often require multimodal integration, increasing both time and healthcare costs.

Pharmacologic treatment similarly presents limitations. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), such as ibuprofen and naproxen, provide symptomatic relief but are associated with gastrointestinal, cardiovascular, and renal adverse effects, particularly with long-term use [12]. Corticosteroid injections demonstrate short-term success rates of 50–80% in trigger finger and related forms of stenosing tenosynovitis [1, 13, 16], yet repeated injections may weaken tendon structure and increase the risk of rupture, especially in diabetic and RA patients [2]. Infectious tenosynovitis requires prompt empiric broad-spectrum intravenous antibiotics, though antibiotic resistance and delayed surgical intervention remain concerns [3]. Conservative measures, including rest and splinting, are foundational but may be insufficient in advanced or recurrent cases, leading to surgical release. Reported complication rates in infectious tenosynovitis reach up to 38%, including stiffness, deformity, and deep-space infections [3]. These limitations highlight the need for more targeted, mechanism-based therapeutic strategies.

To address these gaps, Genome-Wide Association Studies (GWAS) and Gene Expression Profiling (GEO) provide powerful investigative frameworks. GWAS systematically examine millions of genetic variants across

populations to identify susceptibility loci under the common disease–common variant hypothesis. In this study, we combined the GWAS and GEO datasets, to elucidate the candidate novel biomarkers and drug targets for the tenosynovitis. Firstly, we analyzed the tenosynovitis-specific differentially expressed genes by compare with several rheumatic conditions. Then we combined these genes with GWAS genes to find the most relevant tagets. Furthermore, we utilized the molecular dynamics screening to analyze the molecule-protein interactions. To conclute, we reported that IGFBP3 as a potential early detection biomarker and drug target for Tenosynovitis. Our research will shed new light on the detection and treatment of tenosynovitis.

2. Materials and methods

2.1. Bioinformatics screening for candidate genes

The Tenosynovitis candidate gene screening was conducted by a combination of multi-bioinformatics analysis. The GWAS [17, 18] genes and the literature research reported tenosynovitis genes are labeled as "target genes". The RNA-seq data set (GSE93698) was analyzed by R (4.5.1). The R packages ggplot2 (4.0.0) and ggrepel (0.9.6) were used to generate the volcano plot.

2.2. Tenosynovitis-specific gene analysis

The Tenosynovitis candidate genes from bioinformatics were further used for functional analysis. The genes that are not specific to tenosynovitis were beyond the scope of this research and were further removed from the list.

2.3. Molecular dynamics simulation

The molecular dynamics simulation was performed by the Swissdock platform. The molecules that were previously reported to bind to the target protein were further redesigned based on their chemical property and the docking rank score. The molecule-protein interaction images were generated using Chimera (1.19).

3. Results

To elucidate the tenosynovitis candidate genes, we screened the genes from GEO, GWAS, and published literature. As shown in Figure 1, the RNA expression of most of the target genes from GWAS and published literature is not significantly changed in the tenosynovitis patients, including PRTN3, TNF, CRP, FTO, LTBP3, SLC40A1, ADAMTS6, CENPK, WWP2, IL17A, KLHL1, NOD2, and CCL8. The IL6 and IGFBP3 are significantly upregulated, and the CREB5 is significantly downregulated.

Figure 1. The volcano plot shows the differential gene expression of tenosynovitis-specific target genes. The down-regulated genes are labeled cyan, the up-regulated genes are labeled red. The target genes from GWAS gene screen are labeled yellow. The non-significant genes are labeled gray

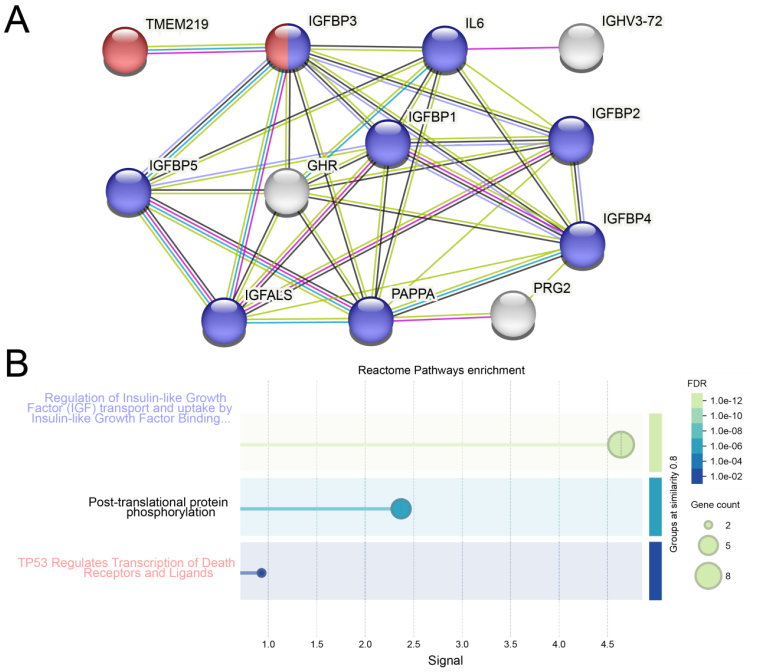

Figure 2. The tenosynovitis-specific gene IGFBP3 interacts with inflammation marker IL6 and apoptocia gene TMEM219. (A)The protein-protein interaction map shows IL6 that works with IGFBP family. (B) The enriched pathways from IL6 and IGFBP3 related proteins

However, IL6 encodes a cytokine that functions in inflammation and the maturation of B cells. Upregulation of IL6 belongs to a transcriptional inflammatory response that is implicated in a wide variety of inflammation-associated disease states. CREB5 belongs to the cAMP Response Element (CRE)-binding protein family. The CREB5 acts as a transcription factor that regulates cellular responses by binding to cAMP-responsive elements. Therefore, neither IL6 nor CREB5 is an ideal drug target for tenosynovitis. IGFBP3 plays a critical role in regulating the availability of IGF1 and IGF2 to their receptors and thereby regulates

IGF-mediated cellular processes, including proliferation, differentiation, and apoptosis. Interestingly, IGFBP3 interacts with IL6 to regulate inflammation, which might regulate the activation of IGF1 and IGF2 (Figure 2).

Since IGFBP3 interacts with IGF1 and IGF2 to regulate cellular functions, blocking the active pocket of IGFBP3 will limit its function, decrease apoptosis, and reduce inflammation. Salvianolic acid B shows specific binding to IGFBP3 in previous studies. We investigated the molecular binding details of Salvianolic acid B (SAB) and its analogs to IGFBP3 (Figure 3). The SAB binds to IGFBP3 on its active pocket and blocks the binding to its natural substrate IGF1. While changing the side chain from the SAB dihydrobenzofuran, they significantly changed the binding details of the active pocket (Figure 3B,C,F,G,J,K). The active pocket remains occupied, while the chemicals did not bind tightly as SAB. However, changing the side chain from the left side catechol ring has significantly increased the binding (Table 1). Our results provide a new insight into the drug design targeting IGFBP3.

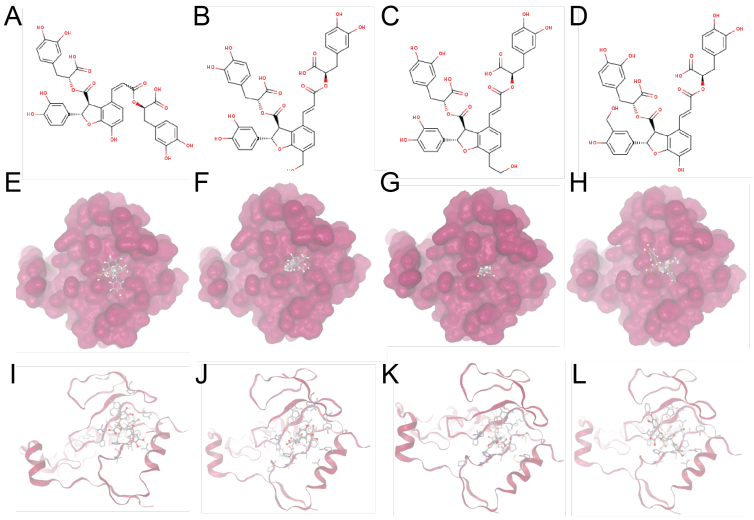

Figure 3. The IGFBP3 interacts with SAB and its analogs. (A-D) The chemical structures of SAB and its analogs. (E-H) The protein surface of IGFBP3 binds to SAB or its analogs. (I-L) The molecular details of IGFBP3 binds to SAB and or analogs

Table 1. The AC score and SwissParam Score of each chemical binding to IGFBP3

Chemical	AC Score	SwissParam Score
C36H30O16 (SAB)	11.552663	-8.6101
C37H32O16	14.475143	-8.6801
C38H34O16	15.570172	-8.3591
C37H32O17	2.599682	-8.7447

4. Discussion

In this study, we employed an integrated bioinformatics and molecular dynamics approach to identify novel biomarkers and therapeutic targets for tenosynovitis, a condition with a rising global burden and limited targeted treatment options. Our analysis revealed that while numerous genes previously associated with

tenosynovitis through GWAS and literature did not show differential expression at the transcriptional level, IGFBP3 emerged as a significantly upregulated and mechanistically promising candidate. These findings position IGFBP3 as a potential dual-function biomarker for early detection and a druggable target for therapeutic intervention [19].

The lack of significant expression changes in most GWAS-derived genes, including TNF, CRP, and NOD2, underscores an important distinction between genetic susceptibility and active transcriptional regulation in tenosynovitis pathology. While these genes may contribute to disease predisposition, their expression levels do not appear to be dynamically altered during active inflammation, limiting their utility as diagnostic biomarkers or therapeutic targets. Conversely, the significant upregulation of IL6 aligns with its established role as a master pro-inflammatory cytokine [20]. However, IL6 is implicated in a broad spectrum of inflammatory conditions including rheumatoid arthritis, systemic juvenile idiopathic arthritis, and Castleman disease, making it a non-specific target for tenosynovitis specifically [21]. Targeting IL6 therapeutically could lead to widespread immunosuppression and off-target effects, diminishing its appeal for a localized musculoskeletal disorder.

The identification of IGFBP3 as a lead candidate is particularly compelling given its multifaceted biological functions. Traditionally recognized for its role in binding and regulating insulin-like growth factors (IGF1 and IGF2), IGFBP3 also exerts IGF-independent effects on apoptosis, proliferation, and inflammation [22]. Our finding that IGFBP3 interacts with IL6 to modulate inflammation suggests that it may serve as a nodal point linking growth factor signaling with the inflammatory cascade in tenosynovitis (Figure 2). This interaction could explain the chronic, fibrotic nature of stenosing tenosynovitis (trigger finger), where both inflammation and aberrant tissue remodeling occur [23]. As reported by Makkouk et al., trigger finger is thought to be caused by inflammation and subsequent narrowing of the A1 pulley, occurring more frequently in the diabetic population [23]. Stahl et al. further demonstrated that the lifetime risk of trigger finger increases to up to 10% in diabetics, with the rate of occurrence associated with disease duration [24]. By regulating the bioavailability of IGFs, IGFBP3 may influence tenocyte proliferation and extracellular matrix deposition, processes central to tendon sheath thickening and adhesion formation. Furthermore, the downregulation of CREB5, a transcription factor involved in cellular stress responses, may represent a compensatory mechanism or a distinct pathological signature that warrants further investigation.

From a translational perspective, the molecular dynamics simulations provide a critical proof-of-concept for targeting IGFBP3. Our data demonstrate that Salvianolic acid B (SAB), a natural polyphenol, binds effectively to the active pocket of IGFBP3, thereby blocking its interaction with IGF1 (Figure 3). This binding mechanism is significant, as it could theoretically limit IGFBP3-mediated apoptosis and pro-inflammatory signaling. Importantly, our structure-based chemical modifications revealed that alterations to the catechol ring of SAB significantly enhanced binding affinity (Table 1). This finding has direct implications for drug development, suggesting that the IGFBP3 active pocket can accommodate optimized ligands with greater specificity and potency. Such targeted inhibition could offer a therapeutic strategy distinct from current options —avoiding the systemic side effects of NSAIDs and the tendon-weakening risks associated with repeated corticosteroid injections [16, 25].

These findings also address the growing clinical need highlighted in our introduction. With the rising prevalence of tenosynovitis linked to metabolic diseases and modern biomechanical stressors (smartphone use, remote work), the demand for precise, mechanism-based therapies is urgent [26]. Fernandez-de-las-Penas et al. demonstrated that problematic smartphone use is associated with a higher prevalence of De Quervain's tenosynovitis symptomatology among young adults, with adjusted prevalence ratios of 1.73 for occasional users and 1.61 for frequent users [27]. Similarly, Saito et al. found that intensive users of information and

communication devices were significantly more likely to have De Quervain's tenosynovitis ($p < 0.001$), with average daily usage times of 5.76 ± 3.00 hours [28]. Current diagnostic workflows rely heavily on physical exams and imaging modalities that are either subjective (ultrasound) or expensive (MRI). An IGFBP3-based biomarker, detectable via serum or synovial fluid assay, could facilitate earlier and more objective diagnosis, particularly in primary care settings where access to specialized imaging is limited. Moreover, a small-molecule inhibitor targeting IGFBP3 could provide a non-surgical option for patients with recurrent or refractory tenosynovitis, potentially reducing the need for surgical release and its associated complications.

Despite these promising findings, several limitations must be acknowledged. First, our analysis is based on a single GEO dataset (GSE93698), which may not fully capture the heterogeneity of tenosynovitis across different etiologies. Validation in larger, independent cohorts with diverse patient demographics is essential. Second, the molecular dynamics simulations, while informative, are in silico predictions that require experimental validation through in vitro binding assays and in vivo efficacy studies. The enhanced binding affinity observed with modified SAB analogs must be confirmed through surface plasmon resonance or cellular thermal shift assays. Third, the functional interaction between IGFBP3 and IL6 in the context of tenosynovitis remains hypothetical; mechanistic studies using tenocyte cell cultures or animal models of tendon inflammation are needed to elucidate the downstream signaling pathways involved.

Future research should focus on several key areas. Clinically, prospective studies should evaluate whether circulating or local IGFBP3 levels correlate with disease severity, treatment response, or progression to chronicity. Experimentally, structure-activity relationship (SAR) studies should be conducted to optimize the lead compounds identified here, assessing their pharmacokinetic properties, bioavailability, and safety profiles. Additionally, given the sex-based disparities in tenosynovitis incidence, exploring whether IGFBP3 expression or function is modulated by hormonal factors could provide insights into personalized treatment approaches.

5. Conclusion

In conclusion, this study establishes IGFBP3 as a biologically plausible and therapeutically attractive target for tenosynovitis. By bridging genomic data with computational drug design, we have laid the groundwork for the development of a first-in-class therapy that addresses both the inflammatory and fibrotic components of the disease. These findings not only position IGFBP3 as a novel biomarker but also lay the groundwork for the rational design of small-molecule inhibitors. Future experimental validation and structure-activity relationship studies will be essential to translate these computational insights into viable therapeutic options, addressing a critical unmet need for targeted, non-surgical interventions in tenosynovitis.

References

[1] Wolfe, S. W., Pederson, W. C., Kozin, S. H., & Cohen, M. S. (2021). *Green's operative hand surgery (8th ed.)*. Elsevier.

[2] Makkouk, A. H., Oetgen, M. E., Swigart, C. R., & Dodds, S. D. (2008). Trigger finger: etiology, evaluation, and treatment. *Current reviews in musculoskeletal medicine, 1*(2), 92-96.

[3] Chapman, T., & Ilyas, A. M. (2019). Pyogenic flexor tenosynovitis: evaluation and treatment strategies. *Journal of hand and microsurgery, 11*(03), 121-126.

[4] Keen, H. I., Brown, A. K., Wakefield, R. J., & Conaghan, P. G. (2005). MRI and musculoskeletal ultrasonography as diagnostic tools in early arthritis. *Rheumatic Disease Clinics, 31*(4), 699-714.

[5] McQueen, F. M. (2008). The use of MRI in early RA. *Rheumatology, 47*(11), 1597-1599.

[6] Wolf, J. M., Sturdivant, R. X., & Owens, B. D. (2009). Incidence of de Quervain's tenosynovitis in a young, active population. *The Journal of hand surgery, 34*(1), 112-115.

[7] Akulwar-Tajane, I., Darvesh, M., Ghule, M., Deokule, S., Deora, B., & Mhatre, V. (2021). Effects of COVID-19 pandemic lock down on posture in physiotherapy students: a cross-sectional study. *Med Clin Res, 6*(1), 91-102.

[8] Ali, M., Asim, M., Danish, S. H., Ahmad, F., & Iqbal, A. (2014). Frequency of De Quervain's tenosynovitis and its association with SMS texting. *Muscles, Ligaments and Tendons Journal, 4*(1), 74-76.

[9] Gelhorn, H. L., Tong, S., McQuarrie, K., Vernon, C., Hanlon, J., Maclaine, G., ... & Tap, W. D. (2016). Patient-reported symptoms of tenosynovial giant cell tumors. *Clinical therapeutics, 38*(4), 778-793.

[10] Asad, M. R., Ahmad, R. K., Almalki, H. A., Alkhathami, K. M., & Alqahtani, B. (2024). Prevalence of de Quervain's tenosynovitis among teenage mobile users: A cross-sectional study. *Journal of Pharmacy and Bioallied Sciences, 16*(Suppl 4), S3341-S3344.

[11] Nie, X., Huang, L., Hou, J., Dai, A., He, L., Zheng, P., ... & Hua, Q. (2023). Smartphone usage behaviors and their association with De Quervain's Tenosynovitis (DQT) among college students: a cross-sectional study in Guangxi, China. *BMC Public Health, 23*(1), 2257.

[12] Jamil, Y., Öktem, H., & Sever, S. N. (2025). The association between digital device usage behaviors and the incidence of de Quervain's tenosynovitis among university students. *Physiotherapy Theory and Practice, 41*(10), 2089-2099.

[13] Gancarczyk, S. M., Jang, E. S., Swart, E. P., & Chen, N. C. (2016). Percutaneous trigger finger release: A cost-effectiveness analysis. *Journal of the American Academy of Orthopaedic Surgeons, 24*(10), 623-629.

[14] Moore, J. S. (2000). Flexor tendon entrapment of the digits (trigger finger and trigger thumb). *Journal of occupational and environmental medicine, 42*(5), 526-545.

[15] Ilyas, A. M., Ast, M., Schaffer, A. A., & Thoder, J. (2007). De quervain tenosynovitis of the wrist. *JAAOS-Journal of the American Academy of Orthopaedic Surgeons, 15*(12), 757-764.

[16] U.S. Food and Drug Administration. (2015). *FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes*. Retrieved from https: //www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-strengthens-warning-non-aspirin-nonsteroidal-anti-inflammatory

[17] Fleisch, S. B., Spindler, K. P., & Lee, D. H. (2007). Corticosteroid injections in the treatment of trigger finger: a level I and II systematic review. *JAAOS-Journal of the American Academy of Orthopaedic Surgeons, 15*(3), 166-171.

[18] Okada, Y., Wu, D., Trynka, G., Raj, T., Terao, C., Ikari, K., ... & Plenge, R. M. (2014). Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature, 506*(7488), 376-381.

[19] Wiberg, A., Ng, M., Schmid, A. B., Smillie, R. W., Baskozos, G., Holmes, M. V., ... & Furniss, D. (2019). A genome-wide association analysis identifies 16 novel susceptibility loci for carpal tunnel syndrome. *Nature communications, 10*(1), 1030.

[20] Nishimoto, N., & Kishimoto, T. (2006). Interleukin 6: From bench to bedside. *Nature Clinical Practice Rheumatology, 2*(11), 619-626.

[21] Tanaka, T., Narazaki, M., & Kishimoto, T. (2014). IL-6 in inflammation, immunity, and disease. *Cold Spring Harbor perspectives in biology, 6*(10), a016295.

[22] Tanaka, T., & Kishimoto, T. (2014). The biology and medical implications of interleukin-6. *Cancer immunology research, 2*(4), 288-294.

[23] Baxter, R. C. (2014). IGF binding proteins in cancer: mechanistic and clinical insights. *Nature Reviews Cancer, 14*(5), 329-341.

[24] Blyth, M. J. G., & Ross, D. J. (1996). Diabetes and trigger finger. *The Journal of Hand Surgery: British & European Volume, 21*(2), 244-245.

[25] Stahl, S., Kanter, Y., & Karnielli, E. (1997). *Outcome of trigger finger treatment in diabetes. Journal of diabetes and its complications, 11*(5), 287-290.

[26] Benites-Zapata, V. A., Jiménez-Torres, V. E., & Ayala-Roldán, M. P. (2021). Problematic smartphone use is associated with de Quervain's tenosynovitis symptomatology among young adults. *Musculoskeletal Science and Practice,* 53, 102356.

[27] Saito, K., & Saito, Y. (2021). Relationship between information and communication device usage and development of hand disorders. *INQUIRY: The Journal of Health Care Organization, Provision, and Financing*, 58, 00469580211029607.

[28] Wakefield, R. J., Balint, P. V., Szkudlarek, M., Filippucci, E., Backhaus, M., D'Agostino, M. A., ... & OMERACT 7 Special Interest Group. (2005). Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *The Journal of rheumatology, 32*(12), 2485-2487.