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Effect of Cabergoline added to Metformin on Glycemic Control, Insulin Resistance and Beta Cell Function in Obese type 2 Diabetic Patients

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Abstract- The aim of this study is to examine the effect of cabergoline added to metformin on glycemic control, insulin resistance and B-cell function in obese type 2 diabetic patients. Forty obese patients with newly diagnosed type2 diabetes were enrolled in this study and randomized by 1:1 ratio into group (I) receives metformin and group (II) receives metformin plus cabergoline for 12 week. We evaluated fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) every 4 week while body weight, glycosylated hemoglobin, fasting plasma insulin, homeostasis model assessment of insulin resistance (HOMA-IR) and B-cell function (HOMA-B) at the baseline and after 12 week. At the end of the study, Cabergoline plus metformin significantly improved FPG, PPG and HOMA-IR more than metformin alone. Beta-cell functions significantly improved by cabergoline plus metformin but not by metformin alone after 12 week compared with baseline. We can conclude that cabergoline added to metformin improved glycemic control and insulin resistance better than metformin alone.

Keywords: cabergoline, glycemic control, insulin resistance, beta-cell function, obesity, type 2 diabetes.

I. Introduction

Type2 diabetes is a complex heterogeneous metabolic disorder of glucose homoeostasis characterized by insulin resistance and impaired B-cell function, as well as dysfunction in multiple other organs or tissues[1]. There is strong association between obesity and T2D development[2]. The incidences of T2D have tripled over the past 30 years mainly because of the global prevalence of obesity[3]. Al though insulin resistance and B-cell dysfunction represent the core defect in pathophysiology of T2D, the Ominous Octet theory of de Fronzo implicates multiple abnormalities in T2D[4]. The brain, as seat of cerebral insulin resistance and neurotransmitter dysfunction, is described as eighth pathophysiologic factor this theory[4]. Plethora of evidence indicated that reduced dopaminergic neurotransmission in the hypothalamus and subsequently enhanced noradrenergic activities in the ventromedial hypothalamic nuclei are directly and casually involved obesity and Insulin resistance[5]. It is fact that obesity and T2D appear to be important side effects dopamine D2 receptorsblocker[6]. Additionally obese individuals have significantly lower D2/D3 receptor levels, which make them less sensitive to reward stimuli and put them at risk for overeating[7]. Chronic over nutrition can trigger Hypothalamic neuroinflammation and stressors like ER stress which impaired insulin signaling in the CNS, central insulin resistance,leads to hyperphagia, weight gain and consequently to hyperinsulinemia as well as hyperglycemia[8,9]. Because of the complex and multifactorial pathogenesis, it is difficult to restore normoglycemia and unlikely to achieve glycemic target by single antidiabetic agent. Therefore there is continuous need to develop new antidiabetic agents that have different mechanism of action targeting known pathogenic abnormalities and can be use in combination to produce an additive effect[4]. Timed-release bromocriptine is the first centrally acting dopamine agonist used for the treatment of T2D as monotherapy and combination with metformin[10]. Cabergoline is a centrally acting dopamine agonist with high specificity for dopamine D2 receptors and binding affinity lasting up to 72 hours. It is more effective, better tolerated and four times more potent than bromocriptine[11]. Some clinical studies reported direct beneficial metabolic effects of cabergoline on glucose level, insulin resistance and inflammation[12, 13]. Therefore this study performed to examine the effect of cabergoline added to metformin on glycemic control, insulin resistance and B-cell function in patients with obesity and T2D.

II. Patient and Methods

a) Study design

The present study is prospective randomized control clinical trial. The study is conducted from March to December /2013 in Obesity Research and Therapy Centre /Al Kindi College of medicine and in Al kindi Specialized Center for Endocrinology and Diabetes in Baghdad. 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

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HbA1c, fasting insulin and HOMA-IR and HOMA-B, were measured at baseline and after 12 weeks.

b) Patients and study group

Forty patients were recruited and enrolled in this study. The included patients were men and women with BMI (BMI ≥ 30 kg/m^2)and with newly diagnosed ofT2D 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 chronic cardiovascular or inflammatory diseases (5) hypersensitivity to ergot derivatives. The patient randomized by 1:1 ratio into two group: Group (I) treated with Metformin 500-850mg three time daily(N=20) and Group (II) treated with metformin 500-850mg three time daily and cabergoline 0.5mg twice weekly (N=20).The treatment and follow up period was 12 week. All patientswere advised for standard dietary therapy and life style modifications.

c) 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. Plasma glucose was assayed by glucose-oxidase method (Cromatest Linear Chemicals.S.L Spain). Glycosylated hemoglobin level was measured by a high performance liquid chromatography (Bio-Rad VARIANT™, USA). Insulin was measured ELISA (Demeditec Diagnostics Gmbh, Germany). Insulin resistance and β-cell function were evaluated by the homeostasis model assessment (HOMA) method which has been suggested as a method to assess insulin resistance (HOMA-IR) and β-cell function (HOMA-β) from the fasting glucose and insulin concentration according to the following formula[14]:HOMA-IR = (glucose × insulin)/405 and HOMA β-Cell=360 ×Fasting insulin (mU/ml)/ (Fasting glucose (mg/dl) — 63)

d) Statistical analysis

Paired Student's t test was used to compare values in same group at different time with baseline. Independent sample t-test was used to compare changes in variables between the two 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)

III. Result

a) Patient's characteristics

Out of the total enrolled patients, 8 patients did not complete the study due to many reasons noncompliance (1), lost to follow up (4), start oral hypoglycemic agent (2) and develop adverse event (1). The remaining 32 patient (17 patients in metformin treated group and 15 patients metformin plus cabergoline treated group). The demographic and baseline clinical characters were not different between the two. Table (1)

Table 1 : Baseline characteristics

Parameters	Metformin (n=17)	Metformin+ Cabergoline (n=15)
Gender(M/F)	(6/11)	(5/10)
Age(years)	44.35±2.5	47.6±2.8
WT(Kg)	99.6±2.4	101±3.0
Height (m)	1.66±0.3	1.65±0.2
BMI(kg/m^2)	36.5±0.89	36.8±0.61
FPG(mg/dl)	161.5±4.7	165.5±5.4
PPG(mg/dl)	205.3±6.9	211.1±6.4
HbA1c	7.95±0.29	8.39±0.34
Fasting Insulin(mU/ml)	16.76±1.3	17.8±1.6
HOMA-IR	6.8±0.67	7.4±0.9
HOMA-B%	62.±4.3	63.3±5.2

b) Effect body weight and BMI

Both group 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 between the two groups. Table (2)

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

Parameters	Time	Metformin	Metformin+ cabergoline
WT	Baseline	99.6±2.4	101±3.0
	12week	95.5±2.3*	95.4±3.1*
	Change	4.1±1.1	5.6±1.5
BMI	Baseline	36.5±0.89	36.8±0.61
	12week	35.0±0.72*	34.9±0.78*
	Change	-1.5±0.47	-1.9±0.54

**=p< (0.05) comparing with baseline*

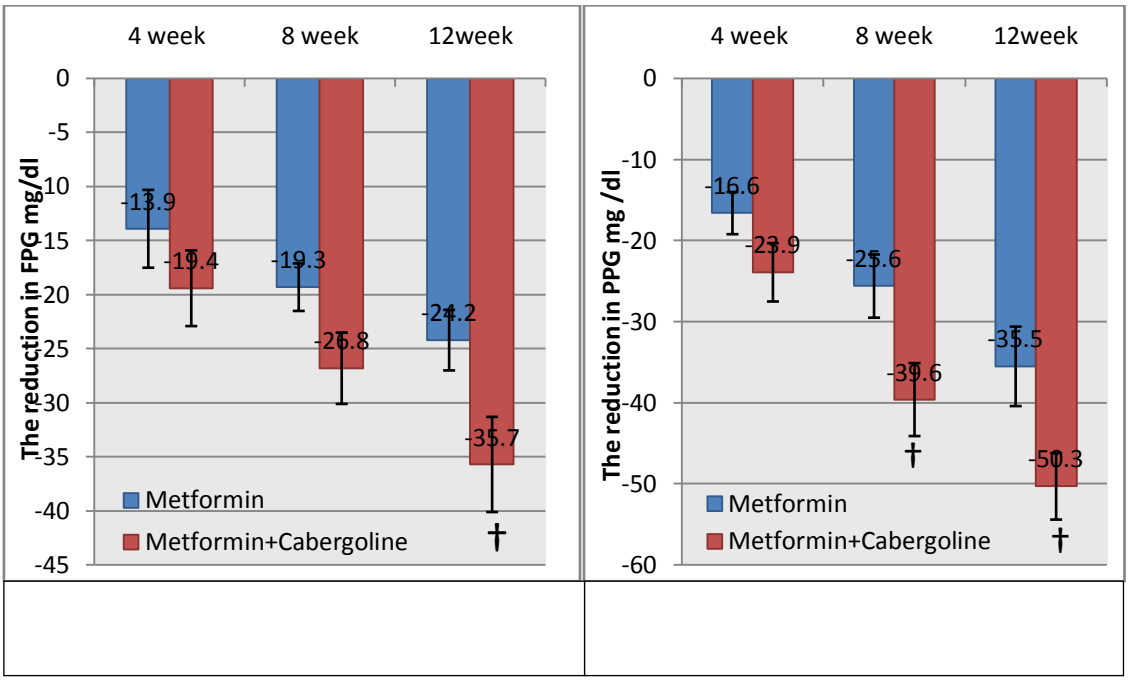
c) Effect of study treatment on glycemic parameters (FPG &PPG)

Both group significantly improved FPG and PPG over time compared with baseline Table(3). The reduction in FPG was significntly greater in metformin plus cabergoline than metformin alone at 12 weeks. Also Metformin plus cabergoline reduced PPG significantly greater than metformin alone at week 8 and 12.

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

Parameters	Time	Metformin	Metformin+ cabergoline
FPG (mg/dl)	0week	161.5±4.7	165.5±5.4
	4week	147.7±5.4*	145.7±6.9**
	8week	142.1±3.7**	138.5±5.0**
	12week	137.4±5.9**	129.7±4.5**
PPG (mg/dl)	0week	205.3±6.9	211.1±6.4
	4week	183.4±7.0*	187.6±6.5**
	8week	174.4±6.2*	171.5±5.4**
	12week	169.8±4.8**	160.8±4.6**

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



†=(p<0.05) in comparing of metformin plus cabergoline group with metformin group

d) Effect on HbA1c

Highly significant (P<0.001) decrease was observed in the two groups after 12 weeks compared to baseline. However, the reduction in HbA1c was not statistically significant between them. Interestingly, the percentage of patients achieving HbA1c <7.0% was 60% by adding cabergoline to metformin vs 41 % by metformin alone.

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

Parameters	Time	Metformin	Metformin+ cabergoline
HbA1c	Baseline	7.95±0.29	8.39±0.34
	12week	7.05±0.23**	7.17±0.29**
	Change	-0.9±0.16	-1.22±0.14

***=P (<0.001) comparing with baseline*

e) Effect of the study treatment on fating insulin level, HOMA-IR and HOMA-B

The decrease in fasting insulin level was significant in metformin group (P<0.05) and highly significant in metformin plus cabergoline after 12 week (P<0.001) compared to the baseline however there was no significant differences between the two group. HOMA-IR decreased significantly in both group after 12 week compared with the baseline (P<0.001). The change in HOMA-IR was significantly greater in metformin plus cabergoline compared with metformin group (P<0.05).HOMA-B% significantly increased by adding cabergoline with metformin (P<0.05) but not by metformin alone (P>0.05) after 12 weeks compared with the baseline However the change in HOMA-B% between the two group was not significant.

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

Parameters	Time	Metformin	Metformin+ cabergoline
Insulin mU/ml	Baseline	16.76±1.3	17.8±1.6
	12week	14.47±1.8*	13.9±1.3**
	Change	2.3±0.95	3.9±0.52
HOMA-IR	Baseline	6.8±0.67	7.4±0.9
	12week	5.2±0.79**	4.5±0.48**
	Change	-1.6 ±0.35	-2.88±0.45†
HOMA-B	Baseline	62.±4.3	63.3±5.2
	12week	69.1±5.7	78.5±7.8*
	Change	7.1±4.5	15.2±5.4

**=p< (0.05) and **=P (<0.001) comparing with baseline, †= (p<0.05) in comparing of metformin plus cabergoline group with metformin group.*

IV. Discussion

a) Effect of cabergoline on glycemic control

This is the first study that examined the effect of cabergoline on glycemic control in treatment naïve T2D with obesity. This study demonstrated a beneficial effect of cabergoline in reducing the hyperglycemia in patient with obesity and newly onset diabetes because add on therapy of cabergoline with metformin improved FPG after 12 week and PPG after 8 and 12 week to significantly greater degree than metformin alone. Although the decrease in HbA1c was higher by adding cabergoline to metformin than metformin (1.22±0.14 and -0.9±0.16 respectively), the difference between them was not significant which might be attributed to the slow effect of cabergoline in achieving glycemic control and the short period of the study. However the percentage of patient reaching to target HbA1c <7.0% was 60% by taking cabergoline along with metformin vs 41 % by metformin monotherapy. At the present time, there is only one published clinical study demonstrated the effect of cabergoline on glycemic control in T2D in which 3 month cabergoline treatment reduced both FPG and PPG as well as caused 0.45–1.11 reduction in HbA1c in patient with failure to oral antidiabetic agent[15]. Also 16 weekcabergoline treatment decreased PPG overtime in healthy obese[12]. Similarly, short term bromocriptine treatment 2.5mg BID significantly reduce FPG and diurnal glucose concentration in obese women[16]. Interestingly, The HbA1c level of a ten patient with acromegaly decreased significantly in the six diabetic patients (from 8.4 % to 6.7 %) compared to no significant reduction of the four non diabetics after 16 week of cabergoline therapy[17]. Furthermore, cabergoline treatment improved glycemic tolerance and decreased

HbA1c in patients with prolactinoma regardless of the degree of reduction in prolactin levels[18]. Most recently, cabergoline was superior tobromocriptine in reducing 2-hr post-challenge plasma glucosedespite a similar reduction in plasma prolactin levels[19]. More over the findings of the present study are in fundamental agreement with responses of centrally acting dopamine agonist, bromocriptine, obtained in T2D[10, 20]. More recently, the combination of bromocriptine with metformin significantly decreased FPG, PPG, and HbA1c compared with metformin alone in T2D[21]. The mechanism by which dopamine agonist therapy improve glycemic control can be explained by

1. Activation of dopamine receptor D1& D2 in the hypothalamus normalizes multiple hypothalamic neurophysiological derangements through enhancing hypothalamic dopaminergic tone and consequently preventing ventromedial hypothalamic noradrenergic and serotonergic over activity, as well as reverting elevated paraventricular hypothalamic neuropeptide Y and corticotrophin-releasing in obese T2D, thus improving peripheral glucose disposal and insulin resistance as well as suppressing of hepatic glucose production[22,23].
2. Regulation food intake by modulating food reward and motivation via the meso-limbic circuitry of the brain, thus suppressing hunger and improving satiation and satiety[7].
3. Activation D2 receptors present on pancreatic beta cells lead to increase the islet insulin content and restores the link between glucose sensing and insulin secretion, thus improving beta cell response to hyperglycemia[24].

b) Effect of cabergoline on insulin resistance and beta-cell function

The relationship between insulin resistance and beta cell dysfunction is dynamic and largely dependent on the metabolic state that is primarily determined by glycemic status and consequently insulinemic status[25].The Homeostasis Model Assessment (HOMA)has considered as a robust clinical tool for the assessment of insulin resistance and has been reported in > 500 publications[26]. Therefore the present study used this model to assess insulin resistance and B-cell function.

Cabergoline therapy profoundly improved the metabolic abnormalities; such as Obesity, hyperinsulinemia, insulin resistance and glucose intolerance associated with hyperprolecteno main dependent from the changes in BMI and normalization of prolactin level. Several Recent studies demonstrated a significant reduction in fasting insulin and HOMA-IR[13,18]as well as a significant improvement in insulin sensitivity indexassessed by both ISI Matsuda and clamp[27,28]. Furthermore, Gibson et al demonstrated tendency towards stabilization or improvement in HOMA-IR and insulin AUC after 16 week of cabergoline treatment in health obese person[12]. Moreover, two week of Bromocriptine treatment reduced fasting plasma insulin level by 35.0% and insulin resistance (HOMA-IR) by 38% and also considered as unique postprandial insulin Sensitizer[29]. All these findings are suggesting a direct beneficial effect of dopamine agonist on insulin resistance.The results of present study further supported this effect of cabergoline because the reductions in fasting insulin and insulin resistance (HOMA-IR) were higher by taking cabergoline with metformin than metformin alone.

Basal hyperinsulinemia associated with obesity and T2D, generates and sustains insulin resistance in all tissue having insulin receptor including pancreatic B-cell and the brain 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[30,31]. Endogenous dopamine regulates insulin release by acting D2 receptors expressed on pancreatic B-cell[32]. It was found that the administration of neuroleptic drugs, D2R-blocker, causes hyperinsulinemia in normal subjects[33].Thus activation of D2R on islet Beta-cells by dopamine agonist result in inhibition of insulin secretion[34].Counterintuitively, 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]

Pancreatic B-cell dysfunction associated with the obesity and insulin- resistant state is characterized by an increased basal insulin secretory rate and a blunted GSIS. Preclinical studies have suggested that treatment with dopamine agonist normalizes basal insulin secretory rate and GSIS and increases the islet insulin content thus improving pancreatic beta cell function[24,34]. The mechanism by which dopaminergic therapy improves islet function in the obese diabetic condition may involve improving B-cell glucokinase (GK), an integral modulator of GSIS, and/or GLUT2 as well as enhancing insulin storage and/or retention, and stabilizing B-cell hyperplasia, thus reducing basal insulin levels[36]. In the present study, interestingly, the combination of cabergoline with metformin significantly improved HOMA-B after 12 week compared with baseline but not by metformin alone. Currently, only two clinical studies in which cabergoline effect on HOMA-B was evaluated. Cabergoline did not show significant effect on HOMA-B in patient with Cushing syndrome[37]while HOMA-B was significantly improved after 24 month of cabergoline treatment compared to baseline in patient with hyperprolactenoma[37]. In contrast to HOMA-IR, it is controversial whether HOMA-B is an accurately reflected pancreatic β-cell function[39]. In

general HOMA model is used 20 times more frequently for the estimation of IR than β-cell function because B-cell dysfunction is longer model and hence the use of HOMA-B associated with some limitations[25]. Therefore the period of the present study is a major limitation to accurately assess the effect on beta cell function.

V. Conclusion

The combination of cabergoline with metformin significantly improved glycemic control and insulin resistance better than metformin alone in patient with obesity and diabetes. Also the combination might have beneficial protective effect on B-cell of pancreas.

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