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SUBCLINICAL INFLAMMATION;

ANTI INFLAMMATORY EFFECT OF SITAGLIPTIN IN TYPE 2 DIABETIC DYSLIPIDEMIC PATIENTS.

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ABSTRACT… Objectives: To evaluate the anti-inflammatory effects of sitagliptin in type 2 diabetic hyperlipidemic patients. **Period:** 25 August 2015 to 25 November 2015 (12 weeks). **Study Design:** Randomized clinical trials. **Setting:** Outdoor of diabetic clinic of Sheikh Zayed Medical College/Hospital, Rahim Yar Khan. **Materials and Methods:** Diabetic patients (n=46) with poor glycemic control(HbA1c > 7.2%) and deranged lipid profile were selected. The patient received sitagliptin 50mg twice daily for 12 weeks. **Results:** A total of 46 patients completed the study. After 12 weeks treatment with sitagliptin, there was a significant reduction in the value of HbA1c from 8.26±0.73% at baseline to 7.33±0.62% ($p < 0.01$). Body mass index also decreased significantly from 31.90±1.57 kg/m^2 at baseline to 27.31±1.60 kg/m^2 at 12 weeks ($p<0.01$). There was also significant reduction in the serum level of total Cholesterol (TC), triglycerides (TG) and Low density lipoprotein cholesterol(LDL-C) were detected(TC: 255.35±13.89 to 220.76±14.65 mg/dl, TG: 188.80±11.62 to 153.39±9.24 mg/dl,; LDL-C 169.89±12.06 to 147.11±8.1 mg/dl with p-value <0.01. High density lipoprotein cholesterol (HDL-C) increased significantly from 41.21±3.11 mg/dl at baseline to 50.21±2.37 mg/dl ($p < 0.01$) at 12 weeks. There is also significant reduction in the value of inflammatory markers after 12 weeks treatment with sitagliptin, ESR: 27.04±4.07 vs 11.43±1.74 mm/hr, WBC count: 6.90±0.51 vs 5.65±0.34 10^9/L and hs-CRP: 4.21±0.37 vs 2.16±0.23 mg/L with p-value <0.01. **Conclusion:** Seeing the multiple benefits of sitagliptin on risk factors and markers of inflammation it is concluded that it should be started early in diabetic patients to prevent micro and macro vascular complications in future.

Key words: Sitagliptin, dyslipidemia, C-reactive protein, lipid profile

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INTRODUCTION

About one third deaths in the world are due to cardiovascular diseases in the form of ischemic heart disease and cerebrovascular disease. This global burden of diseases will be more in future in developing countries like Pakistan as compared to developed countries because of the lack of proper awareness about health education and risk factor reduction by government.[1]

Dyslipidemia is a major risk factor for this cardiovascular disease because it contributes significantly in the pathogenesis of atherosclerosis from its initiation as recruitment of circulating leucocytes to the arterial wall to its progression and finally destabilization in the form eventual rupture of atherosclerotic plaque.[2] Dyslipidemia and its related complications in the form of atherosclerosis are more in type 2 diabetics as compared to type 1 diabetic patients. The most important present therapeutic challenge is to prevent the formation as well as complications of atherosclerosis in these patients.[3]

Regarding pathogenesis of atherosclerosis, Inflammation plays a dominant role. Out of the various inflammatory markers, the importance of C-reactive protein (CRP) in determining the different level of inflammation in a variety of cardiovascular disease cannot be denied.[4] CRP is an acute phase protein that initiates a process of inflammation by causing the expression of monocyte chemotactic protein -1 on vessel wall and intercellular adhesion molecule-1 and vascular adhesion molecule-1 on endothelial cells. Moreover, CRP stimulates the monocyte

release of pro-inflammatory cytokines in circulation that also contribute significantly in the pathogenesis of the cardiovascular diseases.[5] CRP is more reliable inflammatory markers than others because of its stability, long half life (19 hours) and uniformity. By measuring CRP level we can check the fitness level of general population, drug monitoring tool and detection of subclinical vascular inflammation in patients of type 2 diabetes. People who adopt good life style in the form of healthy diet, low body mass index, quiet smoking and increase physical activity are usually associated with low CRP level.[6] In addition to CRP, elevated level of white blood cells and ESR counts are also an indicator of inflammation and they provide valuable information regarding coronary risk in patients with and without coronary heart disease.[7]

Sitagliptin, an oral antidiabetic incretin based therapy that produces its beneficial effect in diabetes mellitus by increasing insulin secretion, suppress glucagon release, delay gastric emptying and increase satiety[8]. Sitagliptin is a well-tolerated profile in most diabetic patients with consistent glycemic control and no major adverse effect such as hypoglycemia and weight gain.[9] In addition to maintain blood glucose level sitagliptin has additional properties in various clinical studies in T2DM such as reduction in blood pressure[10], postprandial lipemia[11], oxidative stress[12], endothelial dysfunction[13] and possibly platelet aggregation[14] and myocardium protection.[15]

But, apart from their beneficial effects on glucose and lipid metabolism, sitagliptin have also anti-inflammatory properties. Sitagliptin reduce various inflammatory markers such as CRP, pro inflammatory mediators such as interleukin (IL)-1, interleukin (IL)-6, tumor necrosis factor –α and also reducing the expression of pro inflammatory mediators on mononuclear cells affecting inflammatory signaling in clinical as well as in animal studies.[16] Sitagliptin also decreases the expression of intercellular adhesion molecule and vascular adhesion molecule 1 by various anti-inflammatory mechanisms[17]

The main focus of this study was to determine the anti-inflammatory effect of sitagliptin in the form of CRP, total white cell count and ESR. In addition lipid profiles, HbA1C and body weight were also investigated

MATERIALS AND METHODS

This randomized controlled trial was approved by ethical committee and was conducted at diabetic clinic of Sheikh Zayed Medical College/ Hospital, Rahim Yar Khan, from 25 August 2015 to 25 November 2015. A written informed consent was obtained from the participants before they were enrolled in the study. A total of 150 patients were screened out of which 46 newly diagnosed diabetic patients; aged 29-56 years of both sexes were enrolled in the study after fulfilling the inclusion and exclusion criteria. The inclusion criteria were that all patients demonstrated poor glycemic control with HbA1c≥ 7.2% and deranged lipid profile i.e. cholesterol ≥ 200mg/dl, serum triglycerides≥ 150mg/dl, LDL-Cholesterol ≥ 160mg/dl and HDL-cholesterol ≤ 45mg/dl in spite of acquiring diet and exercise schedule. The patients were not taking any medicine for diabetes, dyslipidemia and for inflammation.

The exclusion criteria were treatment with insulin, a history of severe diabetic ketoacidosis or coma, severe trauma, pregnancy, lactation, renal impairment, hypothyroidism, liver dysfunction. The drugs which effect glucose, lipids and inflammations such as oral anti diabetics, anti hyperlipidemics, non-steroidal anti-inflammatory (NSAIDS), corticosteroids, immunosuppressives, 2nd generation antipsychotic, beta blockers, thiazide diuretic, antiretroviral and tamoxifen. In addition all those conditions which effect inflammation like acute and chronic bacterial infection, connective tissue disease, arthritis, angina, myocardial infarction, transient ischemic attack, stroke, smoking and alcohol use.

After randomization 46 patients adjusted on sitagliptin at a dose of 50mg twice daily for 12 weeks according to their blood sugar level. Body weight, body mass index were measured before and after the end of study. Fasting blood samples

were drawn from the antecubital vein before and at the end of the study. The samples were used for analyzing HbA1c, Lipid profile {Serum total Cholesterol (TC), HDL- cholesterol (HDL-C), serum triglycerides (TG) and LDL- cholesterol (LDL-C)}, C-reactive protein, ESR and total leukocyte count. HbA1c was measured by high performance liquid chromatography. Lipid profile was done by enzymatic end point method using commercially available kits on spectrophotometer. ESR was measured by westerngren method while total leukocyte count was analyzed by automated hematology analyzer Sysmex KX-21. CRP level was detected by spectro photometry method.

Data Analysis

Statistical package for social sciences SPSS 16 was used for the analysis of data. Values of numeric data were presented as mean ± standard deviation**.** The comparison among the value of HbA1c, body weight, blood pressure, lipid profile, ESR, TLC count and hs CRP was done by paired t-test. Values of $p < 0.01$ were deemed to be statistically significant

RESULTS

Table-I shows the baseline demographics characteristics before treatment with sitagliptin. After 12 weeks of sitagliptin therapy, HbA1c reduced significantly from 8.2% to 7.3% with p value < 0.01, body weight decreased significantly from 91.7 ± 4.8 kg to 82.7 ± 5.2 kg ($p < 0.01$), Notable reduction in BMI from 31.9 ±1.5 kg/m^2 at baseline to 27.3±1.6 kg/m^2 ($p < 0.01$). There is also remarkable reduction in the value of TC, TG and LDL-C was detected (TC: 255±13 to 220±14mg/dl, TG: 188±11 to 153±9 mg/dl; LDL-C 169±12 to 147±8 mg/dl with ($p < 0.01$), HDL-C increased significantly from 41±3 mg/dl at baseline to 50±2 mg/dl at 12 weeks($p < 0.01$). There is remarkable reduction in inflammatory markers after treatment with sitagliptin (ESR: 27±4 to 11±1.7 mm/hr TLC: 6.9±0.5 to 5.6±0.3 10^9/L and CRP: 4.2±0.3 to 2.1±0.2mg/L with p value < 0.01 .These results are shown in Table-II and Figure-1.

Enrolled subjects(n)	46
Age	29-56 years
Gender	Male:63%(n=29) Female:36%(n=17)
Diabetes duration	2.2 years
Systolic Blood pressure(mm hg)	125±8.12
Diastolic Blood pressure(mm hg)	78±5.5
BMI (Body Mass index kg/m^2)	31.90±1.57

Table-I. Baseline Demographics

Parameters	Pre Treatment	Post treatment	Mean difference	p-value
HbA1c	8.26±0.73	7.33±0.62	.928	<.001
Body weight(kg)	91.75±4.83	82.76±5.21	8.99	
BMI((Body Mass index)	31.90±1.57	27.31±1.60	4.58	
TC (mg/dl)	255.35±13.89	220.76±14.65	34.58	
TG(mg/dl)	188.80±11.62	153.39±9.24	35.41	
LDL-C(mg/dl	169.89±12.06	147.11±8.17	22.78	
HDL-C(mg/dl)	41.21±3.11	50.21±2.37	-9.0	
ESR(mm/hr)	27.04±4.07	11.43±1.74	15.60	
TLC Count(10^9/L)	6.90±0.51	5.65±0.34	1.25	
hs-CRP(mg/L)	4.21±0.37	2.16±0.23	2.04	

Table-II. Clinical & Biochemical parameters of patients

HbA1c, hemoglobin A1C; TC, total cholesterol.TG; triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; ESR, erythrocyte sedimentation rate; TLC, Total leukocyte counts, CRP; High sensitivity C - reactive protein

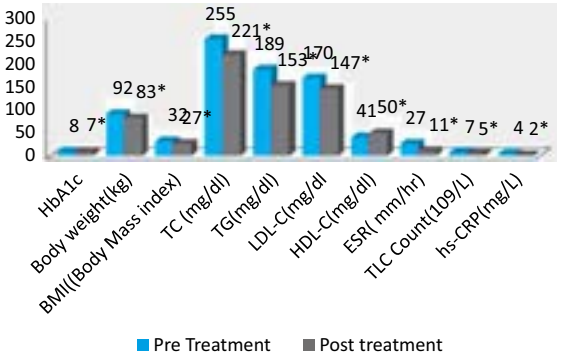


Figure-1. Clinical & Biochemical parameters of patients
HbA1c, hemoglobin A1C; TC, total cholesterol.TG; triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; ESR, erythrocyte sedimentation rate; TLC, Total leukocyte counts, CRP; High sensitivity C - reactive protein*P < 0.01,vs baseline , Paired t-test

DISCUSSION

The main aim of this study was to determine the markers and risk factors for chronic subclinical inflammation in type 2 diabetic patients who have dyslipidemia. This subclinical inflammation is a silent inflammation which cannot manifests itself clinically for a long period of time but it causes significant contribution in the pathogenesis as well as complication of atherosclerosis in future in type 2 diabetic patients.[18]

In our study three risk factors for inflammation that initiate a process atherosclerosis in diabetic patients such as HbA1c, body weight and lipid profile was significantly reduced after 12 weeks treatment with Sitagliptin at a dose of 50mg twice daily. This contribution is significant because all these risk factor initiates a process of atherosclerosis in a different way like hyperglycemia initiates it in the form of advanced glycation end products (AGEs)[19], increase body weight starts it as oxidative stress by generation of reactive oxygen species[20] and dyslipidemia promotes it in the form of oxidized LDL production.[21] Moreover these risk factors increase the level of inflammatory markers in diabetic patients.

In this study sitagliptin causes a reduction in three inflammatory markers such as CRP, Total leukocyte count and ESR. Elevated level of CRP is marker as well as predictor of risk of coronary heart disease. In addition routine blood test which are easily available and interpret easily such as high level of white blood cells and erythrocyte sedimentation rate ESR are also markers of inflammation that are associated with the presence of coronary heart disease, peripheral artery disease and stroke[7]. A study conducted by tong et al[22] in which elevated white blood cells are associated with micro and macro vascular complication of diabetes.

Regarding inflammation C-reactive protein is more important than all other risk factors and markers. Although elevated level of lipid profiles are risk factors for development of cardiovascular disease but they are not good predictor of cardiovascular disease because some studies showed that most of the patient who were presented in emergency with acute heart attack and sudden cardiac death had normal lipid profile and those patients who were taking antihyperlipdemic drugs and their lipid profile were below the standard guidelines also developed cardiovascular disease.[23,24] Similar study in which patients presented in emergency with ST segment and non ST segment elevation acute myocardial infarction had normal serum cholesterol, triglycerides and LDL-Cholesterol but they had increase serum level of C-reactive protein which shows its role in atherosclerosis.[25] In another study which was conducted by Ridker et al[26] concluded that CRP is an important indicator of upcoming cardiovascular events than LDL-cholesterol level and it provides valuable information to Framingham risk score.

The importance of Sitagliptin on reducing C-reactive protein is also investigated in micro vascular complications of type 2 diabetic patients in which inflammatory process causes peripheral neuropathies and micro albuminuria. Sitagliptin improves both conditions by the reduction of C - reactive protein.[27-28]

Regarding inflammation statins are the drug of choice because in addition to improve dyslipidemia statins also exert anti-inflammatory

effect by the reduction of various inflammatory markers especially CRP.[29,30] But some patients cannot tolerate statins due to their adverse effects and contraindications.[31] Seeing the multiple benefits, sitagliptin should be started in diabetic patients because reduction of C - reactive protein by sitagliptin was comparable with statins in various studies.[29,30]

So in addition to lipid profile, C-reactive protein should also be added as routine test in diabetic patients in order to identify asymptomatic patients who have normal lipid profile but having high risk for future cardiovascular disease because it is not only an inflammatory markers but also a direct cause of cardiovascular disease.[32]

CONCLUSION

Seeing the multiple benefits of sitagliptin on risk factors and markers of inflammation it is concluded that it should be started early in diabetic patients to prevent micro and macro vascular complications in future.

REFERENCES

1. Deaton C, Froelicher ES, Wu LA, Ho C, Shishani K, Jaarsma T. **The global burden of cardiovascular disease.** Eur J Cardiovasc Nurs 2011; 10(2):5-13.
2. Drechsler M, Megens RT, Zandvoort MV, Weber C, Soehnlein O. **Dyslipidemia- triggered neutrophilia promotes early atherosclerosis.** Circulation 2010; 122:1837-1845.
3. Dunn FL. **Management of dyslipidemia in people with type 2 diabetes mellitus.** Rev Endocr Mctab Disord 2010; 11: 41-51.
4. Backes JM, Howard PA, Moriarty PM. **Role of C-reactive protein in cardiovascular disease.** Ann Pharmacother 2004; 38:110-8.
5. Pasceri V, Chang J, Willerson JT, Yeh ET. **Modulation of c-reactive protein- mediated monocyte chemo attractant protein-1 induction in human endothelial cells by anti-atherosclerosis drugs.** Circulation 2001; 103:2531-2534.
6. Kao P, Shiesh SC, Wu TJ. **Serum C-reactive protein as a marker of well assessment: a review.** Ann Clin Lab sci 2006; 36(2):163-169.
7. Madjid M, Fatemi O. **Components of the complete blood count as risk predictor for coronary heart disease: a review.** Tex Heart I J 2013; 40(1):17-29.
8. Tahrani AA, Bailey C, Prato SD, Barnett AH. **Management of type 2 diabetes: new and future developments in treatment.** Lancet 2011; 378:182-97.
9. Tanaka T, Nangaku M, Nishiyama A. **The role of incretin in salt- sensitive hypertension: the potential use of dipeptidyl peptidase -1v inhibitors.** Curr Opin Nephrol Hypertens 2011; 20(5):476-481.
10. Brown NJ. **Cardiovascular effects of antidiabetic agent: focus on blood pressure effects of incretin based therapies.** J Am Soc Hypertens 2012; 48(5):592-598.
11. Farr S, Adeli K. **Incretin based therapies for treatment of postprandial dyslipidemia in insulin resistant states.** Curr Opin Lipidol 2012; 23(1):56-61.
12. Rizzo MR, Barbieri M, Marfella R, Paolisso G. **Reduction of oxidative stress and inflammation by blunting daily acute glucose fluctuations in patients with type 2 diabetes: role of dipeptidyl peptidase – 1v inhibition.** Diabetes Care 2012; 35(10):2076-2082.
13. Van PC, Netea MG, Smits P, Tack CJ. **Vidagliptin improves endothelium dependent vasodilatation in type 2 diabetes.** Diabetes Care 2011; 34(9): 2072-2077.
14. Gupta AK, Verma AK, Kailashiya J, Singh SK, Kumar N. **Sitagliptin: Anti-platelet effect in diabetes and healthy volunteers Platelets** 2012; 23(8):565-570.
15. Scheen AJ. **Cardiovascular effect of gliptins.** Nat Rev Cardiol 2013; 10(2):73-84.
16. Makdissi A, Ghanim H, Vora M, Green K, Abuaysheh S, Chaudhuri A. **Sitagliptin exerts an anti-inflammatory action.** J Clin Endocrinol Metab 2012; 97:3333-3341.
17. Matsubara J, Sugiyama S, Akiyama E, Iwashita S, Kurokawa H, Ohba K. **Dipeptidyl peptidase-4 inhibitor sitagliptin improves endothelial dysfunction in association with its anti-inflammatory effect in patients with coronary artery disease and uncontrolled diabetes.** Circ J 2013; 77:1337-1344.
18. Ndip A,Jude EB, Boulton AJ. **Inflammation in type 2 diabetes.** Frontiers in inflammation 2016; 1:164-179.
19. Meerwaldt R, Links T, Zeebregts C, Tio R, Hillebrands JL, Smit A. **The clinical relevance of advanced glycation end products accumulations in diabetes: a review.** Cardiovasc Diabetol 2008; 7:29.
20. Piva SJ, Tatsch E, Carvalho JA, Bochi GV, Kober H,

Duarte T. **Assesment of inflammatory and oxidative biomarkers in obesity and their association with body mass index.** Inflammmtion 2013; 36(1):226 -231.

21. Linna M, Ahotupa M, Lopponen MK, Irjala K,Vasankari T. **Circulating oxidized LDL lipids when proportional to HDL-c emerging as a risk factor of all cause mortality in a population based survival study.** Age Aging 2013; 110:113.

22. Tong PC, Chan WB, Lee KF, Lo MK, So WY, Chan NN. **White blood cells count is associated with macro and micro vascular inflammation complications in Chinese patients with type 2 diabetes.** Diabetes Care 2004; 27:216-222.

23. Domma AM, Gamal MA. **Association between acute myocardial infaraction, lipid profile and smoking habbits.** IOSR-JDMS 2015; 14:6:47-51.

24. Packard RR, Libby P. **Inflammation in atherosclerosis: from vascular biology to biomarkers discovery and risk prediction.** Clin Chem 2008; 54:24-38.

25. Khan HA, Alhomida AS, Sobki SH. **Lipid profile of patients with acute myocardial infaraction and its correlation with systemic inflammation.** Biomark Insights 2013; 8:1-7.

26. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. **Comparison of c-reactive protein and low denisity lipoprotein cholesterol levels in the prediction of first cardiovascular events.** N Engl J Med 2002; 347:1557-65.

27. Esmael A, Hegazy M, Elrabat A. **Can glycosylated hemoglobin and C - reactive a protein level predicts development of subclinical nephropathy in pre-diabetics?** Int Neuropsychiatr Dis J 2016; 6:2:1-8.

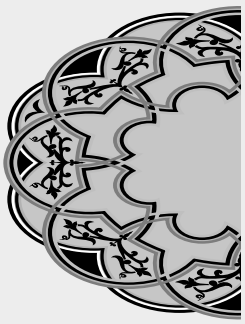
28. Hattori S. **Sitagliptin reduces albuminuria in patients with type 2 diabetes.** Endocr J 2011; 58:1:69-73.

29. Ansell BJ, Watson KE, Weiss RE, Fonarow GC. **Hs-CRP and HDL effects of statins trials (chest) rapid effect of statin therapy on c- reactive protein and high density lipoprotein level.** Heart dis 2003; 5(1):2-7.

30. Wu YW, Kao HL, Huang CL, Chen MF, Lin LY, Wang YC. **The effects of 3 months atorvastatin therapy on arterial inflammation, calcification, adipose tissue and circulating biomarkers.** Eur. J. Nucl. Med. Mol. Imaging 2012; 39:399-407.

31. Kiortsis DN, Filippatos TD, Mikhailidis DP, Elisaf MS, Liberopoulos EN. **Statin associated adverse effect beyond muscle and liver toxicity.** Atherosclerosis 2007; 195(1):7-16.

32. Li JJ, Fang CH. **C-reactive protein is not only an inflammatory marker but also a direct cause of cardiovascular diseases.** Med Hypotheses 2004; 62:499-506.



"Remember, the greatest failure is not to try."

Unknown

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
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2	Dr. Muhammad Bilal Ghafoor	Lab data collection and analysis	
3	Dr. M. Shahbaz Hussain	Lab data collection and analysis and drafting of paper	
4	Dr. Lubna Akhtar	Study design and formatting	