ORIGINAL RESEARCH PAPER

Pharmacology

KEY WORDS: Dyslipidemia, Sitagliptin, Streptozotocin

EVALUATION OF EFFECT 0F SITAGLIPTIN AND COMBINATION THERAPY OF SITAGLIPTIN AND METFORMIN ON HIGH DENSITY LIPOPROTEIN(HDL) AND LOW DENSITY LIPOPROTEIN(LDL) IN DIABETIC RATS

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ABSTRACT

Diabetes mellitus is a multi system disorder leading to multiple complications. Dyslipedemia plays central role in most of the complications. HDL, LDL levels are amongst the parameters which are used to asses dyslipidemia .This study aims to evaluate the effect of sitagliptin and combination of sitagliptin and metformin on HDL, LDL levels in diabetes induced Albino Wistar rats.

Albino Wistar rats were divided into 4 groups . Diabetes was induced by high fat diet and low dose streptozotocin . Metformin was used as standard drug. Rats were administered sitagliptin and combination of both metformin and sitagliptin for 21 days. After treatment LDL and HDL levels were evaluated.

It was found that in groups treated with metformin, sitagliptin and combination of both drugs there was significant increase in HDL and reduction in LDL levels.

INTRODUCTION:

The total number of people having diabetes in India saw an increase from 26 million in 1990 to 65 million in 2016. This increase in diabetes since 1990 in India is the highest among major non-communicable diseases[1]. Hence diabetes is considered as a major pandemic needing immediate attention. Individuals with diabetes are at higher risk of developing complications- macrovascular or microvascular. Microvascular complications of diabetes mellitus include autonomic neuropathy, peripheral neuropathy, retinopathy, nephropathy and macrovascular complications includes coronary and peripheral arterial disease[2]. Dyslipidemia plays a pivotal role in development of these complications. Epidemiological studies have shown that increased LDL-C and non-HDL-C levels and decreased HDL-C levels are associated with an increased risk of cardiovascular complicatuions in diabetics[3].

Hence management of diabetes should address dyslipidemia along with hyperglycemia. Metformin plays the anchor role in the management of diabetetes. Sitagliptin is an inhibitor of the enzyme dipeptidylpeptidase-4, an enzyme responsible, among other roles, degradation of the incretin hormone glucagon-like peptide-1 , which plays a role in regulating insulin secretion. It is used in the treatment of type 2 diabetes mellitus , as monotherapy or as dual therapy with metformin, a sulfonylurea, or a thiazolidinedione[4]. Sitaglipin and metformin is one of the commonly used combination therapy in the management of diabetes which causes reduction in hyperglycemia . Metformin has shown to have a role in controlling dyslipidemia along with hyperglycemia. This study is done to evaluate effect of sitagliptin on LDL , HDL levels which are important parameter to asses dyslipidemia.

METHODOLOGY:

Institutional Animal Ethics Committee permission was taken and all the guidelines of CPCSEA were followed throughout the study. Albino Wistar Rats were used for the study. Albino Wistar Rats were obtained from Central Animal house Reg No: 829/AC/04/CPCSEA, S N Medical College Bagalkot.Animals were allowed to acclimatize for a period of 7 days

Induction Of Diabetes

Diabetes is induced by high fat diet-low dose streptozotocin method .High fat diet was prepared by using vanaspathi ghee and coconut oil. Both oils were mixed at 2:3 ratio. 10ml per kilogram body weight was given by oral feeding[5].

Rats were divided into 4 groups.

Group 1: control: diabetes induced rats treated with normal saline

Group 2: diabetes induced rats treated with metformin 100mg/body wt[6]

Group 3: diabetes induced rats treated with sitagliptin 10mg/kg body wt[6]

Group 4 : diabetes induced rats treated with metformin + sitagliptin

High fat diet feeding was done for 6 weeks. After 6weeks low dose streptozotocin was given at a dose of 35mg/kg[7]. Animals with RBS >200mg/dl were considered diabetic .HDL , LDL levels were assessed after induction of diabetes. Sitagliptin and Metformin were administered Per Oral for 21 days[7].After 21 days HDL and LDL levels were examined

RESULTS

HDL

Table1: Change In Mean HDL By Days Among Study Group

GROUPS	HDL (MEAN±SEM)			ANOVA p value
	DAY 0	After 6 Weeks	After 21 Days	
GROUP I	30.2±1.3	22.1±1.5	20.9±0.9	<0.001*
GROUP II	30.3±1.5	21.7±1.4	29.7±1.2	<0.001*
GROUP III	30.5±1.3	21.1±1.3	26.6±1.4	<0.001*
GROUP IV	30.3±0.8	20.1±0.7	30.4±0.8	<0.001*

Note: * significant at 5% level of significance (p<0.05),

As seen from the table, the HDL levels of group 1,2,3,4 decreased significantly following the induction of Diabetes. After the treatment for 21 days with the drugs - In Group 2 animals treated with Metformin the HDL levels increased from 21.7mg/dl to 29.7mg/dl showing significant increase. [p<.001]In group 3 animals , treated with Sitagliptin the HDL levels increased from 21.mg/dl1 to 26.6mg/dl showing significant increase [p<0.001]Similarly in the animals of group 4 receiving combination therapy of Metformin and Sitagliptin the HDL increased from 20.1mg/dl to 30.4mg/dl Showing significant increase [p<0.001].

LDL Table 2: Change In Mean LDL By Days Among Study Groups

GROUPS	LDL (MEAN±SEM)			ANOVA p value
	DAY 0	AFTER 6 WEEKS	AFTER 21 DAYS	
GROUP I	14.9±1.1	40.4±2.5	38.1±2.3	<0.001*

GROUP II	14.4±1.1	41.3±1.6	21.1±1.7	<0.001*
GROUP III	13.6±1.2	42.1±2.4	27.4±1.7	<0.001*
GROUP IV	13.8±0.8	44.1±3.1	19±2.3	<0.001*

Note:* significant at 5% level of significance (p<0.05),

As seen from the table ,the LDL levels of group 1,2,3,4 increased significantly following the induction of Diabetes. After the treatment for 21 days with drugs - In Group 2 animals treated with Metformin the LDL levels decreased from 41.3mg/dl to 21.1mg/dl showing significant reduction. [p<.001].In group 3 animals , treated with Sitagliptin the LDL levels decreased from 42.1mg/dl to 27.4mg/dl showing significant reduction [p<0.001] .Similarly in the animals of group 4 receiving combination therapy of Metformin and Sitagliptin the LDL reduced from 44.1mg/dl to 19.0mg/dl Showing significant reduction[p<0.001].

CONCLUSIONS:

As seen from above results it can be concluded that rats belonging to groups treated with metformin , sitagliptin and combination therapy of metformin and sitagliptin showed significant increase in HDL and significant decrease in LDL.

DISCUSSION:

Dyslipidemia in Diabetes is a vital factor which is the leading cause of mortality and morbidity. By using High fat diet-Streptozotocin method type-2 DM was induced in Rats. Streptozotocin by affecting pancreatic cells causes hypo insulinemia and high fat diet aids in further insulin resistance apart from direct increase in lipid levels.

Sitagliptin is a reversible inhibitor of the DPP-IV enzyme. 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). Multiple studies shed light on hypolipidemic action of sitagliptin. Sitagliptin in many studies had beneficial effects in targeting dyslipidemia shown by favorable lipid profile [8]. Studies also try to shed light on the probable mechanism of action of sitaglioptin by ,which it causes its hypolipidemic action. Most probable mechanism involved is sitagliptin by reducing hyperglycemia reduces dyslipidemia , other study highlights the role of action on incretins[9].

DPP-4 receptors are found in many location in human body. There strong expression of a gene in human white preadipocytes and adipocytes with possible contribution of DPP4 to the adipocyte differentiation process.[10]

American Diabetes Association in a follow-up study to the trial by Charbonnel et al. was conducted to compare sitagliptin/metformin with glipizide/metformin [11]. It was found the combination of Sitagliptin and metformin to be better. Hypolidimic effect of sitagliptin along with its use for hyperglycemia may further prove its importance in the management of diabetes.

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