Efficiency of Bromocriptine in Glycemic Control and Cardiovascular and Microvascular Complications in Patients with Poorly Controlled Diabetes: A Clinical Trial

Mitra Niafar[1], Nooshin Milanchian[2], Kavous Shahsavari Nia[3], Majid Zamani[4], Amir Ghafarzad[4], Seyed Vahid Seyed Hosseini[5], Mohammad Reza Jafari Nakhjavani[6*]

[1-] Associate Professor of Endocrinology, Bone Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
[2-] Endocrinologist, Bone Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
[3-] Assistant Professor of Emergency Medicine, Road Traffic Injury Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
[4-] Assistant professor of Emergency Medicine, Emergency Department, Faculty of Medicine, Isfahan University of medical sciences, Isfahan, Iran.
[5-] General Surgeon, Surgery ward of Shahid Mahallati Hospital, Tabriz, Iran.
[6-] Assistant Professor of Rheumatology, Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
dr_mrjn@yahoo.com

Abstract: Background: Available studies are seeking new treatments to control diabetes. Thus, the current study aimed to assess the efficiency of Bromocriptine in glycemic control and complications of diabetes. In this clinical trial, 43 patients with poorly controlled type II diabetes were treated with oral Bromocriptine 2.5 mg twice/day. Anthropometric factors, blood glucose, hemoglobinA1C level, waist circumference and blood pressure were assessed for 6 months. To assess the efficiency of Bromocriptine in microvascular and cardiovascular complications of diabetes, serum Hemocysteine and hs.CRP levels were measured. The analyses were performed by paired t-test and repeated measures ANOVA. **Results:** The mean baseline fasting blood glucose of patients reached from 184.3 mg/dl to 155.6, 148.9 and 159.5 mg/dl in the first 45days, the third month and the sixth month, respectively, and2-hour postprandial blood glucose declined from 276.6 mg/dl to 217.0, 205.1 and 201.0mg/dl ($p< 0.0001$). It is worth noting that in the third month a 0.8% reduction was observed in hemoglobin A1C that this reduction reached 0.9% in the six month ($p<0.0001$). Although Hemocysteine level ($p=0.058$) and hs.CRP ($p=0.056$) increased within six months of the study, the increase was not statistically significant. **Conclusions:** The findings of the current study showed that Bromocriptine as a concomitant therapy effectively reduced fasting blood glucose, 2-hour postprandial blood glucose and hemoglobin A1C.

[Niafar M, Milanchian N, Shahsavari Nia K, Zamani M, Ghafarzad A, Seyed Hosseini SV, Jafari Nakhjavani MR. **Efficiency of Bromocriptine in Glycemic Control and Cardiovascular and Microvascular Complications in Patients with Poorly Controlled Diabetes: A Clinical Trial.** *Life Sci J* 2017;14(4):1-8]. ISSN: 1097-8135 (Print) / ISSN: 2372-613X (Online). http://www.lifesciencesite.com. 1. doi:10.7537/marslsj140417.01.

Keywords: hs.CRP, hemoglobin A1C, Bromocriptine

1. Introduction

In recent decades, the prevalence of type 2 diabetes associated with obesity has become a worrying trend. Statistics show that one third of the children born in the last decade will eventually develop type II diabetes (Johnson, 2009). If the condition persists, the number of people with diabetes will exceed all estimates. Diabetes increases the incidence rate of cardiovascular, renal, ocular and neuropathic problems and leads to early disability and death (Whiting, 2011). The diseases with a lot of complications can affect the quality of life of patients with diabetes and impose heavy economic costs on patients and society. In the United States, the direct and indirect health care costs associated with this disease, are estimated 176 and 69 billion USD per year, respectively, and the average life expectancy of diabetic people is 10-15 years less than that of the general population (Home, 2012). Furthermore in Iran, the direct and indirect costs of the disease are estimated 2.04 and 1.73 billion USD annually (Javanbakht, 2011). The high prevalence of diabetes and the staggering costs of treating and caring for that has made diabetes the primary cause of death and disability in the world among the chronic diseases. This illustrates the necessity of serious attention to diabetes.

Achieving treatment goals can prevent the incidence of complications and improve the disease outcome, but unfortunately achieving this goal is observed in only 50-70% of patients (American Diabetes Association, 2008). Over past 15 years modern methods of treating diabetes have made remarkable progress due to researchers' knowledge of the exact pathophysiology of this disease. Thus, the therapeutic goals have intervened in the pathogenetic

mechanisms that have been recently discovered (Nathan, 2007). However, in many cases, there is no desirable control on the disease yet (Kahn, 2006) and although new medical treatments have delayed the disease progression, most of them are too expensive. Furthermore, detailed information regarding their long-term efficiency is not available (Nathan, 2007; DeFronzo, 2009).

Treatment goals in type 2 diabetes have been established based on the effective control of glucose, lipids and blood pressure to minimize the long-term consequences of the disease. These objectives, according to guidelines of the American Diabetes Association (2008), include maintaining hemoglobin A1C level less than 7%, maintaining the fasting blood glucose level between 70 and 130 mg/dl and maintaining 2-hour postprandial glucose less than 180 mg/dl. For this purpose, different strategies have been suggested including lifestyle modification, increased mobility, improvement in nutritional status and ultimately therapeutic intervention (Nathan, 2007). Metformin, insulin stimulants (sulfonylureas and glinides), glucosidase inhibitors, thiazolidinediones (PPARγ agonists) are the most important medical treatments used nowadays (Imam, 2012). But despite these measures, response to treatment is reduced by disease progression with the passage of time. Therefore, access to new treatments is one of the basic needs that should be noted. Several attempts have been made to discover new drugs and new treatments with the aim of preventing or delaying disease course that in some cases have been successful. One of these drugs which have been attended recent years is Bromocriptine. Bromocriptine has attracted special attention to itself on the control of type II diabetes as a sympathomimetic and D2 dopamine receptor agonist (Gaziano, 2010).

Bromocriptine is an ergot derivative at D2 dopamine receptor agonist (Southern, 1990; Pijl, 2000). Studies suggest that Bromocriptine can reverse many metabolic changes associated with obesity in the central nervous system (Southern, 1990; Cincotta, 1991), prevent or reverse the seasonal obesity and insulin resistance; reduce hepatic glucose production in mammals and cause weight loss and improve glucose tolerance in obese people (Cincotta, 1996; Gibson, 2012). This drug can reduce mean plasma glucose, triglyceride and free fatty acids with no impact on weight (Kamath, 1997). In the end, it should be stated that Bromocriptine reduces body fat stores, improves glycemic control and decrease patients' need for hypoglycemic drugs (DeFronzo, 2011). Although the drug was proposed by the Food and Drug Administration in 2010 as an adjuvant therapy to control type II diabetes (Svacina, 2012), the results of studies used by FDA as the basis to confirm Bromocriptine have not yet published, so the methodology and results of these studies have not been assessed.

Furthermore, little is known about the drug efficiency in controlling diabetes complications. Cardiovascular diseases are one of the major complications of diabetes.

Inflammation has a key role in the pathogenesis of cardiovascular complications and measurement of high-sensitivity C-reactive protein (hsCRP) –a sensitive marker for detection of systemic inflammation – can help identify patients at high risk of ischemic heart diseases, insulin resistance and hyperglycemia. Furthermore, elevated serum Hemocysteine levels (Hyperhomocysteinemia) is an independent factor for increased incidence of microvascular diseases including coronary artery disease. The studies suggest that serum Hemocysteine levels in patients with type II diabetes are higher than normal levels (Ghassibe-Sabbagh, 2012; van Meurs, 2013). These researches suggest that hyperhomocysteinemia is observed only in patients with impaired renal function.

Therefore, measurement of serum Hemocysteine level and hs.CRP can indicate a weak kidney function and increased risk of cardiovascular complications in diabetic patients (Elias and Eng, 2005).

The current research aimed to evaluate the efficiency of Bromocriptine in glycemic control in patients with poorly controlled type II diabetes and also investigate the effect of this drug to reduce cardiovascular complications of diabetes.

For this purpose, the effect of this drug on the control of arterial blood pressure, waist circumference measurement and serum level of two markers hs.CRP and Hemocysteine levels in patients under study were assessed at baseline and after six months.

2. Material and Methods

Study Design and Setting

The current study was a pre-post clinical trial (IRCT code 201204156710N3 available www.IRCT.ir)performed in patients with poorly controlled type 2 diabetes admitted to endocrine clinics of 2 third-level hospitals in Tabriz (a city in northwestern of Iran).

The study protocol was studied and confirmed by the ethics committee of Tabriz University of Medical Sciences and researchers throughout the study adhered to the principles of the Helsinki Convention.

Patients

In this study, diabetic patients (type 2) whose blood glucose levels were high despite using anti-glycemic drugs (such as Metformin and Glibenclamide) entered the study.

Exclusion criteria included age less than 30 years and more than 65 years, patient's unwillingness to participate in the study, pregnancy and lactation, history of syncope, acute psychosis, allergy to ergot-related or Bromocriptine drugs, and patient dissatisfaction in any phase of the study.

Our study sample sizes of 43 give a minimum power of 98% to detect a mean serum hs.CRP difference of 1.0 mg/dl between the null hypothesis that baseline mean serum concentration of hs.CRP is 2.99 mg/dl and the alternative hypothesis that the mean serum concentration of hs.CRP after six month is 3.99 mg/dl with baseline standard deviations of 1.75 mg/dl and with a significance level (alpha) of 0.05 using a two-sided Student's t-test, assuming that the true distribution is uniform.

The study consent form was carefully read and completed by all patients. In every part that the patient or his/her attendant had any questions about the study, the researcher answered them. Flowchart for patient selection and entry is shown in Figure 1.

Pharmaceutical interventions

Patients under study started Bromocriptine with 1.25 mg/day at bedtime and every three days, if tolerated by the patient (no gastrointestinal complications), the drug dose was increased 1.25 mg until reaching 2.5 mg twice/day. At baseline, patients became familiar with Bromocriptine, the drug form, modes of drug administration and its possible side effects. On the first visit, after examining lab tests and drug history, Bromocriptine tablets administration was started.

Data Collection

–Anthropometric factors and blood pressure

To study the accuracy of measurement and calibration, every day the patient's weight data were measured by a standard balance and also the height data were collected by a stadiometer. Patient's weight was measured without shoes and heavy clothing. To determine waist circumference a standard flexible tape measure was used. Also body mass index (BMI) was calculated by obtained height and weight data i.e. the weight (in kilograms) divided by height to the power of two (in meters). Patients were divided into 4 groups based on BMI: normal (18.5-24.9), overweight (25-29.9), fat (30-39.9) and obese (≥40). Blood pressure was checked by a calibrated mercury sphygmomanometer. Systolic and diastolic right arm blood pressure was measured after resting for at least 5 minutes twice in a 30 second interval and mean measurements were entered in the analyses.

–Biochemical tests

After 8 hours of fasting, 10 ml venous blood was collected to examine fasting blood glucose, hemoglobin A1C level (HbA1C), Hemocysteine, and hs. CRP. For this purpose, 10 cc of venous blood from cubital vein of the right arm was collected from each patient in a sitting position after 5 min of resting. Then participants were given breakfast and after 2 hours, 3 ml of their blood was collected by the method described to examine blood glucose. It is worth noting that the patients were not given any other food during the two hours. All patients used their previous diet (formulated by a nutritionist). Fasting blood glucose level and 2-hour postprandial glucose lever were measured and evaluated at 1.5, 3 and 6 month intervals after the first visit. Follow-up of the hemoglobin A1C ratio was also performed in the third and sixth months and Hemocysteine level and hs.CRP were assessed at baseline and the end of the study (to assess microvascular and cardiovascular complications of diabetes). The blood sampling was performed between 8-9am.

Follow up

The subjects were asked to refer to medical centers 45 days, 3 months and 6 months after initiation of Bromocriptine treatment so that in this period the patients could be evaluated in terms of drug complications, its tolerance state and biochemical tests. Patients' fasting blood glucose level and 2-hour postprandial blood glucose were assessed on day 45, the third and sixth months. Hemoglobin A1C was also evaluated in patients in the third and sixth months. It is worth noting that serum Hemocysteine level and hs.CRP were measured at the end of the sixth month of follow-up.

All blood tests were performed after 8 hours of fasting.

Data analysis

Data were entered into statistical software SPSS 17.0 and transferring the data into STATA 11.0, they were analyzed. The study variables were expressed as mean±SD with 95% confidence interval. Repeated measures ANOVA and Bonferroni post hoc tests were used to assess time changes in fasting and postprandial blood glucose level and hemoglobin A1C level. Paired t-test was also used to review hs.CRP level, Hemocysteine, waist circumference and blood pressure. $P<0.05$ was considered as significant level.

Figure 1: Flowchart of patients with poorly controlled type 2 diabetes who referred to therapy center

3. Results

Characteristics of samples

Finally, 43 patients were enrolled in the study that 69.8% of them were men (Figure 1). The mean age was 54.7 years, and the mean and standard deviation (SD) of patients' body mass index (BMI) was estimated 30.6 ± 3.9. BMI was normal in 1 patient (2.3%), while 22 patients (51.2%) suffered from overweight and 20 patients (46.5%) suffered from obesity. Patients under study tolerated

Bromocriptine well and the only side effects observed in them included dizziness, nausea and headache in 10 patients (23.25%) and in one case (2.3%) hypoglycemia was observed. In Table 1, the demographic and baseline variables of the patients are shown.

Blood glucose and hemoglobin A1C level

Taking Bromocriptine for 6 months led fasting blood glucose in patients with poorly controlled type 2 diabetes to reduce to 155.6 mg/dl, 148.9 mg/dl and 159.5 mg/dl on day 45, the third and sixth months of treatment, respectively, compared with the initial admission (184.3 mg/dl)(df=3.40; F=7.74; p<0.0001). The serum level of this index was significantly lower than initial admission in all three cut points including the day 45 (p = 0.001), the third month (p<0.0001) and the sixth month (p = 0.002).

Mean postprandial blood glucose reached from 276.6 mg/dl on initial admission to217.0mg/dl within 45 days after the beginning of treatment. Two-hour postprandial blood glucose level was also reduced in the third and six month and reached 205.1 and 201.0mg/dl, respectively, (df=3.40; F=17.8; p<0.0001) (Table 2). Analyses of the current study showed that taking Bromocriptine for six months reduced mean fasting blood glucose to 21.7 ± 7.9mg/dl, and postprandial blood glucose to 73.8 ± 12.3 (Fig. 2).

Also hemoglobin A1C percentage had a decreasing trend during six months. The mean and standard deviation of HbA1C level in the third and sixth month were 8.2±1.4 and 8.1±1.5 percent, respectively, (df=3.40; F=7.06; p<0.0001). It is worth noting that in the third month a decrease of 0.8% was observed in this variable compared with baseline (9.0±1.3) and in the six month it reached 0.9% (Fig. 2).

Changes in hs.CRP and Hemocysteine

Mean serum level of hs.CRP at baseline was 2.99±1.75 mg/dl, but after taking Bromocriptine for six months it reached 3.99±3.1 mg/dl (p=0.058). Hemocysteine level was also similar so that its level increased from 3.99±3.1 mg/dl to 11.6±6.6mg/dl (p=0.056). As it can be seen, Bromocriptine increased hs. CRP level and blood Hemocysteine.

Although this increase was not statistically significant, their close.

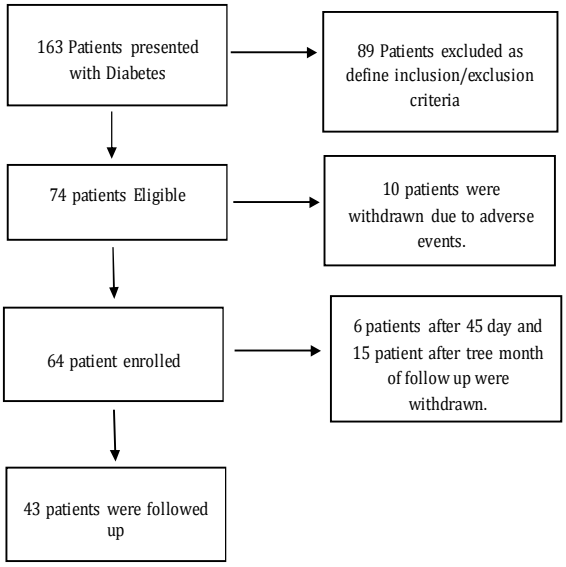

Figure 1: Flowchart of patients with poor control of diabetes referred to medical center

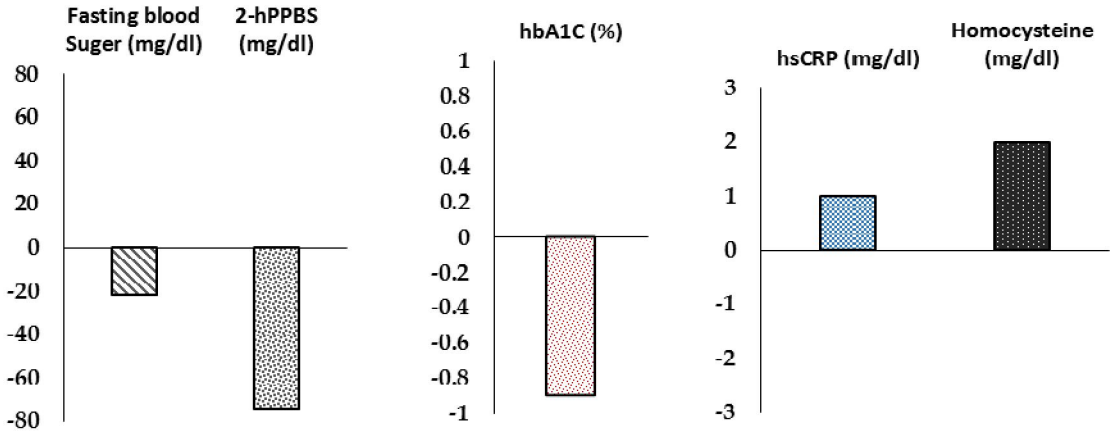

Figure 2: Deviation of FBS, 2hPPBS, HbA1C, hs.CRP after 6 months of taking Bromocriptine

P-value to the significance level suggested the hypothesis that Bromocriptine might be unable to prevent microvascular and cardiovascular complications of diabetes.

Table 1: Demographic and baseline variables of patients with diabetes
Table 2: Mean changes (Standard Deviation) of factors associated with diabetes in response to administration of Bromocriptine
Figure 2: Changes in fasting blood glucose, 2-h postprandial blood glucose (2-hPPBS), hemoglobin A1C, hs.CRP and Hemocysteine after six months of taking Bromocriptine.

4. Discussions

The findings of the current study showed that Bromocriptine was an effective drug to control diabetes and its related biochemical indices. Bromocriptine treatment for six months led to reduced fasting blood glucose about 21.7 mg/dl and 73.8 mg/dl reduction in 2-h postprandial blood glucose. Also hemoglobin A1C had a 0.9% reduction in six months. These results indicated that not only Bromocriptine caused a significant reduction in blood glucose and hemoglobin A1C but also led to achieving the ideal therapeutic goals in a significant number of patients. Although the difference in increase of blood Hemocysteine level and hs.CRP levels was not significant to baseline in the current study, the increase could suggest the hypothesis that Bromocriptine might not be able to reduce the incidence rate of cardiovascular complications of patients with type 2 diabetes. However, the increase in Hemocysteine level may also be due to Metformin as the available studies show that Metformin interferes with intestinal absorption of vitamins especially folate and B12 and deficiency in these vitamins may increase blood Hemocysteine levels (Fonseca, 2002). Therefore, more research is needed to identify the cause of increase in Hemocysteine levels.

Table 1: Demographic and baseline variables of patients with diabetes

Variable	Mean	Standard Deviation	95% Confidence Limit
Age (year)	55.0	7.2	53.2-56.8
Height (cm)	159.7	8.6	157-6-161.8
Weight (kg)	78.7	13.5	75.3-82.0
Body Mass Index	30.9	4.5	29.7-32.0
Waste Circumference(cm)	107.8	9.0	105.5±110.1
Systolic Blood Pressure (mmHg)	129.6	19.0	124.8-134.4
Diastolic Blood Pressure (mmHg)	79.2	11.1	76.5-82.0
Duration of Disease (year)	8.0	4.4	7.0-9.1

Table 2: Mean changes (Standard Deviation) of factors associated with diabetes in response to administration of bromocriptine

Blood biochemical indices	Initial admission	45th day	The third month	The sixth month	P
Fasting Blood Glucose (mg/dl)	184.3(42.4)	155.6(40.8)	148.9(44.5)	159.5(48.8)	<0.0001
2-hour postprandial blood glucose (mg/dl)	276.6(66.3)	217.0(58.1)	205.1(60.5)	201.0(68.0)	<0.0001
Hemoglobin A1C (%)	9.0(1.3)	-	8.2(1.4)	8.1(1.5)	<0.0001
hs.CRP (mg/dl)	2.99(1.75)	-	-	3.99(3.1)	0.058
Hemocysteine (mg/dl)	3.99(3.1)	-	-	11.6(6.6)	0.056
Systolic Blood Pressure (mmHg)	126.5(16.9)	-	-	125.6(18.3)	0.77
Diastolic Blood Pressure (mmHg)	77.1(8.6)	-	-	77.7(7.2)	0.74
Waste Circumference (cm)	107.9(9.5)	-	-	106.5(9.7)	0.054

The mechanism by which Bromocriptine causes blood glucose reduction is unknown, but it is believed that it can be partly due to resetting of the body's circadian clock. The resetting makes peak of sympathetic and dopamine tone that occurs in the central nervous system to pass in the time of the day that is the most common in healthy individuals. The increase in tone is associated with enhanced glucose tolerance and improved insulin sensitivity that may also affect lipids metabolism (DeFronzo, 2011). However, Bromocriptine inhibits the stimulated sympathetic tone which results in reduced plasma glucose levels (Cincotta, 1996; Monti and Monti, 2007). Moreover, Bromocriptine has dopamine and quasi-serotonin characteristics and alpha-1adrenergic receptor antagonist and alpha-2adrenergic receptor agonist. Based on human and animal studies, the drug increases hypothalamus dopamine levels and inhibits sympathetic tone in central nervous system. This reduces blood glucose after meal which is due to

inhibition of hepatic glucose production (DeFronzo, 2011). Perhaps this is why in the current study, the efficiency of Bromocriptine in reducing 2-hour postprandial blood glucose was higher than the other two factors.

Also it was revealed in clinical studies that in a high percentage of patients (25%) that had not shown a favorable response to conventional treatments, Bromocriptine caused hemoglobin A1C to drop below 7% (Scranton and Cincotta, 2010). The study conducted by Vinik et al. also showed that concomitant treatment by Bromocriptine and other drugs to control blood glucose increases the chance of hemoglobin A1C reduction to less than 7%, 6 to 12 times (Vinik, 2012). Pathak et al. showed that Bromocriptine administered 0.8-4.8 mg over six-month period can achieve the goals of treatment successfully (Sinha, 2012). Other studies also show the efficiency of Bromocriptine in dropping this blood indicator to 0.5-0.7% (DeFronzo, 2011) which is consistent with the current study.

Aminorroaya et al. also showed that Bromocriptine could reduce blood glucose and hemoglobin A1C in obese people with type II diabetes. The researchers suggest that this drug can be used as an adjuvant therapy or as mono therapy in patients whose blood glucose is slightly higher than normal (Aminorroaya, 2004). Garber et al. showed that quick-release Bromocriptine was an oral hypoglycemic agent with a new mechanism that promoted morning dopaminergic activity in the central nervous system and ultimately improved insulin sensitivity and reduced hepatic glucose production. In addition, the researchers indicated that adjunctive therapy with quick-release Bromocriptine dosage in the range of 1.6-4.8 mg per day caused a good reduction in hemoglobin A1C (0.69%) (Garber, 2013). Also Ahmad et al in their study review with the aim of medical treatment update for type 2 diabetes states that today Bromocriptine is administered as an anti-hyperglycemic agent in America and as a supplement along with diet and exercise can improve glycemic control in adults with diabetes (Ahmed, 2013). Michael A Via et al in their systematic review on four large studies showed that Bromocriptine was an acceptable drug for patients with diabetes and in average was effective on glycemic control. The findings of these researchers show that the best efficiency of this drug is in the early stages of the disease and can be used with other drugs that control diabetes such as Metformin, thiazolidinediones and GLP-1 agonists (Via, 2010). All of these studies report the results that are in line with recent findings of the current research.

Previous studies show that there is no difference between the incidence rate of drug side effects during treatment of diabetes by Bromocriptine and placebo group. In these studies nausea (32.2%) was reported as the most common complication of Bromocriptine that was higher than the present study (25.6%). Headache, dizziness and diarrhea are other Bromocriptine complications reported in diabetes treatment. It is worth noting that none of these complications was severe and most of them were appeared at the beginning of the titration of Bromocriptine, but after this period their incidence declined substantially (Gaziano, 2010). These reports confirm the findings of the present study because patients of the current study easily tolerated taking Bromocriptine for 6 months and all complications related to baseline were disappeared.

The studies suggest that increased Hemocysteine level is associated with microvascular diseases in patients with type II diabetes. These studies propose that even increase of 1 μmol/l Hemocysteine is an important risk factor for diabetic retinopathy (Brazionis, 2008). There are other studies which all showed that increased levels of Hemocysteine can lead to diabetic nephropathy (Li, 2012; Stabler, 1999). Furthermore, there is a close relationship between increased serum levels of hsCRP and incidence of coronary heart disease. The available reports show that hs.CRP and Hemocysteine are strong predictors for incidence of cardiovascular complications in women. This relationship is observed even in women with no history of hyperlipidemia, hypertension, smoking, diabetes or a family history of cardiovascular diseases (Ridker, 2000; Keavney, 2011). Regardless the mechanism that causes increased serum Hemocysteine level or hs.CRP it seems that Bromocriptine administration has no effect in reducing microvascular and cardiovascular complications of diabetes. Hence it is suggested that in future researches on the efficiency of Bromocriptine in control of diabetes and its complications, serum Hemocysteine and hs.CRP levels also be assessed for more careful decision about the use of this drug in treatment protocols.

The current study had also some limitations. One of these limitations was the lack of a placebo group. If there was a placebo group more accurate comparison was possible, but because of ethical considerations treatment of a group of patients with poorly controlled type 2 diabetes is impossible without intervention. Another limitation of the present study was 6-month follow-up. Due to the relatively short follow-up, no incidence of life-threatening complications in patients can be attributed to taking Bromocriptine. However, short term follow-up prevented the assessment of the incidence and progression rate of microvascular and cardiovascular complications of diabetes. Therefore it is recommended that in future studies longer follow-

up periods will be examined so the effects of this drug in reduction of dangerous complications could be also apparent. On the other hand, the present study investigated a small sample size but a larger sample and placebo controlled is needed to generalize these findings.

Conclusions

The findings of the current study showed that administering Bromocriptine as a concomitant therapy with other medications effectively lowers fasting blood glucose, blood glucose two hours after meal and serum hemoglobin A1C. The present study for the first time showed that using Bromocriptine could not prevent the incidence of cardiovascular and microvascular complications in patients with poorly controlled type 2 diabetes. This finding is proved by no reduction in serum Hemocysteine and hs.CRP levels of patients under study after 6 months taking Bromocriptine.

List of abbreviations

Hemoglobin A1C: Glycated hemoglobin
hs.CRP: high-sensitivity C-reactive protein
USD: US dollar

Competing interests

All authors do not have any financial and Non-financial competing interests.

Corresponding Author:
Dr. Mohammad Reza Jafari Nakhjavani
Emam Reza Hospital, Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
E-mail: dr_mrjn@yahoo.com

References

1. Johnson WD, Kroon JJ, Greenway FL, Bouchard C, Ryan D, Katzmarzyk PT. Prevalence of risk factors for metabolic syndrome in adolescents: National Health and Nutrition Examination Survey (NHANES), 2001-2006. Archives of pediatrics & adolescent medicine. 2009;**163**(4):371.
2. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes research and clinical practice. 2011;94(3):311-21.
3. Home C. Increasing Prevalence of Diagnosed Diabetes—United States and Puerto Rico, 1995–2010. Morbidity and Mortality Weekly Report. 2012;61(45):918-21.
4. Javanbakht M, Baradaran HR, Mashayekhi A, Haghdoost AA, Khamseh ME, Kharazmi E, et al. Cost-of-illness analysis of type 2 diabetes mellitus in Iran. PloS one. 2011;6(10): e26864.
5. American Diabetes Association. Standards of medical care in diabetes--2008. Diabetes Care. 2008 Jan;31 Suppl 1: S12-54. PubMed PMID: 18165335. Epub 2008/01/10. eng.
6. Nathan DM. Finding new treatments for diabetes--how many, how fast... how good? The New England journal of medicine. 2007;356(5):437.
7. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. New England Journal of Medicine. 2006;355(23):2427-43.
8. DeFronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58(4):773-95.
9. Imam K. Management and treatment of diabetes mellitus. Advances in experimental medicine and biology. 2012;771:356-80. PubMed PMID: 23393690. Epub 2013/02/09. eng.
10. Gaziano JM, Cincotta AH, O'Connor CM, Ezrokhi M, Rutty D, Ma Z, et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. Diabetes Care. 2010;33(7):1503-8.
11. Southern L, Cincotta A, Meier A, Bidner T, Watkins K. Bromocriptine-induced reduction of body fat in pigs. Journal of animal science. 1990;68(4):931-6.
12. Pijl H, Ohashi S, Matsuda M, Miyazaki Y, Mahankali A, Kumar V, et al. Bromocriptine: a novel approach to the treatment of type 2 diabetes. Diabetes Care. 2000;23(8):1154-61.
13. Cincotta AH, Schiller BC, Meier AH. Bromocriptine inhibits the seasonally occurring obesity, hyperinsulinemia, insulin resistance, and impaired glucose tolerance in the Syrian hamster, Mesocricetus auratus. Metabolism. 1991;40(6):639-44.
14. Cincotta AH, Meier AH. Bromocriptine (Ergoset) reduces body weight and improves glucose tolerance in obese subjects. Diabetes Care. 1996;19(6):667-70.
15. Gibson C, Karmally W, McMahon D, Wardlaw S, Korner J. Randomized pilot study of cabergoline, a dopamine receptor agonist: effects on body weight and glucose tolerance in obese adults. Diabetes, Obesity and Metabolism. 2012;14(4):335-40.
16. Kamath V, Jones CN, Yip JC, Varasteh BB, Cincotta AH, Reaven GM, et al. Effects of a quick-release form of bromocriptine (Ergoset) on

fasting and postprandial plasma glucose, insulin, lipid, and lipoprotein concentrations in obese nondiabetic hyperinsulinemic women. Diabetes Care. 1997;20(11):1697-701.
17. DeFronzo RA. Bromocriptine: a sympatholytic, D2-dopamine agonist for the treatment of type 2 diabetes. Diabetes Care. 2011;34(4):789-94.
18. Svacina S. Treatment of obese diabetics. Advances in experimental medicine and biology. 2012;771:459-64. PubMed PMID: 23393696. Epub 2013/02/09. eng.
19. Ghassibe-Sabbagh M, Platt DE, Youhanna S, Abchee AB, Stewart K, Badro DA, et al. Genetic and environmental influences on total plasma homocysteine and its role in coronary artery disease risk. Atherosclerosis. 2012;222(1):180-6.
20. van Meurs JB, Pare G, Schwartz SM, Hazra A, Tanaka T, Vermeulen SH, et al. Common genetic loci influencing plasma homocysteine concentrations and their effect on risk of coronary artery disease. The American journal of clinical nutrition. 2013.
21. Elias AN, Eng S. Homocysteine concentrations in patients with diabetes mellitus–relationship to microvascular and macrovascular. Diabetes, Obesity and Metabolism. 2005;7:117-21.
22. Fonseca V, Keebler M, DeSouza C, Poirier LA, Murthy S, McNamara DB. The effect of troglitazone on plasma homocysteine, hepatic and red blood cell adenosyl methionine, andadenosyl homocysteine and enzymes in homocysteine metabolism in Zucker rats. Metabolism. 2002;51(6):783-6.
23. Monti JM, Monti D. The involvement of dopamine in the modulation of sleep and waking. Sleep medicine reviews. 2007;11(2):113-33.
24. Scranton R, Cincotta A. Bromocriptine-unique formulation of a dopamine agonist for the treatment of type 2 diabetes. Expert opinion on pharmacotherapy. 2010;11(2):269-79.
25. Vinik AI, Cincotta AH, Scranton RE, Bohannon N, Ezrokhi M, Gaziano JM. Effect of Bromocriptine-QR on Glycemic Control in Subjects with Uncontrolled Hyperglycemia on One or Two Oral Anti-Diabetes Agents. Endocrine Practice. 2012;18(6):931-43.
26. Sinha PK, Sharma J. BROMOCRIPTINE-A NOVEL APPROACH FOR MANAGEMENT OF TYPE 2 DIABETES MELLITUS. Journal of Drug Delivery and Therapeutics. 2012;2(5).
27. Aminorroaya A, Janghorbani M, Ramezani M, Haghighi S, Amini M. Does bromocriptine improve glycemic control of obese type-2 diabetics? Hormone Research in Paediatrics. 2004;62(2):55-9.
28. Garber AJ, Blonde L, Bloomgarden ZT, Handelsman Y, Dagogo-Jack S. The Role of Bromocriptine-QR in the Management of Type 2 Diabetes Expert Panel Recommendations. Endocrine Practice. 2013:1-22.
29. Ahmed SS, Ali MZ, Laila TR, Begum HA, Ali TMM. Update on Pharmacotherapy for Type 2 Diabetes. KYAMC Journal. 2013;3(1):250-361.
30. Via MA, Chandra H, Araki T, Potenza MV, Skamagas M. Bromocriptine approved as the first medication to target dopamine activity to improve glycemic control in patients with type 2 diabetes. Diabetes, metabolic syndrome and obesity: targets and therapy. 2010;3:43-.
31. Brazionis L, Rowley K, Itsiopoulos C, Harper CA, O'Dea K. Homocysteine and diabetic retinopathy. Diabetes Care. 2008;31(1):50-6.
32. Li J, Shi M, Zhang H, Yan L, Xie M, Zhuang L, et al. Relation of homocysteine to early nephropathy in patients with Type 2 diabetes. Clinical nephrology. 2012;77(4):305-10.
33. Stabler SP, Estacio R, Jeffers BW, Cohen JA, Allen RH, Schrier RW. Total homocysteine is associated with nephropathy in non—insulin-dependent diabetes mellitus. Metabolism. 1999;48(9):1096-101.
34. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. New England Journal of Medicine. 2000;342(12):836-43.
35. Keavney B. C reactive protein and the risk of cardiovascular disease. BMJ. 2011;342.

3/25/2017