

**Saxagliptin induced bilateral knee arthralgia: a rare case report****Akshay Dahiwele<sup>1\*</sup>, Dinesh Kansal<sup>1</sup>, Atal Sood<sup>1</sup>, Dheeraj Kapoor<sup>2</sup>, Parveen Sharma<sup>1</sup>, Aradhna Sharma<sup>1</sup>**<sup>1</sup>Department of Pharmacology, Dr. RPGMC Kangra at Tanda Himachal Pradesh, India<sup>2</sup>Department of Medicine, Dr. RPGMC Kangra at Tanda Himachal Pradesh, India**Received:** 13 July 2016**Accepted:** 10 August 2016**\*Correspondence to:**Dr. Akshay C. Dahiwele,  
Email: [akshaydahiwele021@gmail.com](mailto:akshaydahiwele021@gmail.com)**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.**ABSTRACT**

A 55 year old female patient of type 2 diabetes mellitus on saxagliptin (5 mg once a day), a dipeptidyl peptidase 4 inhibitor (DPP-4 inhibitors) as add on therapy to metformin (1000 mg twice a day). After two months of addition of saxagliptin, the patient had pain in both the knee joints. Saxagliptin was withdrawn and then the knee pain was gradually relieved. Other cause of joint pains like osteoarthritis, rheumatoid arthritis, gout, septic arthritis etc. were ruled out. We consider that this case is important in bringing this potential side effect to the attention of both pharmacologists and primary care physicians as DPP- IV inhibitors has been the most commonly used drug substitute to glimepiride as an add on therapy to metformin.

**Keywords:** Saxagliptin, Knee pain, Adverse drug reaction**INTRODUCTION**

Glucose homeostasis is not only dependent on primary hormones like insulin, glucagon, somatostatin, growth hormone and glucocorticoids but also the endogenous incretins like glucagon-like peptide-1 (GLP 1) and glucose-dependent insulinotropic hormone (GIP) plays very important role. These are released from the L and K cells of the gastrointestinal tract, respectively both GLP-1 and GIP cause a glucose-dependent increase in insulin secretion.<sup>1</sup>

Under normal physiological conditions, GLP-1 and GIP are rapidly degraded by the enzyme system dipeptidylpeptidase-4 (DPP-4). As GLP-1 stimulates insulin secretion only under hyperglycemic conditions, there is minimal risk of hypoglycemia, making this

molecule and its congener's likely candidates for use as anti-hyperglycemic agents.<sup>2</sup>

DPP-4 inhibitors are an important addition to the list of pharmacological options for the treatment of diabetes mellitus. Saxagliptin belongs to DPP-4 inhibitors class of the oral hypoglycemic agents, was approved by FDA on July 31<sup>st</sup> 2009. Other DPP-4 inhibitors are sitagliptin, vildagliptin, alogliptin, linagliptin.<sup>3</sup>

The DPP-4 inhibitors are used as add on therapies in type 2 diabetes mellitus. The most common documented ADRs with saxagliptin are upper respiratory tract infection, urinary tract infection, and headache with rare side effects such as rash and urticarial.<sup>4</sup>

Important causes of non-traumatic joint pain are osteoarthritis, rheumatoid arthritis, gout, septic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis.<sup>5</sup>

Several studies (comparative as well as placebo controlled) have been done for saxagliptin safety and efficacy but to the best of our knowledge saxagliptin causing joint pain have never been documented in the literature till far.

## CASE REPORT

A 55 years old female patient with type 2 diabetes mellitus was started with metformin 500 mg twice daily for the last 2 years and had achieved treatment goals for diabetes with metformin monotherapy. After 9 months again her HbA1c started rising to 9% and subsequently her metformin dose was increased to 1500 mg daily. After 2-3 months when her HbA1c and fasting plasma glucose were not controlled with metformin monotherapy, add-on therapy with saxagliptin 5 mg once a day was initiated.

After two months of the treatment the patient presented with pain in both the knee joints since 15 days. Pain started in both knees with mild aching, which increased gradually, aggravated by walking and relieved by rest. On examination there was absence of classical signs of inflammation like swelling, redness, raised local temperature and tenderness.

On lab investigation her HbA1c was 8.6%, uric acid level was 4.2 mg/dl, rheumatoid arthritis factor was less than 8, and anti CCP antibody was less than 0.50. X ray both knee joints was found to be normal for osteoarthritis.

Saxagliptin was stopped and she was put on the combination of glimepiride (2 mg), pioglitazone (15 mg), metformin (1000 mg) once a day. After one month the patient was relieved of pain completely.

The causality assessment was done using WHO-UMC causality assessment scale and it was found to be certain in nature and also as elucidated by patient's history, lab investigations and dechallenge test with subsequent complete resolution in pain of both knee joints, certainty was ascribed to saxagliptin for inducing knee arthralgia.

## DISCUSSION

Drugs are not the common cause of joint pain in general population. Several drug has been implicated as a cause of joint pain such as statins, clindamycin, febuxostat, nicardipine etc.<sup>6-9</sup>

In the above case the patient was started with saxagliptin as add on therapy to metformin. After two months the patient came with complaint of joint pain, without history of fever or injury. Investigations ruled out common causes of joint pain like rheumatoid arthritis, septic

arthritis and normal x ray both knee joints with orthopedician consultation revealed no osteoarthritis. After saxagliptin dechallenge patient was relieved of pain. Certainty was ascribed to saxagliptin to cause bilateral knee pain as this had plausible time relationship with the drug, bilateral knee pain is usually not associated with the natural history of diabetes mellitus, a positive dechallenge test and in view of the US FDA warning of saxagliptin in July 2015 inducing disabling bilateral knee pain.<sup>10</sup>

Rechallenge was not attempted in the patient in view of ethical considerations. The exact mechanism of saxagliptin causing joint pain is not known. There is a need that such cases should be documented frequently because this is a reversible condition if diagnosed well in time. This possibility of arthralgia should always be kept in mind while prescribing saxagliptin in type 2 diabetes mellitus patients.

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