ORIGINAL ARTICLE

Sitagliptin-Induced Arthropathy in Non-Obese Patients of Diabetes Mellitus Type-2 in Hyderabad, Sindh, Pakistan

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ABSTRACT

Objective: To assess the incidence of Sitagliptin-induced arthropathy in q`non-obese patients with diabetes mellitus type-2.

Methodology: A comparative cross-sectional study was done at the community of Sadder and Latifabad, Hyderabad, Sindh, Pakistan from July 2017 to March 2018. All diagnosed patients with diabetes mellitus aged above 18 years were eligible to partake in the study. For study Group A, patients with DM Type 2 with joint pain were included while for control group, patients with DM Type 2 without joint pain were included. The two groups were prescribed Sitagliptin as an add-on to the on-going treatment regime for diabetes mellitus type 2. Two sets of serology tests were obtained including CRP, Serum calcium, HbA1C at interval of 0 and 24th weeks. Two sets of X-rays of right knee and right wrist joints were obtained at 0 and 24th week.

Results: Hemoglobin A1c was significantly reduced (p=0.05) while there was insignificant alteration note in CRP and serum calcium the p value was 0.06 and 0.07. After sitagliptin use, 35 /68 (50%) had multiple radiological abnormalities seen, most common was reduced joint space and spur formation and p value was significant 0.04 and in control 10 /50 (20%), most common x ray abnormality was osteopenia.

Conclusion: The occurrence of arthropathy was more common among patients using DPP-4 inhibitors as compared to non-users. It is only study as so far done in last couple of years to highlight Sitagliptin induced arthropathy.

Key words: CRP, Sitagliptin, arthropathy, Hyderabad

INTRODUCTION

Diabetes mellitus is a metabolic syndrome characterized by having persistently elevated levels of glucose in the blood. It may be either a deficiency in the release of insulin or issues with insulin's ability to function on the periphery. Type 2 diabetes is the main form of the condition, which affects about 90% of the people who have diabetes.

People with diabetes can also have reduced joint mobility, articular injury, joint infections, and arthritic symptoms. [1] Type 2 diabetes is associated with musculoskeletal disorders and over-representation of these patients in physical therapy is a well-known issue. [2]

Studies show a connection diabetes to increased incidence of musculoskeletal diseases, such as arthritis and gout. Since diabetics suffer more severe and debilitating joint problems, they are vulnerable to painful conditions later in life.

As people with diabetes are more often affected by connective tissue problems, there is good evidence that they are predisposed to nonenzymatic glycosyl and contractural fibrosis. The expert management of this case is vital to the safe and full diagnosis of musculoskeletal injury.

Musculoskeletal conditions contribute to an increased fracturing, entrapment, neuropathies, arthritis, rheumatoid, and frozen joints. [3]

The mainstay in treatment for type 2 diabetes is the use of oral hypoglycemic agents. A wide number of pharmaceuticals is on the market includes metformin, sulfonylureasilureas, GLP-1 analogs (Di-peptid® polypeptide), SGLT-2 (sulfonylpurin), and DPP-4 inhibitors (Dipeptid® polypyhin). In diabetics, the sensitivity to insulin is linked to both how much insulin has been released in the previous 24 hours and the activity of the cells.

In non-diabetic people, incretin hormones, namely glucagon-like polypeptide 1 (GLP-1) and glucose-dependent insulin-inducing peptide (GIP) play a more significant role in the insulin response than pre-meal. [4]

Some studies have shown that incretin hormones improve insulin secretion in people with type 2 diabetes. This idea offered an incretin-based approach, which used DPP4 and other GLP-1-like agents to decrease the enzyme DPP4 was built on. Sitagliptin is the first of this class of DPP4 inhibitors

It is an active, competitive, and reversible DPP4 inhibitor. DPPhenformin Peptide 4 is highly specific. We found that the recommended dose of 100 mg per day was not problematic. [5] islet and beta mass, morphology, and survival are shown to be improved by DPP4 inhibitors in animals. [6]

Treatment with sitagliptin was found to be generally well tolerated. others outcomes which are manageable, such as headache, diarrhea, joint pain, and nausea, but there are also a great deal of other side effects that arise which are intolerable. 7

Since we have treatment for rheumatic conditions, are diabetics now suffering from DPP-4 inhibitor side effects? The use of DPP-4 inhibitor was shown to be beneficial in a study which revealed a significantly reduced risk of rheumatoid arthritis. [8] Another case-control study linked DPP-4 inhibitors with joint inflammation. [9] The other a population-based cohort of approximately fifty thousand Taiwanese adults with type 2 diabetes did not find a correlation with joint pain, suggesting that the findings of

this particular population-based study should be taken with a grain of salt. [10] It has been found that the prevalence of these musculoskeletal disorders in those with Type 2 diabetes is greater than in those who are not diabetic.

By focusing on patients with diabetic osteoarthritis, who do not focus on joint injury, this research will better assess and compare the joint damaging effect of Sitagliptin.

MATERIAL AND METHODS

This comparative cross-sectional trial was performed in sadder clinics in Hyderabad Sindh Pakistan by two doctors, one by the LUMHS Jamshoro, and one by statistician and a junior doctor for the filling of proforma. Nonprobability sampling, a total of 118 patients, ages 30-50 years and up, were recruited from July 2017 to March 2018, and were monitored for 6-9 months to discover whether this procedure improved their sugar control. clinical data, including hemoglobin A1C A1C, serum Ca2+ concentration, and medical history, was documented by using a 10 cc disposable syringe. Samples were sent to the Diagnostic and R&D department or the headquarters of LUMRA. Hb were regarded as abnormally high for the purpose of high-performance liquid chromatography (Bio-Rad) and anything above 6% was abnormal With an enzyme-linked immunosorbentenimetric assay, a value greater than 6mg/dL was identified as indicative of the presence of the C-reactive protein. Laboratory sampling occurred at the rate of 0 and 24 weeks. None of the patients was excluded on the basis of their gender, whether they had diabetes or not, as long as they were over the age of 18. Patients with a Body Mass Index (B.I.) < 30 kg/m2, for hip osteoarthritis, and any history of joint disease, as well as those with multiple illnesses were removed from the analysis -It was made up of 70 participants with no signs of joint pain, so there were 68 cases and 50 control cases to be analyzed (diabetic without joint pain). Hemoglobin A1C, serum calcium reaction strip, height, and three specimens of blood were collected in a 10-cc disposable syringe. This assortment of boxes was sent to Diagnostic and testing labs in Hyderabad.

High-performance liquid chromatography's (Bio-Rad) was performed with a High Performance Liquid Chromatography (HPLC) process, and values greater than 6% were considered elevated. and levels of C-reactive protein have been determined to be greater than six milligrams per milliliter, which classifies it as large.

We took the x-rays of both at two time intervals of two weeks from the Data MRI Center in Hyderabad The controls were equated with age and body mass index (body mass index being used instead of weight.)

The dosage was set at 100 mg per day for the duration of the study. The findings of the test were repeated in the 0th and 24th week of the series. The presence of arthopathies, spurs, reduction in joint space, and effusion is often evidence that drugs have been used; more than two results are assumed to be radiographic, using three values: the average, or midpoint, plus one-one-third, plus the confidence interval, or three quartiles plus the gap between the third and fourth." There was a Chi-square test to measure the categorical variables, and independent-sample t-t analyses compared the means of two separate variables. Computer tests were carried out using the SPS 16 system. The p-value of 0.05 was regarded as important.

RESULTS

Participants mean age was 27 ± 6.5 years, and subjects had diabetic period 3 ± 2.7 years and the mean BMI was 22± 3.2 kg/m^2. The ratio of men to women was 1:1,4 in subjects, and 1:1 in power. There were no major variations in diabetes subjects and controls, HbA1c (Table 1). In diabetic subjects after fourth week of Sitagliptin and after twentieth week, joint pain was aggravated.

Sitagliptin comprised 68 patients with 50 control patients in the 118 patients receiving DPP-4 inhibitor. Hemoglobin A1c was substantially lowered by a value of 0.05 p and an od ratio of 1 while the CRP and serum calcium altered insignificantly by a ratio of 0.06 and 0.07. (Table 2)

In 10/68 (14,5 percent) of subjects, radiological variations were reduced in joint spatial spacing and spur formation (table 3). The most common x-ray abnormalities were osteopenia after use of Sitagliptine, 35/68 (50 per cent) had numerous radiological abnormalities, the lowered space of joint and route and the significant p-value were 0,04, the control 10 /50 (20 percent). (table 4)

Table 1: General characteristics of 118 patients

Characteristics	Subjects (68) Mean	Control (50) Mean
Age	30 ± 10.5	32 ± 11.4
Male	40	25
Females	28	25
BMI	22± 3.2	23 ±3.1
Duration of diabetes	3 ± 2.7	2.9± 2.7
Duration of joint pain	2.1 ±1.7	---
Ares of joint pain	Right knee>left knee Right wrist joint	----------

Tale 2: Biochemical profile of 118 patients

Labs	Subjects		Control		P VALUE
	Male (n=40)	Female(n=28)	Male (n=25)	Female=25)	
Mean HbA1c Pretreatment	6.5 ±1.9	6.7 ± 1.7	6.9± 1.5	6.8 1.6	0.04 OR =1
Post treatment	5.9 ±1.5	6.0 ±1.5	6.1 ± 1.5	6. 2 ±1.1	
CRP Pretreatment	3.2 ±1.7	2.6 ±1.9	4. ± 1.6	3.9 ±1.8	0.06 OR =0.8
Post treatment	2.9± 1.7	3 ±1.9	3.5± 1.7	3.2± 1.7	
CALCIUM Pretreatment	8.5± 1.1	7.7 ±1.8	8.2 ±1.7	8.2± 1.77	0.7 OR=0.9
Post treatment	8.3 ±2	8 ±2.1	8.1± 2.1	8.0± 1.2	

Table 3: Radiological changes in patient's pre and post Sitagliptin treatment

Subjects	Knees or and Wrist joint	Subject No of patients	P value	Subject No of patients	Control No of patients	P value
Pretreatment	Osteopenia Spur reduced joint space, Mild periosteal erosions	10		10	---	
Post treatment	Osteopenia Spur reduced joint space, Mild periosteal erosions	35	0.04	35	10	0.07
			38.1%			

Table 4: Radiological changes in 55 patients post Sitagliptin treatment.

Radiologic change	Subjects(n=45)	Control(n=10)	P value
Osteopenia	12	6	
Spur reduced joint space	25	3	
Mild periosteal erosions	8	1	0.04

DISCUSSION

This has been a rare and outstanding research in our country to the best of our knowledge. DPP4 inhibitors have been regarded as the cornerstone for one decade of diabetes care. Many authorities have identified several cases of rheumatoid arthritis aggravation due to the use of DPP4 inhibitors, but these studies have included reports of a few patients so that health authorities could not pay further attention. [11-14]

Pakistan has greater frequency than Western nutritional, metabolic and degenerative joint diseases. Initially, a medicine that increases pain and handicap leads to non-compliance and eventually leads to diabetes complications.

Our research was continued for 6-9 months with the recruitment of 118 hospital-based patients on Sitagliptin which is comparable to a hospital-based survey15 to determine enrollment of 147 patients who started Sitagliptin between February and May 2010. [15] After 2 months of Sitagliptin therapy, author had noticed the onset of joint pain, while pain worsened in diabetic subjects after one month of Sitagliptin and after 20 week in control.

The average diabetic age for patients was 27 ± 6,5 years, with 3 ± 2,7 years in comparison to many international trials involving old and elderly diabetics. In factuhiko Saito [16] patients enrolled between 48 and 78 years of age, and maintained in Sitagliptin and a major recent Pragya Rai [17] study have enrolled patients with 3 diabetes complications with age ranging from 75 to 85 years.

In the 10/68 (14.5 percent) subjects, radiological changes decreased articulation and spur development and no radiological abnormality was observed in control. Following the use of Sitagliptin, 35 /68 (50%) had numerous radiological anomalies, decreased joint space and spur formation being commonest, and the p-value was important 0.04, and control 10 /50 (20%).

In one study Cričky et al.[18] recorded that in two patients and synovitis with metatarsophangeal articulations and proximal interphalangeal jointes, 3 middle-aged patients with Type 2 diabetes, treated with Sitagliptin, developed mainly symmetric polyarthralgia with knees, ankles, and wrists. The average time to experience joint symptoms was 2 months to 1 year. Joint x-rays were regular, non-érosive arthritis. In comparison, 9 patients (6,7 percent) were experiencing periodic erosion.

In the continuation of the above research, DPP4 inhibitors seemed to cause bilateral, non-erosive, sera-related polyarthritis which fits perfectly well in our study 10 (8.7%) control subjects showed moderate radiological changes.

45 (38.1 per cent) of our studies of 118 patients were arthritis-like X-rays,[19] with the results of arthritis and arthralgia in 60 (30%) out of 200 patients with diabetic type 2.

DPP-4-like inhibition promotes RASF invasion and SCID model cartilage demolition. xenotransplant human RASFs were substantially more invasive into co-implanted human cartilage with DPP-4-like inhibition. [20]

Swelling, limited movements and decreased joint space are the clinically regulated loss of cartilage. In our study 28 patients (23.7 percent) were evidenced of reduced joint space.

The use of Sitagliptin was demonstrated by 33 cases of extreme joint symptoms linked to Sitagliptin, the inhibitor of DPP-4, in our study. It was not a separate DPP4 inhibitor.

Of these 118 patients, 68 with 50 control patients were receiving a DPP-4-inhibitor, Sitagliptin. Hemoglobin A1c was significantly reduced by p and odd at 1 with the addition of Sitagliptin (100 mg/day) significantly reduced by 0.6% compared with placebo. Hemoglobin A1c was comparable to a large multicentric trial in Japan. [22]

The P value of CRP was 0.06 and 0.07 in comparison with Tremblay, 23 of our colleagues, and our study showed that the beneficial effect of higher CRP was in type 2 diabetes mellitus after just six weeks of treatment with Sitagliptin.

CONCLUSION

In patients using DPP-4 inhibitors, the incidence of arthropathy was more frequent relative to non-users. Only in recent years has it been investigated to emphasize arthropathy caused by Sitagliptin. Further studies are needed to enhance understanding for type 2 patients who take Sitagliptin of the side effects of autoimmunity.

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