Beneficial effects of sitagliptin and metformin in non-diabetic hypertensive and dyslipidemic patients

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Abstract: Obesity, dyslipidemia and hypertension are major risk factors for cardiovascular disease and its associated complications. To evaluate the beneficial effects of sitagliptin and metformin in non-diabetic dyslipidemic and hypertensive patients. A prospective randomized clinical trial was conducted on 70 newly diagnosed dyslipidemic patients with BMI ≥ 25 and blood pressure ≥130/80 at outpatient clinic of medical unit-1 of sheikh medical college /hospital Rahim Yar Khan. They were divided in to three groups each containing 35 patients; First group served as a healthy control while second and third study groups were given tablet sitagliptin 50mg and tab metformin 850mg respectively twice a day for twelve weeks. After three months treatment with sitagliptin and metformin there was significant reduction in body weight (Sitagliptin 6.5% vs Metformin 7.65%) and BMI (Sitagliptin 2.2% vs Metformin 2.8%) with p ≤0.05. Metformin caused a significant reduction in blood pressure with p ≤0.05 (i.e. SBP 9.9% & DBP 6.4%) while sitagliptin caused a highly significant p ≤0.01 reduction in blood pressure (i.e. SBP 15.8% & DBP 12.2%). There was significant improvement in lipid profile with sitagliptin p≤0.05. The percent reduction in value of TC, TG and LDL-C was 20.2%, 13.8% and 23.7% while HDL-C value was increased 11.2% respectively. There was highly significant improvement in lipid profile with metformin p≤0.01. The percent reduction in value of TC, TG and LDL-C was 27.8%, 28.2% and 40.4% while HDL-C value was increased 16.8% respectively. Both drugs improve cardiometabolic risk factors independently in non-diabetic patients.

Keywords: Sitagliptin, metformin, dyslipidemia, hypertension, body weight, lipid profile.

INTRODUCTION

The burden of cardiovascular diseases in developing countries (Pakistan) is much higher as compared to developed countries because for the last few years developing countries fails to control and prevent major risk factors which are associated with cardiovascular disease such as diabetes, obesity, dyslipidemia, hypertension, physical inactivity, poor diet, urbanization and smoking (Deaton *et al*., 2011). In addition there are less focus on prevention and health awareness program by the government. If these risk factors cannot control appropriately then the leading cause of death in future will be ischemic heart disease (IHD) and cerebrovascular disease both are components of cardiovascular disease. So the present therapeutic challenge will be to control and prevent the major risk factors of cardiovascular disease in order to reduce enormous burden on health system (Yousif *et al*., 2001).

Sitagliptin and metformin are oral anti diabetic agents use in the treatment of type 2 diabetes. Both drugs are euglycemic and effectively tolerated by most diabetic patients with no threats of hypoglycemia and weight gain (Tahrani *et al*., 2011; Hundal and Bailey, 2003). In addition to control blood sugar level these drugs have potential properties in various clinical as well as in animal studies such as reduction in body weight, blood pressure and serum lipid profile (Hussain *et al*., 2016; Pavo *et al*., 2003), diminution of inflammation and oxidative stress (Rizzo *et al*., 2012 ; Chakraborty *et al*., 2011), cardio protective (Scheen, 2013; Messaouidi *et al*., 2011) and nephro protective properties (Shalaby and Malek, 2014; Nasri *et al*., 2013) treatment of endothelial dysfunctions (Van *et al*., 2011; Mather *et al*., 2001) and non alcoholic fatty liver disease (Li *et al*., 2015; Ozturk and Kadayifci, 2014). They are also having anticancer properties used in the prevention and treatment of various cancers (Nomiyama and Yanase, 2016; Quinn *et al*., 2013).

Seeing these multiple and similar effects of both drugs in diabetic patients there must be something common regarding their mechanism of action and it was found that metformin which is an old antidiabetic agent works in a similar way like new one sitagliptin. Metformin in addition to its direct AMPK dependent effect also has an indirect action similar to that of sitagliptin. These indirect effects increase the physiological concentration of glucagon like peptide-1(GLP-1) in body either by stimulation of glucagon like peptide 1(GLP-1) secretion or by decreasing the plasma dipeptidyl peptidase-4 (DPP-4) activity (Nu *et al*., 2014) and also by stimulating the peroxisome proliferator activated receptor PPAR-α (Maida *et al*., 2011). Metformin also increases the glucagon like peptide-1(GLP-1) concentration in obese non diabetic subject in a similar way as in type 2 diabetics (Mannucciet *et al*., 2004).

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Most of the studies on sitagliptin and metformin were on diabetic patients. Both drugs reduce body weight, blood pressure and lipid profile by increasing insulin sensitivity and reduce insulin resistance a key metabolic abnormality in diabetic patients. However there were no studies to determine the effect of both drugs on cardiometabolic risk factors in non-diabetic subjects. In diabetic patients improvement in glycemic control would definitely improve these parameters. But we want to see the independent effect of both drugs in non-diabetic beyond its glycemic control effect. So this doubt has been investigated in present study.

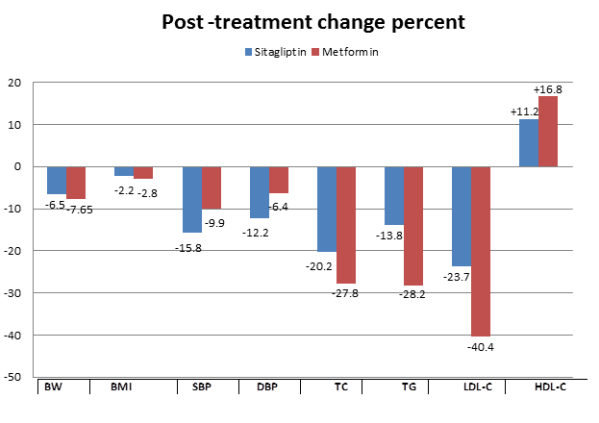

Fig. 1: Post -treatment changes after 12 weeks treatment with sitagliptin and metformin.
BW, body weight; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol.TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

MATERIALS AND METHODS

After taking approval from ethical committee and written informed consent from all participants, a twelve week prospective randomized clinical trial was conducted between February to April 2016 at outpatient clinic of medical unit 1 of Sheikh Zayed Medical College/Hospital, Rahim Yar Khan. Initially 135 patients were screened. Out of which seventy patients aged 35-52 were recruited on the basis of inclusion and exclusion criteria. An inclusion criterion was border-line serum lipid profile according to NCEP-ATP-111 criteria (Stone *et al*., 2005) and mild to mode hypertension according to (WHO and international society of hypertension, 2003) criteria. Patients were not taking any medicine for hypertension and dyslipidemia.

Exclusion criteria were any history of chronic disease, diabetes, hypothyroidism, kidney disease, liver disease, ischemic heart disease, pregnancy, smoking, alcohol and the drugs which disturb serum lipid profile such as thiazide diuretic, beta blockers, corticosteroids, oral contraceptive, Protease inhibitors and 2nd generation antipsychotic.

The patients were randomly divided in three groups each contained 35 patients. First group was served as a healthy control while second and third study group were given tab sitagliptin 50mg and metformin 850mg respectively twice a day for a period of twelve weeks. In addition patients were also advised to do a fifteen to thirty minutes daily walk. Body weight was measured on digital weight scale and blood pressure was measured in both arms twice to avoid errors at interval of fifteen minutes by mercury sphygmomanometer apparatus before and end of the study. Fasting blood samples were drawn from the antecubital vein before and at the end of the study. The samples were used for analyzing fasting blood sugar and Lipid profile. Fasting blood sugar was measured by glucose oxidase peroxidase method to exclude diabetic patients at start of study. Lipid profile was done by semi automated clinical chemistry analyzer (Microlab 300) using spectrophotometery principal.

Data analysis

Data was analyzed by using software statistical package for social sciences SPSS 16. Values of numeric data were presented as mean ± standard deviation. Statistical analysis of data was done using student t-test. P values < 0.05 were deemed to be statistically significant and P values <0.01 were considered highly significant.

RESULTS

Both groups tolerated the drugs very well and completed the study with nice cooperation. No significant adverse effects were noted during the study period. Five patients in the control group were not completed the study because loss of follow up. The baselines demographic characteristics were shown in table1. The pretreatment parameters such as body weight, blood pressure and lipid profile of both study groups were significantly higher p≤0.05 than healthy control (table 1 & 2). After treatment with sitagliptin there was significant reduction in body weight and BMI with p≤0.05. Body weight (90±12.4 to 82±12.6kg) BMI (30.7±4.4 to 27.6±5.2 kg/m^2) Blood pressure was also reduced in sitagliptin with highly significant p value ≤0.01 SBP (150.5±10.2 to 120.6±14.8 mmhg) DBP (94.6±10.5 to 80.5±9.6mmhg). There was significant improvement in lipid profile with three months treatment with sitagliptin with p≤0.05. The percent reduction in value of TC, TG and LDL-C was 20.2%, 13.8% and 23.7% while HDL-C value was increased 11.2% respectively.

On the other hand metformin also caused significant reduction in body weight and BMI with p≤0.05. Body weight (94±16.4 to 84±12.4kg) BMI (31.6±2.4 to 27.2±0.6 kg/m^2) Blood pressure was also reduced significantly in metformin group with p≤0.05 SBP (145±12.9 to 130±10.2mmhg) DBP (92.2±11.1 to 88±10.5mmhg). Metformin caused a highly significant

Table 1: Baseline Characteristics of study groups

Baseline Characteristics	Control Group (n 35)	Sitagliptin Group (n 35)	Metformin Group (n 35)
Age(years)	27±17	25±13	28±15
Sex Male/Female	18/17	22/13	20/15
Body weight(kg)	72±10.8	90±12.4	94 ±16.4
BMI (Body Mass index kg/m^2)	24±5.8	30.7±4.4	31.6 ±2.4
Blood sugar fasting(mg/dl)	78±13.5	86 ±18.4	83±16.5

Table 2: Results of Sitagliptin and Metformin group (pre and post treatment)

Parameters	Control Group (n 30)	Sitagliptin Group (n 35)		Metformin Group (n 35)	
		Pre treatment	Post treatment	Pre-treatment	Post treatment
Body weight(kg)	72±10.8	90±12.4¶	82±12.6*	94 ±16.4¶	84±12.4*
BMI (kg/m^2)	24±5.8	30.7±4.4¶	27.6±5.2*	31.6 ±2.4¶	27.2±0.6*
SBP (mmhg)	115±8.9	150.5±10.2¶	120.6±14.8**	145±12.9¶	130±10.2*
DBP (mmhg)	75±6.6	94.6±10.5¶	80.5± 9.6**	92.2±11.1¶	88±10.5*
TC (mg/dl)	142±4.64	235±15.85¶	188±18.56*	255± 14.69¶	192±10.82*
TG(mg/dl)	161±7.08	227±31.2¶	194±35.42*	180±50.48¶	126±35.42**
LDL-C(mg/dl	106±7.73	146±18.56¶	113±18.17*	161±10.8¶	91±11.98**
HDL-C(mg/dl)	56.45±2.70	38.2±3.93¶	45.4±5.13*	45±1.54¶	54±1.9**

SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol.TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol;
Results represent Mean ± SD
¶ Significantly ($p \leq 0.05$) different with respect to control,
* Significantly ($p \leq 0.05$) different with respect to pre treatment value
** Highly significantly ($p \leq 0.01$) different with respect to pre treatment value

improvement in lipid profile with $p \leq 0.01$. The percent reduction in value of TC, TG and LDL-C was 27.8%, 28.2% and 40.4% while HDL-C value increased 16.8% respectively. These results are shown in table 2 and fig. 1.

DISCUSSION

Benefits of weight reduction in the prevention and progression of cardiovascular diseases cannot be denied. Even 5-10% weight loss is sufficient to reduce risk factors associated with cardiovascular disease (Brown *et al*., 2015). In this study both drugs caused a significant reduction in body weight. The reduction in body weight may be due to increasing glucagon like peptide-1 (GLP-1) mediated release of insulin, suppression of glucagon secretion, delay in gastric emptying time and decrease appetite by both drug (Migoya *et al*., 2010). Moreover obesity in non diabetic patients is strongly associated with insulin resistance and both drugs increases insulin sensitivity and improves insulin resistance which is another beneficial point in these patients (Derosa *et al*., 2012). There were limited studies on body weight in non-diabetic subjects. In one study (Seifarth *et al*., 2013) concluded that metformin reduce body weight 5.8kg over a period of six months significantly in a dose dependent manner while in another study conducted by (Chun *et al*., 2013) metformin reduced body weight and lipid profile in clozapine treated psychotic patients however effect was disappeared after discontinuing the drug (Chun *et al*., 2013). Although sitagliptin reduced body weight in diabetics in various clinical studies explained by (Hussain *et al*.,) however there was no study so far to see the effect of sitagliptin in non-diabetics.

The increase level of glucagon like peptide-1(GLP-1) in body by both drugs made them render to reduce blood pressure due to the following mechanism, stimulation of vasodilatory peptide nitric oxide in vessels by glucagon like peptide-1(GLP-1) agonist indirect effect, direct and independent vasodilatory effect of glucagon like peptide-1(GLP-1) agonist (Ban *et al*., 2008) and finally urinary loss of sodium by renal tubules (Gutzwiller *et al*., 2004). In addition weight reductions by both drugs discussed above provide additional benefits and its role cannot be denied. Mistry *et al*., 2008 showed that sitagliptin has a modest effect on blood pressure in non-diabetic patients with mild to moderate hypertension while metformin had no significant effect on blood pressure in various studies in non diabetics. In our study both drug reduced blood pressure significantly but it was more with sitagliptin.

Both drugs caused a significant improvement in lipid profile but it was more with metformin. The dyslipidemic effect of both drugs may be related through glucagon like peptide -1(GLP-1) mediated effect of decrease in the intestinal lymph flow, reduced absorption of triglycerides from intestinal cells, reduced VLDL release from the liver (Qin *et al*., 2005), reduction in the synthesis of intestinal and hepatic derived apoB-48 and apoB-100 containing lipoprotein (Tremblay *et al.,* 2014). The antidiabetic drugs

which have well documented lipid lowering effect in diabetic patients include pioglitazone, acarbose, metformin and sitagliptin and their efficacy and comparison was proven in various studies (Monami *et al*., 2012; Pavithra *et al*., 2015).

However limited work was done in non-diabetic patients. A study conducted by (Kocer *et al*., 2014) showed that metformin improved lipid profile in non diabetic polycystic ovarian female patients while study conducted by (Preiss *et al*., 2014) showed that metformin significantly reduced body weight and body fat but failed to improved lipid profiles in non diabetics. No clinical data is available to see the effect of Sitagliptin in non-diabetic patients.

The result of our studies showed that metformin and sitagliptin has independent effect on body weight, blood pressure and lipid profile in non-diabetics. These independent effects will be very beneficial for those who are obese, mild hypertensive with deranged lipid profile. In addition these effects will be more enhanced if both drugs will be used in combination as they are widely prescribed in combination currently in diabetics due to better safety profiles (Hayes *et al.,* 2016).

CONCLUSION

Glucagon like peptide 1(GLP-1) agent's sitagliptin and metformin show great potential regarding improvement in body weight, blood pressure and lipid profile even in non-diabetics.

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