EJR European Journal of Rheumatology

DOI: 10.5152/eujrheum.2022.21124

Case-based Review

Sitagliptin-induced Achilles enthesopathy: Case report and literature review

İbrahim Halil Rızvanoğlu[1], Bünyamin Kısacık[2]

Abstract

Achilles enthesopathy is a pain caused due to inflammation of the insertion area of the Achilles tendon on the posterosuperior aspect of the calcaneus. Sometimes, isolated Achilles enthesopathy can be occurred, while, mostly, it is observed with rheumatological diseases. We herein aimed to report a case presentation, sitagliptin-induced enthesopathy, and literature review on musculoskeletal manifestations of gliptins. A 63-year-old man was diagnosed with type II diabetes mellitus, recently started sitagliptin. After the sitagliptin administration, bilateral Achilles enthesopathy has emerged. Afterward, he was diagnosed with sitagliptin-induced enthesopathy, and it was stopped. Following the termination of sitagliptin, all signs and symptoms related to Achilles enthesopathy disappeared. Gliptin-induced enthesopathy was reported rarely. To the best of our knowledge, this is the second case of gliptin-induced Achilles enthesopathy in the literature. Gliptins might not innocent drugs about musculoskeletal disorders.

Keywords: Sitagliptin, enthesopathy, tendinitis, DPP-4 inhibitor, musculoskeletal manifestation

Introduction

Achilles enthesopathy is a pain caused due to inflammation of the insertion area of the Achilles tendon on the posterosuperior aspect of the calcaneus. This inflammation leads erosion on the calcaneus and degeneration in the tendon. If Achilles enthesopathy cannot be diagnosed or treated appropriately, it can cause partial or total tendon rupture.[1] Although enthesopathy is frequently seen as an extra-articular manifestation of seronegative spondyloarthropathies, sometimes, it can be seen as an isolated enthesopathy without a rheumatologic disorder.[2,3]

In the last decade, the popularity of gliptins, used in the treatment of type 2 diabetes mellitus (DM), which is inhibiting dipeptidyl peptidase 4 (DPP-4), is increasing day by day. Although there are a few reports that gliptins cause side effects such as myalgia, arthralgia, muscle weakness, only one case report has been made regarding enthesopathy.[4] This paper aimed to report a case report, sitagliptin-induced enthesopathy, and also narrative review of the literature about musculoskeletal manifestations of gliptins. An informed consent and permission about the demonstration of his USG images were obtained from the patient.

Case Presentation

A 63-year-old man was diagnosed with type II DM and admitted to rheumatology outpatient service with complaints of bilateral posterior heel pain started 3 months ago. He did not have any chronic disease except DM, which was diagnosed about 7 years ago. The patient history revealed that he was followed-up regularly by an endocrinologist and was taking gliclazide 60 mg and metformin 2 g day^{-1}. His blood glucose level was 290 mg dL^{-1}, HbA1c was 9.5 in his last endocrinology out-patient visit, and a sitagliptin 100 mg day^{-1} was started additionally. In the fourth week of sitagliptin therapy, bilateral heel pain started.

After he was consulted to rheumatology clinic, then we investigated the patient for isolated Achilles enthesopathy, seronegative spondyloarthropathy, Behcet's disease, and rheumatoid arthritis. He had pain, swelling, redness, and mild heat on the bilateral insertion point of Achilles tendons to the calcaneus. His blood pressure was 130/80 mm Hg, the pulse rate was 84 BPM (beats per minute), and examination of his cardiovascular and respiratory systems was normal.

Laboratory findings were not significant: C-reactive protein (CRP), 2.7 mg/L; sedimentation rate, 17 mm h^{-1}; hemoglobin level, 13.6 g dL^{-1}; WBC, 7.2 mcl. Additionally, rheumatoid factor, antinuclear antibody, anticyclic citrullinated peptide antibody, and human leukocyte antigen-B27 were negative. In the

ORCID iDs of the authors:
İ. H. R. 0000-0002-7341-3733;
B. K. 0000-0002-3073-9098.

Cite this article as: Rızvanoğlu İH, Kısacık B. Sitagliptin-induced Achilles enthesopathy: Case report and literature review. *Eur J Rheumatol.* 2022;9(2):111-113.

[1] Department of Orthopedics and Traumatology, NCR International Hospital, Şehitkamil, Gaziantep, Turkey
[2] Department of Rheumatology, Gaziantep Medicalpark Hospital, Şehitkamil, Gaziantep, Turkey

Address for Correspondence: İbrahim Halil Rızvanoğlu; Department of Orthopedics and Traumatology, NCR International Hospital, Şehitkamil, Gaziantep, Turkey

E-mail: dr.rizvanoglu@gmail.com

Submitted: June 16, 2021
Accepted: July 16, 2021
Available Online Date: January 21, 2022

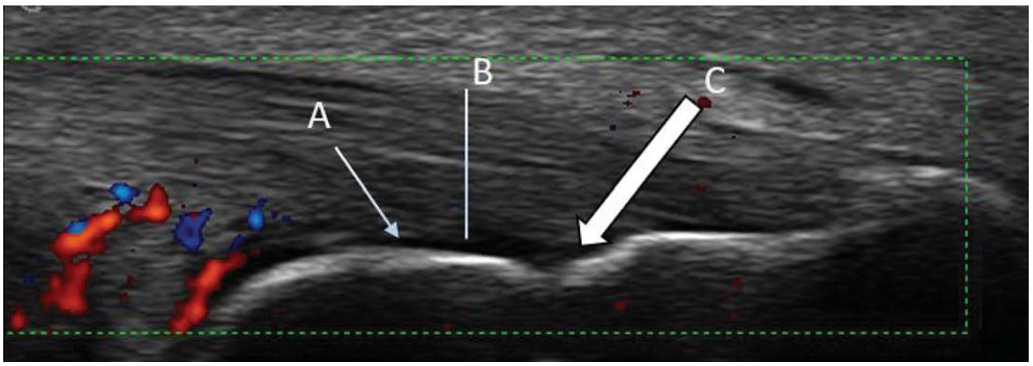

Figure 1. USG image of patient. (A) Loss of fibrillar formation of tendon (thin arrow). (B) Thickening of tendon (bar). (C) Irregularities on calcaneal surface (thick arrow).

Table 1. Musculoskeletal disorders in DPP-4 inhibitor users.

Study	**Drug** (Administered Case Number)	Disorder	Involved Case/Total Case (%)
Saito et al.[13]	Sitagliptin	Polyarthropaty	13/385 (3.4%)
Sayiner et al.[14]	Sitagliptine, vildagliptine, saxagliptine	Arthritis/arthralgia	41/93 (44%)
Men et al.[15] (meta-analyze)	Sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin	Arthritis/arthralgia	1 424/41 468 (3.4%)
Wang et al.[16] (meta-analyze)	Sitagliptin, vildagliptin, saxagliptin, linagliptin	Arthritis/arthralgia	949/11 406 (8.3%)
Hou et al.[17]	Sitagliptin, saxagliptin, linagliptin, alogliptin	Severe joint pain	679/4 743 (14.3%)
Huang et al.[6,*]	Sitagliptin (400), Vildagliptin (17), Saxagliptin (32) Linagliptin (35) (totally, 582 musculoskeletal disorders reported from 484 patients)	Arthritis/arthralgia	273
		Extremity pain/ Miyalgia	299
		Fracture	10
Tarapués et al.[4,*]	Sitagliptin (27), vildagliptin (6), saxagliptin (1) (totally 45 musculoskeletal disorders reported from 34 patients)	Arthritis/arthralgia	9
		Extremity pain/ miyalgia	23
		Others[†]	13
Crickx et al.[18] (case report)	Sitagliptin (2), vildagliptin (1)	Polyarthritis	3
Yamauchi et al.[19] (case report)	Sitagliptin (1), vildagliptin (1)	Synovitis	2
Chaicha-Brom and Yasmeen[20] (case report)	Sitagliptin	Arthralgia	1
Bussey et al.[5] (case report)	Sitagliptin	Enthesopathy	1

[*]Received spontaneous total reports of suspected ADRs (not only musculoskeletal findings but also include all disorders) from healthcare professionals and the pharmaceutical industry due to all kinds of DPP-4 inhibitors.
[†]Includes: muscle weakness,[4] joint stiffness,[2] muscle spasms,[2] polyarthritis,[1] cervical pain,[1] backache,[1] swelling joint,[1] and musculoskeletal discomfort.[1]

radiologic assessment, thoracolumbar and sacroiliac MRIs were normal; there was no spondyloarthropathy finding. In Achilles USG, power doppler signal increment revealing inflammation in the insertion of Achilles tendon was observed as a presence of hypoechogenicity. There was loss of fibrillar pattern of tendon, tendon thickening, calcification, and erosion seen in the insertion area of the tendon, with irregularities on bone surface (Figure 1).

There was no rheumatological disease symptom or sign detected in patient's comprehensive musculoskeletal examination. We diagnosed this patient as sitagliptin-induced Achilles enthesopathy. After termination of the sitagliptin treatment and starting an anti-inflammatory drug therapy, 1 month later, a follow-up visit was planned. There was no clinical finding-associated enthesopathy.

Main Points

- DPP-4 inhibitors are not entirely innocent, especially in terms of musculoskeletal side effects.
- Although not frequently encountered, DPP-4 inhibitors can cause Achilles enthesopathy.
- Clinicians should be aware of potential musculoskeletal adverse effects of gliptins.

Discussion

This study presents a sitagliptin-induced isolated Achilles enthesopathy. Clinical symptoms and characteristics of current case that distinguished it from the spondyloarthropathy group were significantly assessed. Unlike spondylarthritis cases, the patient was older than 60. While the symptoms onset was slow in spondylarthritis, it was sudden in our patient. There were no symptoms such as inflammatory back pain, uveitis, or arthritis. In addition, HLA-B27 test and acute phase reactants were normal titers. These findings were important in differential diagnosis. Achilles enthesopathy was thought to be associated with DPP-4 treatment because all complaints of the patient disappeared within 1 month after stopping sitagliptin.

To the best of our knowledge, this is the second case reported in the literature. First case was reported by Bussey et al.,[5] it was sitagliptin-induced Achilles enthesopathy, too. Recently, the musculoskeletal manifestations related to DPP-4 inhibitors have been reported. Tarapués et al. investigated 332 individual side effects of gliptins reported to Spanish Pharmacovigilance System. Of the total side effects, 34 of them were related musculoskeletal system and the ratio of musculoskeletal manifestations to reported ADRs (adverse drug reactions) of DPP-4 was 10.2%.[4] Huang et al. collected data from the FDA Adverse Event Reporting System about DPP-4 inhibitors adverse effects and published in their study. Totally, 9 706 adverse events was reported, and 582 of them (5.99%) were related to musculoskeletal system.[6] Due to frequent musculoskeletal system complaints, FDA warned that DPP-4 inhibitors may cause severe joint pain in August 2015. Gliptins are not innocent drugs about musculoskeletal symptoms. Here, we display the rate of musculoskeletal manifestations from recent studies (Table 1).

We also reviewed on drug-induced Achilles enthesopathy, we noticed; retinoids, adalimumab, fluoroquinolones, corticosteroids, statins, and fibrates can cause Achilles enthesopathy.[1,7–10] In our recent study, related to retinoids, we found Achilles enthesopathy in three patients.[11] The patient, presented in this report, had not undergo any of these drugs.

Delaying in diagnosis or late treatment initiation in Achilles enthesopathy may result in partial or total tendon rupture, which may require surgical treatment. Partial or complete tendon rupture has been described in almost half of the reported cases of Achilles tendinitis.[1] Yasui et al.[12] reported that the rate of Achilles tendon rupture in Achilles tendinitis was 4%. Additionally, they notified that older patients with Achilles tendinopathy were most vulnerable. The patient, presented in this study, was 63 years old, and he was in risk potent group in terms of Achilles tendon rupture.

In light of these observations, our recommendation for clinicians is caring about musculoskeletal adverse effects of DPP-4 inhibitors. Our case was the second gliptin-induced Achilles enthesopathy patient, but some of the cases may have been overlooked in other clinics. Further studies, especially query about Achilles enthesopathy, may shed light on the adverse effects of DPP-4 inhibitors.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - I.H.R, B.K.; Design - I.H.R; Supervision - B.K.; Resources - I.H.R, B.K; Materials - I.H.R, B.K.; Data Collection and/or Processing - I.H.R, B.K.; Analysis and/or Interpretation - I.H.R, B.K.; Literature Search - I.H.R, B.K.; Writing Manuscript - I.H.R, B.K.; Critical Review - B.K.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

References

1. Khaliq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: A critical review of the literature. *Clin Infect Dis*. 2003;36(11):1404-1410. [CrossRef]
2. Rudwaleit M, Landewé R, van der Heijde D, et al. The development of assessment of Spondylo-Arthritis international society classification criteria for axial spondyloarthritis (part I): Classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheumat Dis*. 2009;68(6):770-776. [CrossRef]
3. Genc H, Cakit BD, Tuncbilek I, Erdem HR. Ultrasonographic evaluation of tendons and enthesal sites in rheumatoid arthritis: Comparison with ankylosing spondylitis and healthy subjects. *Clin Rheumatol*. 2005;24(3):272-277. [CrossRef]
4. Tarapués M, Cereza G, Figueras A. Association of musculoskeletal complaints and gliptin use: Review of spontaneous reports. *Pharmacoepidemiol Drug Saf*. 2013;22(10):1115-1118. [CrossRef]
5. Bussey MR, Emanuele MA, Lomasney LM, Tehrani R. Sitagliptin-induced bilateral Achilles tendinitis. *Rheumatology (Oxford, England)*. 2014;53(4):630-630. [CrossRef]
6. Huang J, Jia Y, Sun S, Meng L. Adverse event profiles of dipeptidyl peptidase-4 inhibitors: Data mining of the public version of the FDA adverse event reporting system. *BMC Pharmacol Toxicol*. 2020;21(1):68. [CrossRef]
7. Bottomley WW, Cunliffe WJ. Acute Achilles tendonitis following oral isotretinoin therapy for acne vulgaris. *Clin Exp Dermatol*. 1992;17(4):250-251. [CrossRef]
8. Mease PJ, Van den Bosch F, Sieper J, Xia Y, Pangan AL, Song IH. Performance of 3 enthesitis indices in patients with peripheral spondyloarthritis during treatment with adalimumab. *J Rheumatol*. 2017;44(5):599-608. [CrossRef]
9. Blanco I, Krähenbühl S, Schlienger RG. Corticosteroid-associated tendinopathies: An analysis of the published literature and spontaneous pharmacovigilance data. *Drug Saf*. 2005;28(7):633-643. [CrossRef]
10. Chazerain P, Hayem G, Hamza S, Best C, Ziza JM. Four cases of tendinopathy in patients on statin therapy. *Joint Bone Spine*. 2001;68(5):430-433. [CrossRef]
11. Alkan S, Kayiran N, Zengin O, et al. Isotretinoin-induced spondyloarthropathy-related symptoms: A prospective study. *J Rheumatol*. 2015;42(11):2106-2109. [CrossRef]
12. Yasui Y, Tonogai I, Rosenbaum AJ, Shimozono Y, Kawano H, Kennedy JG. The risk of Achilles tendon rupture in the patients with Achilles tendinopathy: Healthcare database analysis in the United States. *BioMed Res Int*. 2017;2017:1-4. [CrossRef]
13. Saito T, Ohnuma K, Suzuki H, et al. Polyarthropathy in type 2 diabetes patients treated with DPP4 inhibitors. *Diabetes Res Clin Practice*. 2013;102(1):e8-e12. [CrossRef]
14. Sayiner ZA, Okyar B, Kısacık B, Akarsu E, Özkaya M, Araz M. DPP-4 inhibitors increase the incidence of arthritis/arthralgia but do not affect autoimmunity. *Acta Endocrinol*. 2018;14(4):473-476. [CrossRef]
15. Men P, He N, Song C, Zhai S. Dipeptidyl peptidase-4 inhibitors and risk of arthralgia: A systematic review and meta-analysis. *Diabetes Metabol*. 2017;43(6):493-500. [CrossRef]
16. Wang CY, Fu SH, Yang RS, Hsiao FY. Use of dipeptidyl peptidase-4 inhibitors and the risk of arthralgia: Population-based cohort and nested case-control studies. *Pharmacoepidemiol Drug Saf*. 2019;28(4):500-506. [CrossRef]
17. Hou WH, Chang KC, Li CY, Ou HT. Dipeptidyl peptidase-4 inhibitor use is not associated with elevated risk of severe joint pain in patients with type 2 diabetes: A population-based cohort study. *Pain*. 2016;157(9):1954-1959. [CrossRef]
18. Crickx E, Marroun I, Veyrie C, et al. DPP4 inhibitor-induced polyarthritis: A report of three cases. *Rheumatol Int*. 2014;34(2):291-292. [CrossRef]
19. Yamauchi K, Sato Y, Yamashita K, et al. RS3PE in association with dipeptidyl peptidase-4 inhibitor: Report of two cases. *Diabetes Care*. 2012;35(2):e7. [CrossRef]
20. Chaicha-Brom T, Yasmeen T. DPP-IV inhibitor-associated arthralgias. *Endocr Pract*. 2013;19(2):377-381. [CrossRef]