Research Article

Effect of Cabergoline on Body Weight, Glycemic Control and Insulin Resistance in Patient with Obesity and Prediabetes

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ABSTRACT

Dopaminergic hypofunction have been involved in the pathogenesis of obesity and impaired glucose homeostasis. The aim of this study is to determine the effect of cabergoline on body weight, glycemic control and insulin resistance in pre-diabetic obese patients. This 12 week prospective control clinical study randomized 44 obese pre-diabetic patients into three groups. Group 1(N=13) the control, group 2 (N=16) received metformin 500mg-850mg BID and group 3 (N=15) received cabergoline 0.25-0.5mg twice weekly. The weight loss was not different among the three groups. Significant glycemic improvement started after 8 week of cabergoline while after 4 week of metformin treatment. At the end of study, cabergoline improved glycemic control and insulin resistance greater than control group. Metformin improved glycemic control greater than cabergoline while the change in insulin resistance was not significant between metformin and cabergoline. We can conclude that cabergoline improve glycemic control and insulin resistance in obese pre-diabetic patients

Keywords: Cabergoline, Glycemic control, Insulin resistance, Obesity.

INTRODUCTION

Type 2 diabetes mellitus (T2D) is preceded by an intermediate stage known as pre-diabetes which typically represents an elevation of blood glucose levels higher than normal but lower than diabetes thresholds.[1] American Diabetes Association[2] define pre-diabetes as having either impaired fasting glucose (IFG) 100 to 125 mg/dl or impaired glucose tolerance (IGT) 140 to 199 mg/dL (2 hours after an oral load of 75 g dextrose), or Hemoglobin A1C 5.7% to 6.4% . The number of individual having pre-diabetes will increase globally to 472 million by 2030.[1] Obesity, sedentary lifestyle and high fat and saturated fatty acid diets are predisposing factors for pre-diabetes. These factors, in turn, can slowly induce peripheral and hepatic insulin resistance which places a major stress on the pancreatic B-cells and subsequently dysfunction.[3] Pre-diabetes confers a 3- to 7-fold increase in the risk of developing T2D compared with normal individuals[4] and 70% of individuals with pre-diabetes will eventually progress to T2D.[5] Therefore diagnosis of pre-diabetes presents to the health care providers with an opportunity to identify patients at increased risk for T2D and to implement interventions that can delay or prevent T2D and to minimize the burden of its complications.[5] Brain plays an important role in eating behavior and also in peripheral glucose homeostasis.[6] The central and peripheral dopaminergic system is involved in the regulation of whole-body fuel and energy homeostasis.[7] Besides dopamine role in the control of complex processes driving feeding behavior, dopaminergic neurotransmission profoundly affects both glucose and lipid metabolism.[8] Morbidly obese subjects have lower than normal D2 receptor availability and this reduction is correlated with their BMI.[9] Also in D2R knockout mice exhibited an impairment of insulin response to glucose and high fasting glucose levels and were glucose intolerant.[10] Furthermore, antipsychotic drugs, blocking the dopamine D2 receptor, have been associated with weight gain, insulin resistance and new-onset T2D.[11] The hypothalamus is a main target of dopamine agonist action to improve peripheral metabolic, autonomic, and neuroendocrine functions. Recently dopamine agonist bromocriptine has been approved for the treatment of T2D.[12] Cabergoline is a potent long-acting dopamine agonist and has high binding affinity and specificity for dopamine D2 receptors. It is more effective, better tolerated and four times more potent than bromocriptine.[13] Interestingly, beneficial metabolic effects of cabergoline on glucose level and insulin resistance have been reported in some clinical studies.[14,15] Therefore, the present study was designed to examine the metabolic effect on cabergoline on glycemic control and insulin resistance in patient with obesity and pre-diabetes.

Patient and methods

Study design

The present study is prospective randomized control clinical trial. The study is conducted from March to December /2013 and carried out in Obesity Research and Therapy Centre in Al Kindi College of medicine. This study is approved by Institutional Ethics Committee. Fasting plasma glucose (FPG) and post prandial plasma glucose (PPG) level were measured every four week during the treatment period while HbA1c, fasting insulin and HOMA-IR were measured at baseline and after 12 weeks.

Patients and study group

The potential participants for the study were obese men and women (BMI ≥ 30 kg/m^2) who attend the obesity Centre. The patients were screened by either FPG or PPG for diagnosis of pre-diabetes according to ADA guidelines criteria.[2] Patients excluded from the study were: (1) Patients on oral hypoglycemic agent or insulin; (2) patient with impaired renal or hepatic function; (3) Pregnancy or breastfeeding; (4) Patients with acute illness or chronic illness other than impaired glucose tolerance that would impact glucose metabolism or was not controlled; (5) hypersensitivity to ergot derivatives. The eligible patients were 53 and enrolled in the study. Out of the total enrolled patients, 9 patients did not complete the study due to many reasons noncompliance (3), lost to follow up (4) and develop adverse event (2). The remaining 44 patients divided into three groups I-Control group (N=13). This group only advised for dietary therapy plus life style modifications. II-Metformin group (N=16). This group treated with metformin 500-850 mg twice daily for 12 weeks plus dietary therapy & life style modifications. III-Cabergoline group (N=15). This group treated with Cabergoline 0.25 twice weekly for two week then 0.5mg twice weekly for another 10 weeks plus dietary therapy & life style modifications.

Measurements

Height and weight were obtained using a standard stadiometer and electronic scale, respectively. Body mass index was calculated using the standard formula, weight (kg)/height (m)^2. 12 hours fasting and Post prandial blood samples were collected from all subjects at zero time and after 4,8,12 weeks. 1ml of the whole blood with anticoagulant tube is used for HbA1c analysis at zero time and at 12 week. Plasma glucose was assayed by glucose-oxidase method (CromatestLinear Chemicals.S.L Spain). Glycosylated hemoglobin level was measured by a high performance liquid chromatography (Bio-Rad VARIANT^{TM}, USA). Insulin level was measured by ELISA based on sandwich principle (Demeditec Diagnostics Gmbh, Germany).Insulin resistance (HOMA-IR)was evaluated at baseline and after 12 weeks by the homeostasis model assessment (HOMA) method from the fasting glucose and insulin concentration according to the following formula[16]: HOMA-IR = (glucose × insulin)/405.

Statistical analysis

Paired Student's t test was used to compare values obtained before and after 12 week treatment in each group. Multiple comparisons were also carried out by using Analysis of variance (ANOVA) with LSD post-hoc testing to compare changes in variables between groups. Data are presented as mean ± Standard error mean (SEM). Statistical analysis of data was performed using the Statistical Package for Social Sciences software version 16.0 (SPSS, Chicago, IL).

RESULTS

Baseline characteristics of patients

44 patients completed the study protocol. All those patient were obese with BMI range from 30-42. The age range of the patients was between 23-64 years old. There was no statistically differences in the baseline characteristics between the groups table (1).

Table 1: Baseline characteristics

Parameters	Control (n=13)	Metformin (n=16)	Cabergoline (n=15)
Gender (M/F)	(5/8)	(6/9)	(5/11)
Age (years)	42.8±3.4	44.9±2.2	46.0±3.6
WT9 (Kg)	98.1±2.3	101.7±3.9	97.4.5±4.6
Height (m)	1.65±0.02	1.67±0.024	1.65±0.03
BMI (kg/m^2)	35.7±0.76	36.4±1.01	35.4±0.87
FPG (mg/dl)	116.1±1.8	117.4±1.6	116.8±1.6
PPG (mg/dl)	160.54±5.	163.2±4.4	159.3±4.7
HbA1c	6.31±0.17	6.13±0.22	6.45±0.21
Fasting Insulin (mU/ml)	12.23±1.15	11.7±0.98	12.6±1.1
HOMA-IR	3.5±0.33	3.4±0.34	3.64 ±0.32

Effect on Body weight and BMI

All the study groups demonstrated a significant decrease in the body WT and BMI at the end of 12 weeks compared with the baseline. But the change was not significant among the three groups. Table (2)

Table 2: Body weight (WT), body mass index (BMI) before and after 12 week treatments and the change from baseline

Parameters	Time	Control	Metformin	Cabergoline
WT	Baseline	98.1±2.3	101.7±3.9	97.4.5±4.6
	12week	94.9±1.9*	96.8±3.2*	93.2±4.5*
	Change	3.15±1.14	4.9±1.3	4.2±0.76
BMI	Baseline	35.7±0.76	36.4±1.01	35.4±0.87
	12week	34.6±0.93*	35±0.84*	34.1±0.86*
	Change	-1.1 ±0.49	-1.4±0.45	-1.3±0.23

*=p< (0.05) comparing with baseline

Effect of study treatment on glycemic parameters (FPG & PPG)

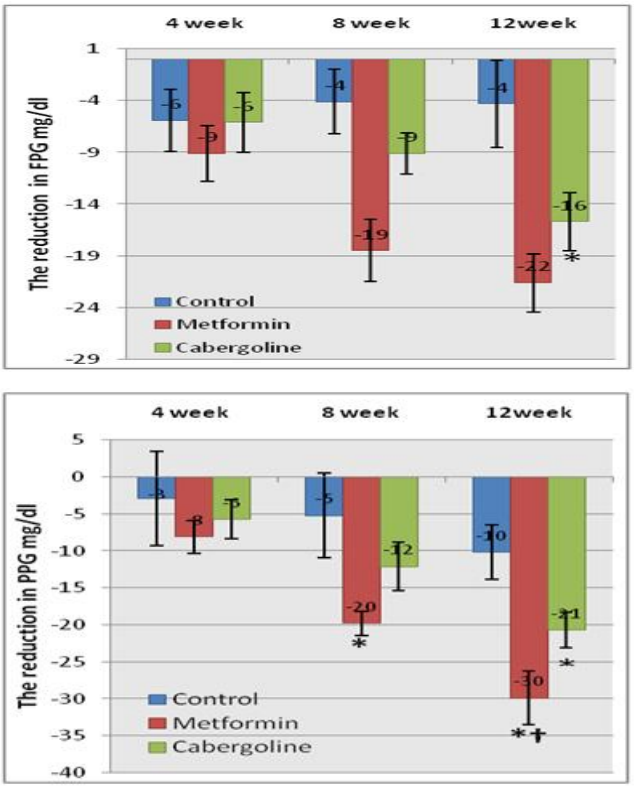
In comparing with baseline; Control group showed no significant improvement in FPG over the 12 weeks of the study while a significant decrease was noted in PPG after 12 week (P<0.05). Metformin significantly improved FPG and PPG after 4 weeks (P<0.05) and highly significantly improved after 8 and 12 weeks (P<0.001). In cabergoline group, the decrease in FPG and PPG was not significant after 4 weeks while the decrease was significant (p<0.05) after 8 weeks and highly significant after 12 weeks (P<0.001) Table (3). In comparing with control group, the

reductions in FPG & PPG were significantly greater in metformin group at week 8 and 12 of the study (P<0.05) while in Cabergoline group, the reduction FPG and PPG was significantly greater at week 12 (p<0.05) Figure (1) & Figure (2). In comparing of Cabergoline vs. metformin, the reduction in FPG was significantly greater in metformin group at week 8 (P<0.05) but not significant at week 4 and12. PPG dropped more significantly in metformin group at week 12 but not at week 4 & 8.

Table 3: Treatment effect on FPG (mg/dl) and PPG (mg/dl) at the different duration of the study

Parameters	Time	Control	Metformin	cabergoline
FPG (mg/dl)	0week	116.1±1.8	117.4±1.6	116.8±1.6
	4week	111.2±1.9	108.3±2.0*	110.8±2.3
	8week	112.1±2.7	98.9±2.2**	107.7±1.4*
	12week	111.8±3.3	95.7±1.8**	101.2±2.4**
PPG (mg/dl)	0week	160.54±5.	163.2±4.4	159.3±4.7
	4week	154.2±5.3	153.4±3.8*	154.4±5.2
	8week	156.7±3.7	144.0±4.9**	149.7±3.9*
	12week	150.3±5.0*	133.3±3.3**	138.6±3.7**

*=p< (0.05) and **=P (<0.001) comparing with baseline



*=p< (0.05) comparing with the control, †=p<0.05 comparing between Metformin & Cabergoline

Figure 1: Comparison of the reduction in fasting glucose level

Effect on HbA1c

HbA1c significantly decreased in both metformin and Cabergoline groups (P<0.05) but not in the control group after 12 week compared with the baseline However, the change in HbA1c was statistically significant in metformin vs. control (P<0.05) but not in Cabergoline vs. control. Table (4).

Table 4: HbA1c before and after 12 week and the change from baseline

Parameters	Time	Control	Metformin	Cabergoline
HbA1c	0week	6.31±0.17	6.13±0.22	6.45±0.21
	12week	6.2±0.18	5.51±0.16*	6.05±0.15*
	Change	0.09±0.18	-0.62±0.17†	-0.4±0.17

*=p< (0.05) comparing with the baseline, †=p<0.05 comparing with the control

Effect of the study treatment on fating insulin level and insulin resistance (HOMA-IR)

Statistically significant decrease in fasting insulin level was observed in both metformin and Cabergoline group after 12 weeks of the treatment (P<0.05) compared the baseline while there was no significant decrease over time in the control group. The changes in fasting insulin level of metformin vs. control and Cabergoline vs. control were statistically significant (P<0.05) but not in Cabergoline vs. metformin. Regarding HOMA-IR, the decrease was highly significantly in metformin (P<0.001) and significantly in Cabergoline after 12 week (P<0.05) compared to the baseline but not significant in the control group statistically significant changes were observed in metformin vs. control and Cabergoline vs. control (P<0.05) while the change between metformin and Cabergoline was not significant. Table (5)

Table 5: Fasting insulin level and HOMA-IR before and after 12 week and the change from baseline

Parameters	Time	Control	Metformin	Cabergoline
Insulin	Baseline	12.23±1.15	11.7±0.98	12.6±1.1
	12week	11.84±1.21	8.3±0.75*	9.9±0.84**
	Change	-0.31±0.7	3.4±0.8†	-2.7±0.5†
HOMA-IR	Baseline	3.5±0.33	3.4±0.34	3.64 ±0.32
	12week	3.36±0.42	2.0±0.2*	2.52 ±0.26*
	Change	-0.11±0.27	-1.4±0.2†	-1.12±0.18†

*=p< (0.05), **=p (<0.001) comparing with the baseline, †=p<0.05 comparing with the control.

DISCUSSION

Effect on body weight and body mass index

Obesity is the result of a disproportionately high energy intake compared to energy expenditure. The hypothalamus play a pivotal role in regulation of food intake and energy expenditure as well as the utilization and partitioning of nutrients, the regulation of glucose homoeostasis and peripheral lipid metabolism.[17] Central dopaminergic signaling has been implicated in the regulation of feeding behavior, insulin sensitivity and energy partitioning.[7,8] Antipsychotic drugs that block D2 receptors are associated with increased appetite and

metabolic disturbances that include weight gain, exacerbations of preexisting diabetic conditions and development of new-onset diabetes.[18] Conversely, whereas drugs that increase brain dopamine concentration, are anorexigenic.[19] However the previous studies showed controversy regarding the effect of central dopamine agonist on the body weight and BMI. Some studies demonstrated significant weight loss with dopamine agonist therapy[20,21] while other studies did not show significant effect on body weight.[15,22] In The current study, although significant weight loss was observed in all study groups over 12 week, Cabergoline plus dietary/life style modification did not lower body weight more effectively than dietary/life style modification alone . The reasons behind this discrepancy in effect of dopamine agonist on body weight may be due differences in the duration of the study, dietary and life-style modifications and patient characteristics.

Effect of Cabergoline on glycemic control

This is the first study that examined the effect of Cabergoline on glycemic control in obese treatment naïve pre-diabetes. Our data suggested that Cabergoline plus dietary/life style modifications significantly lowered FPG & PPG. This reduction in FPG and PPG was evident after 8 and 12 week of Cabergoline treatment. The reductions in FPG and PPG were significantly greater in cabergoline group than control group after 12 week. In metformin groups, significant glycemic improvement observed at week 4 which is earlier than that achieved by Cabergoline. This slow onset of effect of Cabergoline might be attributed to the complex mechanism of acting through CNS and/or might be related to the dosing regimen. Interestingly the reduction in FPG by Cabergoline was comparable to that of metformin at the end of study. However Metformin decreased FPG significantly more at week 8 and decreased PPG significantly greater at week 12 compared with Cabergoline treated group.

The findings of present study are consistent with results of the following clinical studies. In 16 week placebo control study on healthy obese person, PPG decreased overtime after Cabergoline treatment.[15] Additionally, Cabergoline significantly decreased FPG in 19 patients with prolactinoma independently from the changes in prolactin level.[14] Furthermore, in a preliminary open-label study of 12 nondiabetic obese hyperinsulinemic subjects, bromocriptine (1.6 mg/day for 2 weeks) reduced FPG and PPG without change in body weight.[21] Similarly, short term bromocriptine treatment 2.5mg BID significantly reduce fasting glucose and diurnal glucose concentration in obese women.[22] In patient with Cushing disease, also it has been demonstrated that fasting serum glucose and the prevalence of impaired glucose tolerance or diabetes mellitus significantly decreased during long term Cabergoline treatment independently of the change in cortisol secretion.[23]

The reduction of HbA1c overtime was significant in metformin and Cabergoline group respectively but not in control group. However Metformin reduced HbA1c significantly more than control group but the difference between Cabergoline and control group was not significant which might be attributed to the slow effect of Cabergoline in achieving glycemic control and the short period of the study. To our knowledge, there is only one published clinical study demonstrated the effect of Cabergoline on glycemic control in T2D. Our findings are consistent with this study which Cabergoline (0.5 mg weekly) for 3 months reduced both FPG and PPG and caused 0.45–1.11 reduction in HbA1c in patient with failure to oral antidiabetic agent.[24] Additionally, The HbA1c level of a ten patient with acromegaly decreased significantly from 7.05 % to 6.15 % after 16 week Cabergoline therapy and when a subgroup analysis was performed between diabetic and non-diabetic, interestingly, the reduction in HbA1c was more pronounced in the six diabetic patients (from 8.4 % to 6.7 %) compared to no significant reduction of the four non diabetics (from 6.1 % to 5.8 %).[25] Dopamine agonist therapy improved glucose and energy homeostasis by central mechanism through activation of dopamine receptor D1 & D2 in the hypothalamus leading to improve hypothalamic dopaminergic tone and inhibit ventromedial hypothalamic noradrenergic and serotonergic activity, thus improving peripheral glucose disposal and insulin resistance.[26] In addition to that, dopamine regulate food intake by modulating food reward and motivation via the meso-limbic circuitry of the brain, thus suppressing hunger and improving satiation and satiety.[27]

Effect of cabergoline on fasting insulin and insulin resistance

Insulin resistance and beta-cell dysfunction are key player in pathophysiology of prediabetes.[1,3] The HOMA or log (HOMA) model has proved to be a robust clinical and epidemiological tool for the assessment of insulin resistance (HOMA-IR) and has been widely used in large epidemiological studies, prospective clinical trials, and clinical research studies. It has been reported in > 500 publications.[28] Therefore the present study used this model to assess insulin resistance. Obesity, hyperinsulinemia, insulin resistance and glucose intolerance have been frequently described as metabolic consequences in patients with hyperprolactenoma. Several recent studies have been demonstrated a significant improvement of these metabolic abnormalities reflected by a significant reduction in fasting insulin and HOMA-IR with a significant increase in insulin sensitivity index after cabergoline treatment independent from the changes in BMI and normalization of prolactin level.[29,30] Furthermore, in health obese person, demonstrated tendency towards stabilization or improvement in HOMA-IR and insulin AUC after 16 week of cabergoline treatment while there was a tendency for HOMA-IR and insulin AUC to increase by (40% and 16%, respectively) in the placebo group[15]. All these findings are suggesting a direct beneficial effect of dopamine agonist on insulin

resistance. The results of present study were in agreement with these findings. We found a significant decrease in fasting insulin and HOMA-IR after 12 week of Cabergoline treatment and these improvements were significantly greater than control group. Although metformin profoundly reduce fasting insulin and HOMA-IR, the difference was not significant between metformin and Cabergoline. Basal hyperinsulinemia, insulin resistance and disturbances in insulin release are the characteristic metabolic abnormalities of obesity-associated diabetes.[31] Basal hyperinsulinemia generates and sustains insulin resistance in all tissue having insulin receptor including pancreatic B-cell and the brain. Basal hyperinsulinemia perpetuates insulin resistance by several mechanisms, reduction in number of insulin receptor, serine phosphorylation of IRS-1 and elevated level of inflammatory markers, including cytokines and C-reactive protein.[31,32] The endogenous dopamine acts in an autocrine/paracrine manner on the insulin-secreting β-cells that express D2-like receptors to regulate insulin release.[33] Activation of D2R on islet Beta-cells by dopamine agonist result in inhibition of insulin secretion.[34] This can explain the effect of cabergoline in lowering fasting insulin level. In a counterintuitive manner, the ability of dopamine agonist to suppress insulin secretion might be at the basis of its beneficial effect on glucose homeostasis by preventing long-lasting hyperinsulinemia and therefore prevent subsequent development of insulin resistance and beta cell failure.[35,36]

CONCLUSION

Cabergoline is effective in improving glycemic control and reducing basal hyperinsulinemia as well as insulin resistance. However Cabergoline effect is slow and not profound as that of metformin.

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