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EFFECT OF SITAGLIPTIN ON LIPID PROFILE OF TYPE 2 DIABETES MELLITUS PATIENTS

Biochemistry

Dr. Priyanka Malik Senior Resident, Department of Biochemistry, Rajindra Hospital, G.M.C. Patiala.

Dr. Yogesh Garg* Junior Resident, Department of Radiodiagnosis, Rajindra hospital, G.M.C. Patiala. *Corresponding Author

Dr.Navpreet Kaur Junior Resident, Department of Biochemistry, Rajindra Hospital, G.M.C. Patiala

ABSTRACT

Background: Sitagliptin is a dipeptidyl-peptidase inhibitor (DPP-4 inhibitor) Like other DPP-4 inhibitors its action is mediated by increasing levels of the incretin hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). The study was aimed to evaluate the effect of sitaglipt in on lipid profile in patients with type-2 Diabetes Mellitus at 0 level and after 16 weeks of treatment with sitagliptin.

Material and Methods: A prospective study comprising 70 diagnosed cases of type 2 diabetes mellitus was carried out. These patients were put on sitaglipt in 100 mg OD for 16 weeks and venous blood samples were taken at 0 level and after 16 weeks.

Results The decrease in mean serum cholesterol levels at 0 week and 16 weeks was 17.84mg/dl (6.64%) . The change in mean serum triglycerides level was 42.30mg/ dl (18.75%). On Statistical analysis, the reduction in serum cholesterol levels and in serum triglycerides levels in total number of patients was highly significant ($p<0.001$). The mean increase in serum high density lipoprotein cholesterol (HDL-C) level was 0.08 mg/dl and mean% increase in HDL-C level was 0.25% at 4 months from baseline. On statistical analysis the increase in mean serum HDL-C level in study group was non-significant (p 0.223).

Conclusions: The study concludes that Sitagliptin represents a substantial advance in antidiabetic therapy and it helps in improving the lipid profile of type 2 diabetes patients.

KEYWORDS

Dipeptidyl-peptidase inhibitor (DPP-4 inhibitor), Diabetic Profile,,Lipid Profile, Sitagliptin, Type 2 Diabetes Mellitus

INTRODUCTION

Diabetes mellitus is a well-known risk factor for cardiovascular disease. Dyslipidemia is an essential determinant of cardiovascular risk in type 2 diabetes.[1] Patients with type 2 diabetes are more likely to be dyslipidemic than the general population.[2] Dyslipidemia is characterized by hypertriglyceridemia and diminishment of High Density Lipoprotein-Cholesterol (HDL-C). In severe forms of insulin resistance, Low Density Lipoprotein-Cholesterol (LDL-C) may also be elevated.[3] The coexistence of diabetes and lipid abnormalities can further increase the risk of cardiovascular disease. Antihyperglycemic agents had positive effects on the dyslipidemia and may contribute to reduce the excessive risks of cardiovascular events in a person with diabetes.

T2DM is of multifactorial origin. The pathogenesis is complex and results from disturbance in insulin secretion, hepatic glucose production, and insulin resistance. Insulin is released from β-cells of the pancreas in a glucose-dependent manner via the action of incretins (GLP-1, gastric inhibitory peptide) secreted in response to oral carbohydrate. The prevalence of type-2 DM is rapidly increasing all over the world. The prevalence of diabetes for all age groups worldwide was estimated to be 2.8% in year 2000 and 4.4% in year 2030[4]

Sitagliptin is the first dipeptidylpeptidase-4 inhibitor to be used in the management of type 2 diabetes. It has been found to be beneficial in improving β-cell function and glycemic control.[5]

ROLE OF SITAGLIPTIN (A DPP-IV INHIBITOR) IN T2DM

In T2DM patients, the effect of the glucose-dependent insulinotropic polypeptide (GIP), as well as the secretion of the glucagon-like peptide-1 (GLP-1), is diminished or absent, contributing to insulin secretion deficiency.[6] These two incretins are secreted by the intestine[7] and stimulate insulin secretion by beta-cells, in a glucose-dependent manner[8], preventing hypoglycemia. Despite the beneficial actions of GLP-1 and GIP, their use as antidiabetic agents (mimetics) is impractical due to their short half-lives, as a result of their rapid inactivation by dipeptidyl peptidase-IV (DPP-IV).[9,10] Thus, orally administered DPP-IV inhibitors have emerged as a new class of anti-hyperglycaemic agents with the ability for extending the biological effects of incretin hormones through the inhibition of their degradation[11,12] with the advantage of higher stability and bioavailability when compared with the mimetics. Sitagliptin is a dipeptidyl-peptidase inhibitor (DPP-4 inhibitor) that has recently been approved for the therapy of type 2 diabetes. Like other DPP-4 inhibitors its action is mediated by increasing levels of the incretin hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). Sitagliptin is effective in lowering HbA1c and fasting as well as postprandial glucose in monotherapy and in combination with other oral antidiabetic agents. It stimulates insulin secretion when hyperglycemia is present and inhibits glucagon secretion.[13]

Mechanism of Action :-

Post–meal ingestion, GLP-1 and GIP are released from the small intestine and are rapidly degraded by the enzyme DPP-4. Inhibition of DPP-4 prevents the breakdown of GLP-1 and GIP and enhances glucose-stimulated insulin secretion (incretin action). GLP-1 and GIP act on the pancreatic β-cell to increase insulin release. GLP-1 also acts on the α-cell to suppress glucagon release and ultimately suppress hepatic glucose production. Together, the increased cellular glucose uptake and the decreased hepatic glucose output offer physiologic glucose control.[14]. Therefore, not only insulin secretion and insulin resistance are altered, as by the previously used oral antihyperglycemic agents, but also unmet needs of type 2 diabetes therapy are covered by this novel therapeutic principle.[15] Sitagliptin could also have the potential to be useful in pre-diabetic stages and early stages of type 2 diabetes to retard or prevent the disease progression.[16]

MATERIAL AND METHODS

The present study was conducted on 70 diagnosed cases of type-2 DM in a tertiary health care centre in North India referred by department of internal medicine to the department of Biochemistry. These patients were put on sitagliptin 100 mg OD for 16 weeks.

Inclusion criteria:-

1) Patients clinically confirmed as type-2 DM.
2) HbA1C $\geq$ 7%.
3) Age >18.
4) Type-2 diabetes patients not on sitagliptin.
5) Type-2 diabetes patients on sulfonylurea group and metformin which were poorly controlled with these drugs.

Exclusion criteria:-

1) Patients with diabetic ketoacidosis coma.
2) Patients with renal diseases.
3) Patients with history of pancreatitis.
4) Chronic hepatitis B or C, liver disease.
5) Patients with contraindication to sitagliptin.

A written consent was taken from all selected patients and approval of Institutional Ethics Committee was procured. A detailed history of each patient was also taken .

Detailed lipid profile levels were estimated in all patients. It included serum cholesterol, triglycerides, VLDL, HDL-C and LDL-C.

Blood samples were collected under all aseptic conditions. Statistical analysis was performed using t -test and results were analysed accordingly

Determination of Total serum cholesterol
Normal Range: 150-250 mg/dl
It was analyzed by in vitro enzymatic colorimetric method described by Allain et al[17] (1974).

Determination of Triglycerides
Normal Range: 30-180 mg/dl
It was analyzed by in vitro enzymatic colorimetric method described by McGowan et al[18] (1983).

Standard HDL-Cholesterol
Normal Range: 35-80 mg/dl
Phosphotungstate and magnesium chloride method [19]

Determination of LDL-Cholesterol
Normal Range 114-153mg/dl
LDL–Cholesterol was determined by the formula devised by Friedewald et al (1972)[20]

Formula
LDL–Cholesterol= Total Cholesterol - (Triglycerides/5+HDLCholesterol)

Determination of VLDL-Cholesterol
Normal Range 20-40mg/dl
Formula:
VLDL–Cholesterol= Triglycerides/5

RESULTS

Table – 1 Comparison Of Mean Serum Cholesterol In Total Number Of Patients At Baseline And After 4 Months Of Sitagliptin Therapy

Time Interval (month)	Range (mg/dl)	Mean±SD (mg/dl)	Mean fall (mg/dl)	Mean % fall	T	p	S
0	118-356	260.07±46.27	17.84	6.64	13.09	<0.001	HS
4	158-330	242.24±41.34					

The Serum Cholesterol ranged between 118-356 mg/dl at the start of study and 158-330mg/dl after 4 months. The mean serum cholesterol levels changed from 260.07±46.27mg/dl to 242.24±41.34mg/dl. The mean fall in serum cholesterol levels was 17.84 mg/dl and means% fall in serum cholesterol level was 6.64% at 4 months from baseline.

On Statistical analysis the reduction in mean serum cholesterol levels in study group was highly significant (p<0.001).

Table – 2 Comparison Of Mean Serum Triglyceride Level (tgs) In Total Number Of Patients At Baseline And After 4 Months Of Sitagliptin Therapy

Time Interval (month)	Range (mg/dl)	Mean±SD (mg/dl)	Mean fall (mg/dl)	Mean% fall	t	p	S
0	69-470	203.50±75.66	42.30	18.75	8.11	<0.001	HS
4	58-288	161.20±56.25					

The serum triglycerides level ranged between 69-470 mg/dl at the start of study and 58-288 mg/dl after 4 months. The mean serum triglycerides levels changed from 203.50±75.66 mg/dl to 161.20±56.25 mg/dl at 4 months. The mean fall in serum triglycerides level was 42.30 mg/dl and mean% fall in serum triglycerides level was 18.75% at 4 months from baseline. On Statistical analysis the reduction in mean serum triglycerides level in study group was highly significant (p<0.001).

Table – 3 Comparison Of Mean Serum High Density Lipoprotein Cholesterol (hdl-c) In Total Number Of Patients At Baseline And After 4 Months Of Sitagliptin Therapy

Time Interval (month)	Range (mg/dl)	Mean ± SD (mg/dl)	Mean increase (mg/dl)	Mean% increase	T	p	S
0	30-68	47.47±8.25	0.08	0.25	1.23	0.223	NS
4	33-68	47.55±8.09					

The mean serum high density lipoprotein cholesterol (HDL-C) levels ranged between 30-68 mg/dl at the start of study and 33-68 mg/dl after 4 months. The mean serum high density lipoprotein cholesterol levels changed from 47.47±8.25 mg/dl to 47.55±8.09mg/dl at months. The mean increase in serum high density lipoprotein cholesterol (HDL-C) level was 0.08 mg/dl and mean% increase in HDL-C level was 0.25% at 4 months from baseline. On statistical analysis the increase in mean serum HDL-C level in study group was non-significant (p 0.223).

Table – 4 Comparison Of Mean Serum Low Denisty Lipoprotein Cholesterol (LDL-C) In Total Number Of Patients At Baseline And After 4 Months Of Sitagliptin Therapy

Time Interval (month)	Range (mg/dl)	Mean±SD (mg/dl)	Mean fall (mg/dl)	Mean% fall	t	p	S
0	54-269	172.11±41.01	9.30	5.30	9.47	<0.001	HS
4	54-265	162.81±39.47					

The mean serum low density lipoprotein-cholesterol (LDL-C) level ranged between 54-269 mg/dl at the start of study and 54–265 mg/dl after 4 months. The mean serum LDL-C level changed from starting level of 172.11±41.01 mg/dl to 162.81±39.47 mg/dl at 4 months. The mean reduction in mean serum LDL-C level was 9.30 mg/dl and means% fall in mean LDL-C level was 5.30% at 4 months from baseline.

On Statistical analysis, the reduction in mean serum low density lipoprotein-cholesterol (LDL-C) level was highly significant (p<0.001).

Table – 5 Comparison Of Mean Serum Very Low Denisty Lipoprotein (VLDL) In Total Number Patients At Baseline And After 4 Months Of Sitagliptin Therapy

Time Interval (month)	Range (mg/dl)	Mean±SD (mg/dl)	Mean fall (mg/dl)	Mean% fall	t	p	S
0	14-94	40.65±15.04	8.42	18.77	8.14	<0.001	HS
4	12-58	32.23±11.25					

The mean serum very low density lipoprotein-cholesterol (VLDL-C) Levels ranged between 14-94 mg/dl at the start of study and 12-58mg/dl after 4 months. The mean serum (VLDL-C) Levels changed from starting level of 40.65±15.04 mg/dl to 32.23±11.25 mg/dl at 4 months. The mean falls in serum VLDL Levels was 8.42 mg/dl and means% fall in VLDL Levels was 18.77% at 4 months from baseline. On Statistical analysis the reduction in mean serum VLDL levels was highly significant (p<0.001).

DISCUSSION

DYSLIPIDEMIA IN DIABETES

Insulin resistance and Hyperinsulinaemia are associated with an atherogenic plasma lipid profile. Hyperinsulinemia enhances the biogenesis of SREBP-1c, which in liver increases the synthesis of fatty acids and the production of VLDL particles.[21] .Sitagliptin decreases serum Cholesterol and serum Triglycerides by increasing insulin sensitivity in sitagliptin monotherapy as well as adjuvant therapy.

Elevated plasma insulin concentrations enhance very low-density lipoprotein-cholesterol (VLDL-C) synthesis, leading to Hypertriglyceridemia. Progressive elimination of lipids and apolipoprotein from the very low-density lipoprotein-cholesterol (VLDL-C) particle leads to an increased formation of intermediate-density and low density lipoprotein-cholesterol, both of which are atherogenic. Insulin enhances cholesterol transport into arteriolar smooth muscle cells and increases endogenous lipid synthesis by these cells.[22] . Hypertriglyceridemia is due to an increase in the rate of synthesis of very low-density lipoprotein-cholesterol (VLDL-C) in the liver and a reduction in their breakdown by the lipoprotein lipase in non-hepatic tissue.[23] Cholesterol synthesis is up-regulated and

absorption is down-regulated in insulin resistance and in type 2 diabetes.[24]

CONCLUSION

Diabetes mellitus describes a metabolic disorder of multiple aetiology, characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. The present study was conducted with an aim to evaluate the effect of sitagliptin (100mg) , a dipeptidyl peptidase inhibitor on lipid profile in type 2 diabetic patients at baseline and after 16 weeks of commencement of sitagliptin therapy. This study revealed that sitagliptin(a DPP-IV inhibitor) significantly improved serum Cholesterol, Triglycerides, LDL and VLDL levels in patients with type 2 diabetes mellitus. The beneficial effect of sitagliptin on serum lipid parameters could be partly explained by an improvement in glycemic control and insulin resistance. GLP-1 inhibits small intestinal lipoprotein synthesis and secretion, and reduces the accumulation of fat in the liver by inhibiting enzymes involved in lipid synthesis. So, Sitagliptin represents a substantial advance in antidiabetic therapy, combining several advantages over other insulin secretagogues.

REFERENCES

1. Gaede P, Lund-Andersen H, Parving HH, et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580–591. [PubMed] [Google Scholar]
2. Tan CE, Chew LS, Chio LF, et al. Cardiovascular risk factors and LDL subfraction profile in Type 2 diabetes mellitus subjects with good glycaemic control. Diabetes Res Clin Pract 2001; 51:107–114. [PubMed] [Google Scholar]
3. Chehade JM, Gladysz M, Mooradian AD. Dyslipidemia in type 2 diabetes: prevalence, pathophysiology, and management. Drugs 2013; 73:327–339.
4. The IDF Diabetes Atlas 5th Edition. Available at : http: //www. idf. org/ sites/ default/files/The%20IDF%20Diabetes%20Atlas%205th_Ed.ppt
5. Brunner Y, Schvartz D, Priego-Capote F, Couté Y, Sanchez JC. Glucotoxicity and pancreatic proteomics.c J Proteomics. 2009;71(6):576-91.
6. Nauck MA, Baller B, Meier JJ. Gastric inhibitory polypeptide and glucagon-like peptide-1 in the pathogenesis of type 2 diabetes. Diabetes. 2004;53 Suppl 3:S190-6.
7. Drucker DJ. The biology of incretin hormones. Cell Metab. 2006;3(3):153-65.
8. McIntosh CHS. Incretin-based therapies for type 2 diabetes. Canadian Journal of Diabetes 2008; 32(2):131-139.
9. Deacon CF. Incretin-based treatment of type 2 diabetes: glucagon like peptide-1 receptor agonists and dipeptidyl peptidase inhibitors. Diabetes Obes Metab. 2007;9 (Suppl 1):23-31.
10. Drucker DJ and Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006;368(9548):1696-705.
11. Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, Holst JJ. Both subcutaneously and intravenously administered glucagon-like peptide I are rapidly degraded from the NH2-terminus in type II diabetic patients and in healthy subjects. Diabetes. 1995;44(9):1126-31.
12. Ahrén B, Landin-Olsson M, Jansson PA, Svensson M, Holmes D, Schweizer A. Inhibition of dipeptidyl peptidase-4 reduces glycemia, sustains insulin levels, and reduces glucagon levels in type 2 diabetes. J Clin Endocrinol Metab 2004;89(5):2078-84.
13. Deacon CF and Holst JJ. Dipeptidyl peptidase IV inhibition as an approach to the treatment and prevention of type 2 diabetes: a historical perspective. Biochem Biophys Res Commun 2002;294(1): 1-4.
14. Cobble M. DPP-4 Inhibitors: A New Therapeutic Class for the Treatment of Type 2 Diabetes. The Journal of Family Practice 2009;58(10).
15. Ahrén B. What mediates the benefits associated with dipeptidyl peptidase-IV inhibition? Diabetologia. 2005;48(4):605-7
16. Gallwitz B. Therapies for the treatment of type 2 diabetes mellitus based on incretin action. Minerva Endocrinol. 2006;31(2):133-47.
17. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem 1974;20(4):470-5.
18. McGowan MW, Artiss JD, Strandbergh DR, Zak B. A peroxidase-coupled method for the colorimetric determination of serum triglycerides. Clin Chem 1983;29(3):538-42.
19. Burstein M, Schalnick H R, Morfin R. Rapid Method for the isolation of Lipoproteins from human serum by precipitation with polyanions. J Lipid Res 1970;11(6):583-95.
20. Friedewald WT, Levy RJ, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 1972;18(6):499-502
21. Horton JD, Goldstein JL, Brown MS. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. J Clin Invest 2002;109:1125-31.
22. DeFronzo RA and Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991;14(3):173-94.
23. Krone W, Müller-Wieland D, Wirth H. Dyslipoproteinemia and metabolic syndrome. Effects of insulin resistance and hyperinsulinemia on lipid metabolism. Fortschr Med 1992;110(34): 645-48.
24. Gylling H, Hallikainen M, Pihlajamäki J, Simonen P, Kuusisto J, Laakso M et al. Insulin sensitivity regulates cholesterol metabolism to a greater extent than obesity: lessons from the METSIM Study. J Lipid Res 2010;51(8):2422-7.