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Research Article

THE EFFECT OF SITAGLIPTIN TREATMENT ON METABOLIC PARAMETERS

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ABSTRACT
Aim: The aim of the present study was to determine the effect of the addition of sitagliptin to the treatment of Type II Diabetes patients receiving metformin or sulphonylurea combined with metformin to metabolic parameters 6 months later.
Methods: Information in files of overall 54 (29 female, 25 male) patients between the ages of 35-78, who were followed in Diabetes and Internal Medicine outpatient clinics was collected. Baseline data were compared with those obtained six months after the onset of sitagliptin.
Results: The decrease in mean HbA1c values and mean weight at 6th month compared to baseline values was found to be statistically significant, ($p<0,01$, $p<0.01$). In addition, the decrease in mean blood sugar values and LDL cholesterol values was found to be statistically significant.
Conclusion: In patients in whom adequate glicemic control could not be obtained with metformin or metformin sulfonylurea combined treatment, significant improvement in metabolic and glicemic parameters and significant weight established with the addition of sitagliptin to treatment.

Key words: *Sitagliptin, Type II Diabetes, Treatment*

INTRODUCTION
Type II Diabetes Mellitus (DM) is a chronic diases that courses with hyperglicemia due to insulin deficiency or defect in the effect of insulin. The regulation of diabetes is very important in the prevention of macro and microvascular complications of diabetes. The risk of microvascular complication is low in patients with HbA1c < % 7, while it is very high in those with HbA1c > % 7. In the treatment of type II DM, adequate glicemic control is not usually obtained with the use of a single oral antidiabetic (OAD) drug (DeFronzo, 1987). Usually, OAD combinations are required. Currently, metformin, of biguanid group, is the most commonly used OAD as well as being the most frequently used drug in combinations (Drucker, 2001). Sulphonylureas, like metformin, are OAD's used commonly in monotherapy and combination therapy. Sitaglipin is an oral antidiabetic which increases incretin and is used as single dose daily. Hormones from increting group such as glucagon like peptide 1 (GLP-1) and gastric inhibitor peptide are released from endocrine cells in the intestines as a response to food and contributes to the regulation of glucose by increasing the release of glucagon dependent insulin (Deacon, 2004). It has been shown in various studies that at normal or high glucose levels, glucagon like peptide 1 induces the release of glucose and inhibits the release of glucagon and that these effects disappear when glucose concentrations attain normal levels. Glucagon line peptide 1 inhibits the release of glucagon delays gastric emptying (Kim, 2005). However, these hormones are inhibited by dipeptyl peptidase IV enzyme. Sitagliptin increases active incretin hormone levels by inhibiting dipeptyl peptidase IV and enhances the control of blood glucose by potentiating isulin stimulating and glucagon inhibiting effects (Herman, 2006). Although both sitagliptin and sulphonylurea stimulate insulin secretion from pancreas beta cells, their mode of action is different. Sitagliptin, which exerts effect via the increase in insulin levels in a glucose dependent manner with increased levels of intracellular cyclic adenosine monophosphate levels (Idris, 2007). It has been demonstrated that sitagliptin reduces insulin concentrations in a fashion that can contribute to the insulin decrease caused by the other agent. When varying modes of action of sitagliptin

and sulfonylurease agents are taken into account, combination therapy with these two agents seems to be a reasonable approach in making glicemic control possible.

MATERIALS AND METHODS

Overall 54 patients (29 female, 25 male) followed in Internal Diseases and Diabetes outpatient clinics of İstanbul Haseki Training and Education Hospital were included in the present study. Approval was obtained from the ethical committee of hospital. As study subjects, patients whose HbA1c value was not at the desired level (> % 6,5), who received metformin full dose monotherapy or metformin and sulfonylurea combination treatment for at least three months, whose ages range between 35-78 and whose BMI was > 24 kg/m2, who underwent diet and exercise treatment for at least three months without adequate glicemic control were selected. Patients who used OAD treatment other than metformin and sulfonylurea in the three months before the addition of sitagliptin were not included in the study. In addition, patients with chronic renal failure, chronic liver disease, stage 3-4 congestive heart failure were not included in the study. Using the files of the patients, metabolic parameters at the baseline and six months after the addition of sitagliptin were evaluated. Patients were also asked about side effects developing during treatment. Finally, the measurements were evaluated statistically. In statistical evaluation, SPSS (Statistical Package for Social Sciences for Windows) 16.0 program was used. Numerical data were expressed as mean ± standard deviatin and categorical data as frequency and percentage. Whether the distribution of values in each group was homogenous was evaluated with Kolmogorov-Smirnov Z testi. In normally distributed numerical data, Student's t test was used in two by two comparions. If the distribution was not normal, then Mann-Whitney U test was used instead.

RESULTS

The present study was carried out with overall 54 cases 29 female (%53.71) and 25 male (46.29%) whose ages ranged between 35-78. Mean age was 55.2 ± 8.22 (35-78). Mean duration of diabetes was 5,85 ± 3.04 years. In the present study, significant decrease was found in mean weight of patients at 6th month compared to baseline values, (table 1). Significant decrease was found after treatment in mean Hb1Ac value compared to baseline. In addition, the decrease in mean blood sugar levels and LDL levels was found to be significant respectively (p:0.045, p:0.043). A slight increase in amylase values after six months sitagliptin treatment compared to baseline with no clinical significance. However, there was no clinical findings suggesting pancreatitis and no pancreatitis case was detected.

DISCUSSION

In the present study, it was demonstrated that in patients receiving metformin or metformin with sulfonylurea, after the addition of sitagliptin to treatnment regime, statistically significant decrease occurred in HbA1c values ($p < 0,001$), with a mean decrease of % 0,88(±1,28) at the sixth month (Del Prato, 2006). In a study carried out by Charbonnel et al, 453 patients who received metformin monotherapy and had mild or moderate glicemia with HbA1c %7-10, additionally received sitaglipitin and after 6 months HbA1c was found to be decreased by 0.67% (Charbonnel, 2006). In a study carried out in China in 2012 with 395 cases, sitagliptin was added to the treatment regime of patients whose mean HbA1c value was %8,5 and after 24 weeks, HbA1c decreased at the rate of 0.9%. In the present study, a similar rate of fall in HbA1c was observed. In the patient group whose baseline HbA1c value was ≥8%, the decrease in HbA1c value was significantly higher than that in the patient group whose baseline HbA1c value was <8% (Wenying, 2012). That is, there was more marked decrease in patients with higher baseline HbA1c values, which is also observed with other antihyperglicemic agents. Metformin inhibits hepatic glucose output and regulates insulin resistance. In addition, there are findings indicating that metformin may increase total GLP-1 release. It is thought that marked effect of metformin on glicemia is most probably associated with the release of this peptide. Based upon the complementary effects of each agent in the regulation of glucose and their reliability profiles, it may be suggested that combination

treatment with sitagliptin and metformin may be a beneficial clinical treatment for patients with type II DM.

Table 1: Metabolic parameters of the patient

Parameters	n	Baseline		After treatment		p value
		Mean	SD	Mean	SD	
FBG (mg/dl)	54	180,72	58,817	164,04	61,709	**0,045**
Weight (kg)	54	84,04	16,289	80,78	14,96	**0,0001**
BMI	54	31,811	6,64	30,56	9,17	0,252
HbA1c (%)	54	8,24	1,33	7,36	1,39	**0,0001**
HDL cholesterol (mg/dl)	54	43,13	8,98	43,15	8,74	0,984
LDL cholesterol (mg/dl)	54	125,37	36,96	114,67	38,26	**0,043**
Triglyceride (mg/dl)	54	249,94	193,72	215,83	182,11	0,227

(FBG: fasting blood glucose, BMI: body mass index, SD: standard deviation)

In the present study, it was demonstrated that addition of sitagliptin to metformin and/or sulphonylurea treatment improved glicemic control without any hypoglicemia. The decrease in fasting blood sugar observed with sitagliptin is interesting and suggests that increase in active incretin concentration observed in fasting also leads glucose levels to decrease. As hepatic glucose production is an important determinant of fasting blood sugar and higher active GLP-1 levels reduce glucagon concentrations, the probabale mechanism of the fall in fasting blood suger caused by sitagliptin may be that high insulin secretion corresponding to decreased glucagon levels leads to decreased hepatic glucose production at night (Migoya, 2007). In the present study, the decraase in 6th month mean blood sugar levels compared to baseline was found to be statisticallly significant, (p:0.045). As the present study was of retrospective nature, there was no baseline evaluation, but no side effects requiring the discontinuation of treatment occurred. Sitagliptin was usually tolerated well. There was no hipoglicemic attack developing during sitagliptin treatment. It has been demonstrated that the effect of incretin stimulating insulin secretion is glucose dependent. i.e. it does not exert its effect when glucose levels are low (DeFronzo, 2004). Sitagliptin has no effect on weight (Herman, 2005) in the present study, with the addition of sitagliptin, statistically significant weight loss was obtained ($p<0.001$). Sitagliptin added to metformin treatment brought about a small but statistically significant increase in HDL cholesterol compared to placebo as well as leading to small but significant decreases in cholesterol, trigliceride and non HDL cholesterol while no difference was found in LDL cholesterol levels (Charbonnel, 2006). In the present study, with the addition of sitagliptin to treatment, statistically significant decrease was found in LDL cholesterol levels (p:0.043). However, no statistically significant difference was found in HDL and triglyceride values.

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