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Co-Administration of Cabergoline and Gliclazide Improve Glycemic Parameters and Lipid Profile in T2DM

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Abstract

Type 2 diabetes mellitus (DM) is a progressive metabolic disorder that is associated with basal hyperinsulinemia, insulin resistance and impaired insulin release. Glycemic control is a fundamental part of the management of type 2 DM and difficult to achieve. Different antidiabetic agents can handle diabetic metabolic abnormalities. The development of antidiabetic agents with novel mechanisms of action is highly desirable. Cabergoline, D2 agonist, is expected to play a role in the glycemic control.

Objective: Evaluation of the glycemic efficacy of cabergoline on diabetic patients.

Design: Fifty type 2 diabetic patients participated in the study for four months; 25 patients receive gliclazide (60-120 mg) once daily and 25 patients receive cabergoline 0.5 mg twice weekly within 2 hrs of wakening plus gliclazide. 10 healthy people with matched age participated as a control group. Fasting and post prandial BG level were measuredmonthly. HbA1c, fasting insulin, HOMA IR and lipid profile were measured at baseline and after four months.

Results: Treatment of the patients with cabergoline and gliclazide resulted in greater significant ($p<0.05$) decrease in FBG, PPBG, HbA1c compared treatment with gliclazide only. Insulin levels were reduced and insulin sensitivity was enhanced with improvement in lipid profile.

Conclusion: Cabergoline is well-tolerated new antidiabetic line acting with a unique insulin sensitizing actions.

Keywords: T2DM, Dopamine; D2 receptors; Cabergoline; SCN; Insulin resistance; Food reward; VMH; Free fatty acids

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases in nearly all countries [1] with prevalence continues to increase at a worrying rate around the world. The number of diabetic patients is expected to be 438 million by 2030 and one in every 10 persons will have diabetes mellitus in 2040 [2]. T2DM is a multifactorial disease in which an ominous octet represents its pathophysiologic defects. Exhaustible compensatory hypersecretion of insulin on the background of insulin resistance causes gradual loss of islets secretory function [3,4]. In addition to the muscle, liver, and β-cells; the fat cells, gastrointestinal tract hormones [5], α pancreatic cells [6], the kidney and brain [7] are eight members play important roles in the development of type 2 DM [8].

Metabolism and glucose hemostasis are managed at centers in the medial basal hypothalamus [9,10]. The ventromedial nucleus of the hypothalamus (VMH) that is glucose sensitive, involved in regulating peripheral autonomic nervous system and endocrine functions controlling glucose metabolism [11]. The hypothalamic suprachiasmatic nucleus (SCN), plays a key role in the regulation of seasonal and diurnal variations of insulin sensitivity, glucose and lipid metabolism through the circadian rhythm of dopamine release [12-14]. Diminished hypothalamic dopaminergic activity results in hypothalamic dysfunction of fuel sensing. Reductions in hypothalamic dopaminergic activity in insulin resistant states are coupled to elevations of noradrenergic and serotonergic activities at VMH and elevated NPY and corticotropin releasing hormone levels at the hypothalamic paraventricular nucleus [15].

Increased sympathetic nerve activity is responsible for dissipation of energy after food consumption through beta-receptors activation. Chronic over activity or down regulation of beta adrenoceptors potentiate obesity and insulin resistance. Diabetic patients have impaired responses to sympathetic signals to liver, pancreas, skeletal muscle, adrenal medulla and adipose tissue and show elevations in hepatic glucose production, insulin resistance and impaired pancreatic β-cell function [16]. In type 2 diabetic patients, fat cells tend to be enlarged and resistant to insulin's antilipolytic effect releasing large quantities of fatty acids and glycerol into the circulation [17]. FFA levels stimulate gluconeogenesis, induce hepatic and muscle insulin resistance and impair insulin secretion. Enlarged fat cells have diminished capacity to store fat. When adipocyte storage capacity is exceeded, lipid "over-flows" into muscle, liver and β-cells, causing insulin resistance and impaired insulin secretion [18-20]. Insulin

resistance induces compensatory Hyperinsulinemia that exerts sympathoexcitatory effects [21] though suppressed inhibition of neuropeptide Y (NPY) neurons. Activated NPY neurons induce potent orexigenic effects via increased sympathetic outflow to the liver resulting in hepatic insulin resistance and increased endogenous glucose production [22,23]. The metabolic control pathways of the CNS are modulated, in part, by dopaminergic signaling.

Dopamine is one of the major neurotransmitters in the brain which controls a variety of key functions such as locomotion, feeding behavior, energy homeostasis, motivation, punishment, mood and hormone secretion. Dopamine locally acting in the hypothalamus inhibits hypothalamic NPY with subsequent potent inhibition of feeding. Dopamine is the key member involved in the mediation of the reinforcing effects of foods. Central dopaminergic reward pathways contribute to appetite control beside the classic system of energy homeostasis [24]. Significant release of dopamine in dorsal striatum is observed during feeding in humans and the degree of pleasure from eating correlates with amount of dopamine release [25]. Intake of delicious food downregulates D2 receptors, reduces D2 sensitivity, and decrease sensitivity of reward circuitry that increases risk for overeating to counteract a reward deficit but this overeating may further impair response of reward circuitry in a feed-forward process [26,27].

Early identification of diabetic patients and good glycemic control are very important because chronic hyperglycemia is associated with diabetic macrovascular and microvascular complications [28,29,30]. Although several classes of antidiabetic agents are available, only half of the patients achieve the recommended hemoglobin A1c target [31]. Annoying hypoglycemia, weight gain, β-cell dysfunction [32], cardiovascular risks, gastrointestinal upset and renal impairement resulted from antidiabetic drugs, make management of type 2 DM a challenging task [14,33-35]. To improve glycemic control and avoid such pitfalls, new therapeutic approaches are developed [36]. Given hyperlipidemia as a hyperglycemic risk factor and the complex role of hypothalamic dopamine activity in the regulation of glucose homeostasis and its disruption in patients with T2DM, restoring proper dopamine rhythms and normalization of lipid profile can alleviate multiple attributes of T2DM. Cabergoline is D2 agonist with a completely novel mode of action for glycemic control. It does not have specific receptors that mediate its action on glucose metabolism nor increase insulin secretion [37]. Glycemic efficacy of cabergoline on type 2 diabetic patients is evaluated in our study.

Patients and Methods

Fifty type 2 diabetic patients participated in the study for four months. The study was conducted from October 2015 to October 2016 in Internal Medicine Outpatient Endocrinology Clinic, Tanta University Hospital, Tanta, Egypt. Ten healthy volunteers with matched age and sex served as control group. All the participants were informed about the study and signed informed consent. The study was carried out according to the ethical guidelines approved by the ethical committee of faculty of pharmacy, Tanta University. The included patients were men and women with mild to moderate type 2 diabetes mellitus (glycated haemoglobin (HbA1c) less than 9%). Patients with D1M, cardiovalvupathy, known hypersensitivity to either of the study drug components, gastrointestinal obstructions or biliary disorders and kidney or hepatic dysfunctions were excluded from the study.

Patients were divided into two groups

Diamicron group: 25 patients received diamicron (gliclazide 60-120 mg/day, Servier Co, Egypt).

Combination group: 25 patients received cabergamoun (cabergoline 0.5 mg twice weekly within 2 hours of wakening, Amon Co., Egypt) plus diamicron (gliclazide 60-120 mg/day, Servier Co., Egypt). Body weight and height were measured and body mass index was calculated by dividing the patient weight (kg) by square of patient's height (m^2).

The mean age of diamicron and combination treated patients were 49.72 ± 1.51 and 46.88 ± 2.50 years, respectively. The patients enrolled in the study were overweight or obese having BMI 26 kg/m^2 or greater. The diagnosis of T2DMwas confirmed according to criteria of ADA 2016. The epidemiological data of the patients and controls are shown in (Table 1).

Group		Control group	Diamicron group	Combination group
Number		10	25	25
Sex (M/F)		3/7	6/19	8/17
Age (years)	Range	33-68	28-62	23-66
	Mean ± SEM	51.60 ± 4.16	49.72 ± 1.51	46.88 ± 2.50
BMI (kg/m2)	Range	23-31.04	28.4-33.7	26.07-34.94
	Mean ± SEM	28.144 ± 0.872	31.208 ± 0.271	30.964 ± 0.528
FBG (mg/dL)	Range	75-99	95-286	130-241
	Mean ± SEM	86 ± 2.37	162.7 ± 10.4	190.04 ± 6.17
Waist circumference	Range	78-119	98-118	90-127
	Mean ± SEM	93.9 ± 4.28	106.68 ± 1.1	112.44 ± 1.93
BMI: Body mass index, FBG: Fasting blood glucose				

Table 1: Epidemiological data of the patients and controls.

Fasting blood glucose (FBG) and post prandial blood glucose (PPBG) level were measured every four weeks during the treatment period while HbA1c, fasting insulin, HOMA-IR, lipid profile (triglycerides, LDL cholesterol , HDL cholesterol and total cholesterol) were measured at baseline and after four months. After overnight fasting, blood samples were collected in the morning. Each blood sample was divided into two portions. The first portion was allowed to clot, centrifuged by 4000 rpm for 15 minutes using Sigma laborzentrifugen3 k15 centrifugation, the first portion of serum was used for immediate measurement of fasting glucose. The second portion of serum was stored at -20°C till analysis of insulin and lipid profile. The second portion of blood sample was added to ethylenediamine tetraacetic acid disodium salt (EDTA), centrifuged 4000 cycles for 15 minutes and used for immediate measurement of glycated hemoglobin.

After 2 hours of breakfast, blood samples were collected, allowed to clot, centrifuged, used for immediate measurement of post prandial glucose. Serum glucose were measured colorimetrically using kits obtained from biodiagnostic company, Egypt. Glycated hemoglobin were measured by immunoturbidimetric method using kits obtained from Biotecnica instruments, Italy. Fasting insulin were measured by chemiluminent immunometric assay using kits obtained from Siemens health care diagnostics, USA. Homeostatic model assessment of insulin resistance (HOMA IR) was calculated. Plasma levels of total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol were measured by enzymatic colorimetric methods using kits obtained from biodiagnostic company, Egypt. Data were analyzed by minitab 6 system and presented as Mean ± SEM. The experimental data were analyzed for significant differences by paired T-test. The level of significance was set at $P<0.05$.

Results

The mean values of FBG, PPBG, were significantly ($p<0.05$) higher in diabetic patients of both groups compared to that in the control results before treatment. Treatment of group 2 diabetic patients with diamicron plus cabergoline for 4 months resulted in significant ($p<0.05$) decrease in FBG, PPBG compared to pretreatment levels. FBG showed a greater decrease (-40.2%) in combination group versus (-16%) in group 1. PPBG decreased (-41.44%) in combination group versus (-12.69%) in diamicron group.

At the start of the study, the mean values of HbA1c were significantly ($p<0.05$) higher in diabetic patients of both groups compared to that in the control results.At the end of the treatment of group 2 diabetic patients with diamicron plus cabergoline, they showed significant ($p<0.05$) decrease in HbA1c compared to pretreatment levels. The decrease in HbA1c in combination group were higher (-11.24%) than decrease in diamicron group (-4.89%). Patients showed significant ($p<0.05$) decrease in fasting insulin compared to pretreatment levels. The reduction in fasting insulin in combination group were higher than decrease in diamicron group (-11.24% vs. -1.84%) respectively. The two groups of the study show insulin resistance as shown by the mean values of HOMA-IR. HOMA-IR were significantly ($p<0.05$) higher in diabetic patients of both groups compared to that in the control results at baseline. Group 2 diabetic patients exhibit a significant decrease in HOMA IR and enhancement of insulin sensitivity. Insulin resistance decrease (-46.33%) in combination group and (-20.89%) in diamicron group (Tables 2 and 3). Fasting insulin shows positive correlations with HOMA IR in both groups (Figures 1 and 2).

Parameter		Control group	Diamicron group		
			Pre-treatment	Post-treatment	Change%
FBG (mg/dL)	Range	75 -99	95-286	90-200	↓ 16.04%
	Mean ± SEM	86 ± 2.37	162.7 ± 10.4	136.6 ± 6	
PPBG (mg/dL)	Range	120 -135	150-402	140-361	↓ 12.69%
	Mean ± SEM	127.8 ± 1.62	245.8 ± 15.8	214.6 ± 11.2	
Glycated hemoglobin %	Range	04-May	6.4-9	6-9.5	↓ 4.89%
	Mean ± SEM	4.52 ± 0.12	8.016 ± 0.193	7.624 ± 0.21	
Insulin (µIU/mL)	Range	Jun-13	3.3-17.4	3 -17.1	↓ 1.84%
	Mean ± SEM	8.95 ± 0.681	9.77 ± 1.01	9.59 ± 1.01	
HOMA-IR	Range	1.11 -2.530	0.78-12	0.890-8.4	↓ 20.89%
	Mean ± SEM	1.886 ± 0.131	4.395 ± 0.689	3.477 ± 0.492	
FBG: Fasting blood glucose, PPBG: Post prandial blood glucose, HOMA-IR: Homeostasis model assessment of insulin resistance, Change%: percent change compared to control,					
SEM: standard error of the mean.					

Table 2: Results of glycemic parameters of diamicron treated patients compared to control group.

Parameter		Control group	Combination group		
			Pre-treatment	Post-treatment	Change%
FBG (mg/dL)	Range	75-99	130-241	82-135	↓ 40.20%
	Mean ± SEM	86 ± 2.37	190.04 ± 6.17	113.64 ± 3.07	
PPBG (mg/dL)	Range	120-135	225-366	105-216	↓ 41.44%
	Mean ± SEM	127.8 ± 1.62	294.12 ± 7.88	172.24 ± 5.75	
Glycated hemoglobin %	Range	4-5	7.1-9	6.6-8.4	↓ 11.70%
	Mean ± SEM	4.52 ± 0.12	8.544 ± 0.12	7.544 ± 0.0928	
Insulin (μIU/mL)	Range	6-13	3.13-17	2.9-15.8	↓ 9.79%
	Mean ± SEM	8.95 ± 0.681	10.77 ± 1.01	9.716 ± 0.977	
HOMA-IR	Range	1.11-2.530	1-9.69	0.58-5	↓ 46.33%
	Mean ± SEM	1.886 ± 0.131	5.157 ± 0.554	2.768 ± 0.289	

Table 3: Results of glycemic parameters of combination treated patients compared to control group.

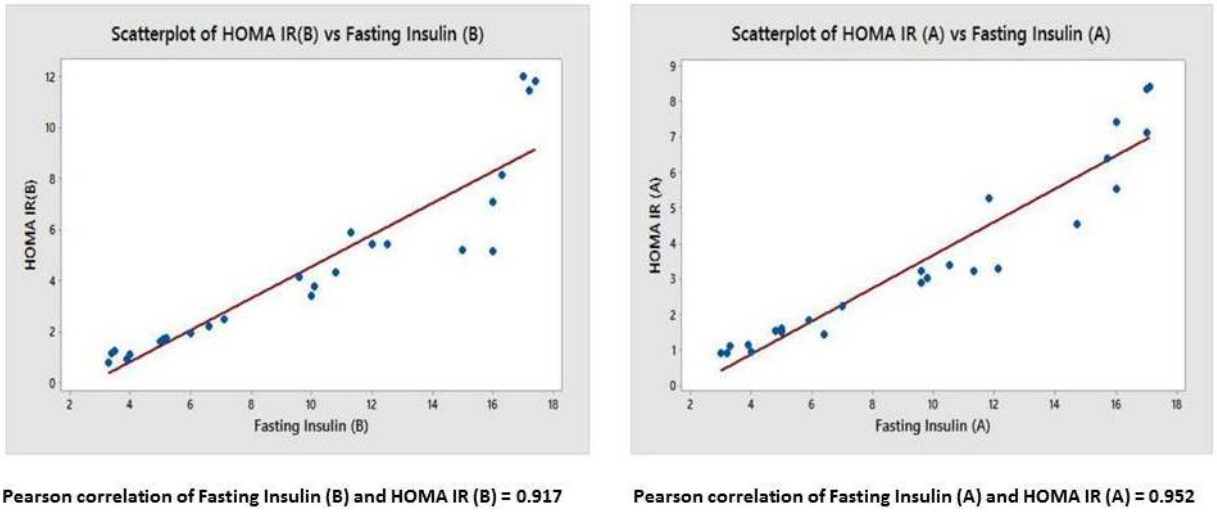

Figure 1: Correlation between Fasting insulin and HOMA IR before and after treatment with diamicron.

The pretreatment mean values of total cholesterol, triglycerides and LDL were significantly ($p<0.05$) higher in diabetic patients before cabergoline treatment compared to that in the control results.

The differences between baseline measurement and after four months of treatment with cabergoline and gliclazide show significant ($P<0.05$) decrease in total cholesterol, triglycerides and LDL with a significant ($P<0.05$) increase of HDL compared to pretreatment results. Percent decrease in total cholesterol and LDL levels in combination group were higher than percent decrease in diamicron group; ↓ 6.92% and ↓ 14.22% vs ↓ 5.28% and ↓ 12.51%, repectively (Tables 4 and 5).

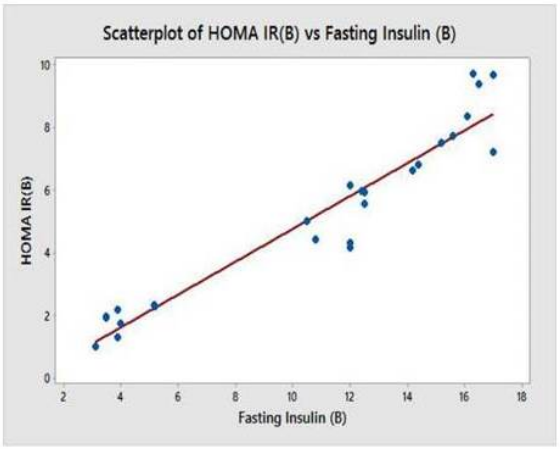

Figure 2: Correlation between Fasting insulin and HOMA IR before and after treatment with cabergoline and diamicron.

Parameter		Control group	Diamicron group		
			Pre-treatment	Post-treatment	Change %
Cholesterol	Range	134-173	162-297	145-244	↓ 5.28%
	Mean ± SEM	159.4 ± 3.98	200.04 ± 6.11	189.48 ± 4.42	
TG	Range	67-108	81-262	75-231	↓ 7.83%
	Mean ± SEM	84.8 ± 3.79	147.6 ± 9.51	136.04 ± 7.64	
HDL Cholesterol	Range	47-86	34-70	40-79	↑ 12.48%
	Mean ± SEM	69 ± 4.22	52.56 ± 2.14	59.12 ± 2.25	
LDL Cholesterol	Range	42-97	74.80-197	66-147	↓ 12.51%
	Mean ± SEM	73.10 ± 5.63	117.62 ± 6.40	102.90 ± 4.77	
TG: Triglycerides, HDL cholesterol: High density lipoproteins cholesterol, LDL: Low density lipoproteins cholesterol.					

Table 4: Results of Lipid profile in group 1.

Parameter		Control group	Combination group		
			Pre-treatment	Post-treatment	Change%
Cholesterol	Range	134-173	158-277	141-245	↓ 6.92%
	Mean ± SEM	159.4 ± 3.98	197.56 ± 6.23	183.88 ± 4.85	
TG	Range	67-108	90-262	88-221	↓ 7.13%
	Mean ± SEM	84.8 ± 3.79	148.12 ± 8.64	137.56 ± 6.85	
HDL	Range	47-86	30-79	32-82	↑ 9.46%
	Mean ± SEM	69 ± 4.22	52.88 ± 2.4	57.88 ± 2.84	
LDL	Range	42-97	79-176	68-157	↓ 14.22%
	Mean ± SEM	73.10 ± 5.63	113.68 ± 5.48	97.52 ± 4.78	
TG: Triglycerides, HDL cholesterol: High density lipoproteins cholesterol, LDL: Low density lipoproteins cholesterol					

Table 5: Results of Lipid profile in group 2.

Discussion

Diabetes mellitus is a multifactorial disease in which different organs, hormones and neurotransmitters participate in its pathogenesis. Studies on mammalian species of seasonal obesity offer new insights into the etiology and the treatment of T2DM. Treatment should be based upon reversal of known pathogenic abnormalities and not simply on reducing the A1C. Despite the recent advent of antidiabetic agents, new therapeutic approaches are needed to correct hyperglycemia and hyperlipidemia in T2DM patients as reductions of percentage glycated HbA1c of 0.55 or more can reduce risk of diabetes related complications [11]. Important roles of ventromedial hypothalamic noradrenergic and dopaminergic activities in the regulation of annual cycles of the obese insulin resistant conditions led to the investigations of the metabolic responses dopamine receptor 2 agonists in humans [38,11]. Our work deals with cabergoline, dopamine receptor (D2) agonist, to correct glucose intolerance in type 2 diabetic patients. This study has been conducted to evaluate glycemic efficacyof cabergoline in T2DM patients with reference to sulfonylureas, gliclazide. Two groups were treated with either gliclazide or gliclazide plus cabergoline.

In our study, after 4 months of treatment, cabergoline decreased fasting blood glucose, postprandial blood glucose and HbA1C significantly. By delivering exogenous cabergoline in the morning, a circadian resetting occur within the dopamine signals and sympathetic tone within the CNS [39]. Cabergoline augments low hypothalamic dopamine levels and inhibit excess sympathetic tone in the CNS [40]. This mechanism is consistent with the studies that show both serotonin and noradrenergic levels and activity are increased and dopamine levels are decreased during the insulin-resistant state and return to normal with return to the insulin-sensitive state in animals that live in the wild and undergo seasonal changes in metabolism according to food availability [41,42]. During transition to the insulin-resistant state, basal lipolytic activity increases to spare glucose, fat oxidation becomes predominant, hepatic glucose production and gluconeogenesis rise to supply glucose to the CNS. Development of the insulin-resistant state during these periods of seasonal change precisely mimics the type 2 diabetic state. At the end of the season, animals revert back to their insulin-sensitive state with correction of these metabolic abnormalities [37,43,44].

Additional support of this mechanism was provided by the study of [45] in which chronic infusion of noradrenaline into VMH of normal animals induced severe hyperinsulinemia, insulin resistance, glucose intolerance and obesity. Increased activities of norepinephrine have been shown to increase sympathetic tone, pancreatic secretion of glucagon and insulin, and plasma glucose with rapid activation of hepatic gluconeogenesis and to increase lipolysis and plasma levels of free fatty acids, which are common features of T2DM [46].

Other study of [47] showed that administration of dopaminergic neuron neurotoxin (6-hydroxy dopamine; 6-OHDA) that selectively destroy dopaminergic terminals directed to the suprachiasmatic nuclei (SCN), show significant increase in daily food consumption and weight gain. 6-OHDA administration significantly increased plasma glucose and insulin concentration during the glucose tolerance test (GTT). Body weight gain, glucose intolerance and insulin resistance result from decreased dopaminergic input to the area of the SCN.

On the other hand, intracerebroventricular (ICV) administration of bromocriptine, dopamine receptor 2 agonist, reduced insulin resistance, glucose intolerance and hyperlipidemia in seasonal animals [11]. Such impact on regulatory systems of metabolism suggests that similar responses can be observed in humans; obese and diabetic animal models have increased hypothalamic noradrenergic and serotonergic activities and decreased brain dopamine synthesis relative to normal animals [11,48]. Bahar et al. [49] showed that cabergoline lowers FBG and A1c due to increased dopamine levels and decreased noradrenergic activities in the hypothalamus, resulting in enhanced insulin sensitivity in peripheral tissues and reduced liver gluconeogenesis and insulin resistance. Compared to bromocriptine, cabergoline is more long-acting, administered in lower doses, has fewer side effects. The hypoglycemic effect of cabergoline in our study is in agreement with the study that showed, after four months of cabergoline administration in acromegalic patients, the improvement in disease activity was accompanied by reduction in certain metabolic parameters namely fasting insulin and HbA1c [50]. The obtained results of [51] showed that antipsychotic drugs that act through dopamine 2 and serotoninergic receptors, cause metabolic disturbances characterized by weight gain, glucose intolerance, insulin resistance and beta cells exhaustion with increased risk of T2DM [13].

In our study, fasting insulin decreased by 9.79% in the group treated with gliclazide plus cabergoline compared to control levels. In the type 2 diabetic β-cells, insulin secretory rate exceeds the biosynthetic rate leading to a progressive depletion in insulin stores. Islet β-cell hyperplasia and progressive deterioration of beta cell mass and function in patients with type 2 DM may not only be the consequence of hyperglycemia, but can also be due to the compensatory insulin secretion itself. Suppression of insulin secretion induces β-cell rest, which allow β-cells to refill insulin stores, enhance the secretory capacity in the long run and increase the number of organ-specific insulin receptors leading to improved insulin sensitivity [52,53]. Inhibition of glucose stimulated insulin secretion (GSIS) can avoid long-lasting hyperinsulinemia andprevent subsequent development of insulin resistance and beta cell failure [54,55]. D2 receptors agonists give a similar action of endogenous dopamine and diminished human islet GSIS [51]. The use of dopaminergic agonists attenuated proliferative activity. The inhibition of GSIS induced by D2 agonist may occur through α2 adrenergic receptors [56,54].

These results are in agreement with the study that shows short-term treatment with bromocriptine reduces diurnal glucose and insulin concentrations in obese women. It may facilitate glucose homeostasis through sympatholytic properties in addition to a reduction in hypothalamic NPY [57].

In our work, insulin sensitivity was improved and HOMA IR decreased by 46.33% in combination group compared to control values. Reduction in plasma glucose levels is related to increased peripheral insulin sensitization via dopaminergic modulation of the hypothalamiccircuits [14]. Improvement of insulin sensitivity occur due to reduction of neuropeptide Y (NPY) that is in accordance with

the study that show chronic infusion with NPY acutely impairs the ability of hyperinsulinemia to inhibit glucose production. Reduction of hypothalamic NPY is necessary to avoid its acute inhibitory action of insulin on EGP production [58,59]. Concurrent increases of Neuropeptide Y (NPY) and coticotropin releasing hormone (CRH) in discrete hypothalamic nuclei function potentiate hyperphagia, fattening, hyperglycemia and insulin resistance. Such a consequence may contribute to increases in both parasympathetic stimulation of insulin secretion (via NPY) and sympathetic stimulation of hepatic glucose output and adipose lipolysis (via CRH). Treatment with dopamine agonist substantially reduces elevated hypothalamic neuropeptide Y (NPY) levels and paraventricular dorsomedial tract coticotropin releasing hormone in mice [22,60-62].

Twice weekly administration of long acting cabergoline within 2 hours of wakening reestablish the daily peak in SCN dopaminergic activity and consequently reverses the central abnormalities; elevations of noradrenergic and serotonergic activities at the ventromedial hypothalamus (VMH) and elevated Neuropeptide Y and corticotropin releasing hormone levels at the hypothalamic paraventricular nucleus [15].

A study of Krysiak et al. [63] that compared the effect of different dopamine agonists on carbohydrate metabolism markers in patients with elevated prolactin levels, cabergoline was superior to bromocriptine in reduction of 2 hrs post-challenge plasma glucose levels, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and improving glucose intolerance.

More than one study observed a significant improvement in glucose tolerance with a decrease in insulin levels and enhancement in insulin sensitivity regardless of prolactin levels in patients with hyperprolactinemia treated with cabergoline in addition to reduction in HbA1c in the study of [64]. The pretreatment mean values of total cholesterol, triglycerides and LDL were significantly ($p<0.05$) higher in diabetic patients before cabergoline treatment compared to that in the control results. The results of our study indicate that differences between baseline measurement and after four months of treatment with cabergoline showing statistically significant ($P<0.05$) decrease in total cholesterol, triglycerides and LDL with a significant ($P<0.05$) increase of HDL.

These results are consistent with the study that show fasting plasma glucose, LDL-cholesterol and TG in cases were similar to that of controls after completion of 6 months of cabergoline treatment, indicating cabergoline reverse these metabolic abnormalities [65]. Improvement of lipid profile after treatment by cabergoline refer to sympatholytic effects of dopamine 2 receptors activation [38,57].

The fact that circulating FFA concentrations were lower following dopamine agonist administration, is consistent with the possibility that adipose tissue had become more sensitive to the ability of insulin to inhibit lipolysis and enhance reesterification. Inhibition of hepatic lipogenesis and glucose output lead to a decrease in body-fat stores and in plasma FFA and triglyceride (TG) concentrations [66]. Total and LDL cholesterol decreased significantly after treatment with DA agonists in patients with hyperprolactinemia in addition to improvement in insulin sensitivity [67]. These results agree with the results of our study demonstrating the beneficial effect of cabergoline on reducing hyperglycemia and hyperlipidemia .

In conclusion, cabergoline normalizes increased sympathetic overactivity, enhances hypothalamic dopaminergic tone and reduces hypothalamic neuropeptide Y to improve insulin resistance and suppress hepatic glucose production. Cabergoline decreases insulin production from pancreatic beta cells to protect beta cells from hypersecretory exhaustion to increase the islet insulin content and improve β-cell response to hyperglycemia [68-70].

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