

Efficacy of bromocriptine on glycemic and metabolic control of prediabetic patients

Saied Hossein Khalilzade, Ashraf Aminorroaya, Silva Hovsepain¹, Masoud Amini

Isfahan Endocrine and Metabolism Research Center, ¹Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract **Background:** It is suggested that bromocriptine could be effective in treatment of prediabetic patients and, consequently, in preventing type 2 diabetes (T2DM). In this study, we investigated the effectiveness of bromocriptine on glycemic and metabolic control of prediabetic patients.

Materials and Methods: In this double-blind, placebo controlled trial study, prediabetic patients diagnosed during Isfahan Diabetes Prevention Project (IDPP) were enrolled. They randomized in two bromocriptine (2.5 mg) and placebo-treated groups, for 12 weeks. After physical examination, fasting plasma glucose (FPG), HbA1c, Insulin, cholesterol, HDL-c, and triglyceride were measured and glucose tolerance test (OGTT) was performed. HOMA-IR and LDL-c were calculated. The mean of the data were compared in the bromocriptine and placebo treated groups, before and after intervention by intention to treat analysis using mixed effect model. *P* values < 0.05 were considered, statistically, significant.

Results: In this study, 53 prediabetic patients (27 in the bromocriptine group and 26 in the placebo group) were treated. There were no differences between data of two groups at baseline (*P* > 0.05). The mean body mass index, systolic blood pressure, fasting plasma glucose and glucose of 30 min, 60 min, 120 min of post OGTT, HbA1c, insulin, HOMA-IR, lipid profile did not change, significantly, in both bromocriptine and placebo-treated groups after 12 weeks (*P* > 0.05). However, diastolic blood pressure (*P* = 0.02) and the area under the curve of glucose (*P* = 0.045) were decreased in the bromocriptine-treated group.

Conclusion: Bromocriptine did not have significant effect on glycemic control of prediabetic patients. Further studies, with bigger sample size are recommended.

Key Words: Bromocriptine, prediabetics, type 2 diabetes

Address for correspondence:

Prof. Massoud Amini, Isfahan Endocrine and Metabolism Research Center, Sedigheh Tahereh Research Complex, Khorram Street, Isfahan, Iran.

E-mail: m_amin@med.mui.ac.ir

Received: 26.06.2014, Accepted: 20.10.2014

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.170678

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a growing global pandemic and it is estimated to be one of the ten leading causes of death worldwide by 2030.^[1] Considering the burden of T2DM and its related morbidity and mortality, the concept of its prevention through identifying at-risk population, prediabetics, prior to diagnosis had been developed widely.

Copyright: © 2015 Khalilzade. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

How to cite this article: Khalilzade SH, Aminorroaya A, Hovsepain S, Amini M. Efficacy of bromocriptine on glycemic and metabolic control of prediabetic patients. Adv Biomed Res 2015;4:253.

Prediabetes, an intermediate form of dysglycemia, is a high-risk condition for diabetes. Individuals with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) according to the WHO criteria classified as prediabetic patients. It is characterized by both β -cell dysfunction and insulin resistance.^[2,3]

Epidemiological studies estimated that approximately 1 in 7 adults in the North America, Europe and Asia are prediabetic.^[4-7] According to the International Diabetes Federation, the prevalence of prediabetes is increasing and it is estimated that it would be projected to more than 470 million by 2030.^[8]

The above mentioned epidemiological feature emphasizes on the importance of targeted diabetes prevention programs. Several studies indicated the potential benefits of lifestyle modification and pharmacotherapy in preventing T2DM among prediabetic patients. Moreover, others suggest that proper management of prediabetic population also could reduce the risk of CVD and its related morbidity and mortality.^[9,10]

Lifestyle modification considers the cornerstone of diabetes prevention and its beneficial effect on improving insulin sensitivity and β -cell function and consequently diabetes prevention has been confirmed in several studies.^[11]

Though several pharmacological interventions confirm the effectiveness of some agents in reducing the incidence of T2DM in prediabetics but some studies have not approved the use of pharmacotherapy in this field.^[12]

Recent studies reported that centrally acting antidiabetic agents such as bromocriptine could reduce plasma glucose, free fatty acid (FFA) and triglycerides levels through their novel mechanism of action. It is suggested that bromocriptines have modulatory effect on central glucose and energy metabolism pathways.^[13,14]

Bromocriptine is a sympatholytic D2-dopamine agonist. Its pharmacological activity is due to activation and inhibition of CNS D2 and D1 receptors, respectively. It has also inhibitory and partial agonist effect on 5-HT_{2A} and 5-HT_{2B} receptors, respectively.^[15,16]

Though, the effectiveness of bromocriptine on glycemic control of type 2 diabetic patients have reported in many clinical trials and its use among patients with T2DM have been approved by the United States Food and Drug Administration (FDA) but its mechanism of action have not identified yet.^[17-19]

Considering the pathogenesis of T2DM, it is suggested that bromocriptine could have similar effect on prediabetic patients and consequently in preventing T2DM. The utility of bromocriptine in this high risk population have not been studied.

In this study, we investigated the effectiveness of bromocriptine on glycemic and metabolic control of prediabetic patients. However, the results of current research would be helpful in improving the burden of T2DM in our community.

MATERIALS AND METHODS

In this double-blind, placebo controlled trial study, prediabetic patients, aged 40-70 years, diagnosed during Isfahan Diabetes Prevention Project (IDPP) were enrolled. They selected by consecutive sampling method.

IDPP started in Isfahan Endocrine and Metabolism Research Center, since 2004. According to the protocol of the project, the first degree relatives (FDR) of type 2 diabetic patients including their siblings and offspring screened for T2DM using OGTT test. According to the criteria of ADA, those with impaired glucose tolerance test (IGT) or impaired fasting glucose (IFG) considered as prediabetic patients.^[20]

The protocol of study was designed and approved by the Institutional Review Board of Isfahan Endocrine and Metabolism Research Center and Regional Bioethics Committee of Isfahan University of Medical Sciences (Research project number: 389113).

Informed consent was obtained from all selected patients.

Patients with T2DM and type 1 diabetes were not enrolled. Prediabetic patients with renal failure, those who were on treatment with oral anti-diabetic agents, weight reduction drugs, patients with pituitary adenoma, hyperprolactinemia, hypothyroid patients and those with history of psychological disorder and anti psychotic medication use were excluded from the study.

The selected patients randomized in two intervention ($n = 28$) and placebo ($n = 27$) groups. In each group after OGTT, one of the patients had 120 min post OGTT more than 200 mg/dl. Therefore, these two patients were excluded from the analysis and 27 patients in the bromocriptine-treated group and 26 patients in the placebo-treated group were, finally, analyzed.

Consort diagram of the study is presented in Figure 1.

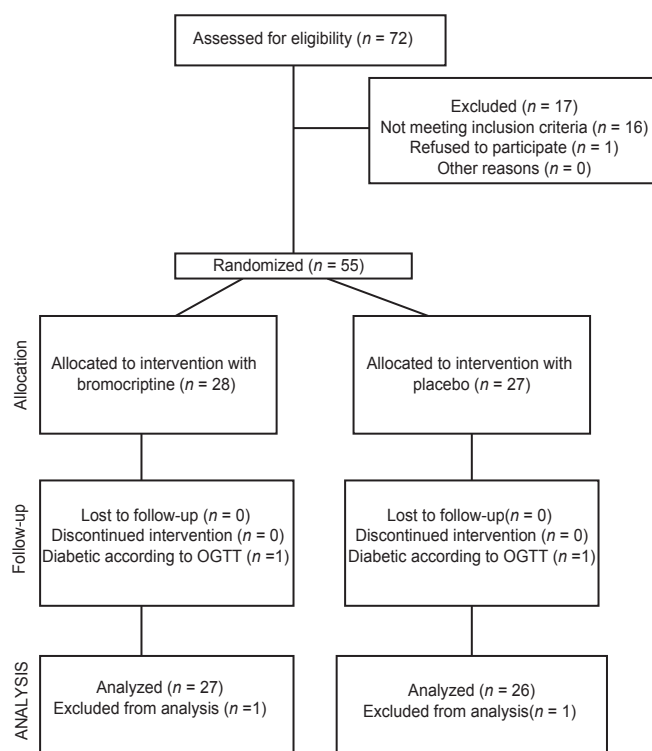


Figure 1: Consort diagram of the clinical trial

Bromocriptine was initiated with half of a bromocriptine 2.5 mg tablet (1.25 mg) and the dose titrated up to 2.5 mg per day during the first week of trial. The medication was prescribed before sleeping to reduce the probable orthostatic hypotension. The medication was continued for 12 weeks.

Bromocriptine supplied by Iran Hormone Pharmaceutical Company (Tehran-Iran) and placebo supplied by the same company.

The patients were clinically examined (Kh.SH). Baseline characteristics of patients recorded using questionnaire.

Physical examination

Height and weight were measured in their light clothing and bare foot using Seca scale by a trained nurse. Body mass index (BMI) was calculated as weight divided by square of height (kg/m^2).

Blood pressure was measured by a physician on the right arm in the seated position twice after at least 15 minutes of rest with 10 minutes interval between two measurements. The manometer was placed at the heart level.

Laboratory measurements

After an 8 hour of overnight fasting, blood samples were taken for measuring FPG, HbA1c, Insulin, cholesterol, HDL-c, and triglyceride and a standard

OGTT was performed and plasma glucose was measured before and 30, 60 and 90 min after taking of 75g glucose, orally (15). Participants with IGT (a 2-h plasma glucose between 140 and 200 mg/dl after a 75-g oral glucose tolerance test) and IFG (fasting plasma glucose of 100 to 126 mg/dl) considered as prediabetic patients based on ADA criteria.^[18]

Homeostasis model assessment of insulin resistance (HOMA-IR), as an index of insulin resistance, was calculated as the product of FPG (mmol/l) and insulin ($\mu\text{IU}/\text{ml}$) divided by 22.5.

LDL-c was calculated as far as TG was less than 400 mg/dl by Friedewald formula.

Results of these measurements compared in intervention and placebo groups, before and after intervention.

Plasma glucose and plasma lipids (total cholesterol, HDL cholesterol, Triglyceride) measured by enzymatic colorimetric techniques using auto analyzer (Liasys, Italy).

HbA1c measured by chromatographic-spectrophotometric method (BioSystems SA-Spain).

Insulin measured by Immunoradiometric assay method (Diosource Europe S.A-Belgium).

Statistical analysis

Statistical analysis was performed using SPSS version 18 (SPSS Inc., Chicago, IL, USA). The normal distribution of data was assessed by Kolmogorov-Smirnov test. All the data had normal distribution. They were presented as the mean \pm SD. The comparison of quantitative data between the bromocriptine-treated and placebo-treated groups was done with the independent T test. The comparison of such data before and after intervention, in each group (bromocriptine or placebo-treated) was done by intention to treat analysis using mixed effect model (within group). The comparison of sex between groups was done using the Chi-square test. P values < 0.05 were considered, statistically, significant.

RESULTS

In this study 53 prediabetic patients (27 in bromocriptine group and 26 in placebo group) were studied. According to the results of OGTT test the distribution of IFG and IGT in bromocriptine and placebo groups were as follows;

In the bromocriptine group, 20 (74.1%), 5 (18.5%) and 2 (7.4%) were classified as IFG, IGT and IFG and IGT, respectively.

In the placebo group, 17 (65.4%), 8 (30.8%) and 1 (3.8%) were classified as IFG, IGT and IFG and IGT, respectively.

Basal characteristics of studied population in two studied groups are presented in Table 1.

The mean \pm SD of data in bromocriptine and placebo treated prediabetic patients before and after intervention are presented in Table 2.

There was no statistically, significant difference in BMI, fasting plasma glucose, 30, 60, 120 min post OGTT, HbA1c, Insulin, HOMA-IR, area under the curve of glucose, lipid profile and systolic and blood pressure between bromocriptine and placebo-treated groups ($P > 0.05$). Diastolic blood pressure ($P = 0.02$) and the area under the curve of glucose ($P = 0.045$) were decreased in the bromocriptine-treated group. Mean differences between two studied groups were significant only for AUC ($P = 0.04$) and cholesterol ($P = 0.05$).

DISCUSSION

In this trial we evaluated the effectiveness of bromocriptine on glycemic and metabolic control of prediabetic patients. Our results indicated that, bromocriptine had no significant effect on glycemic

control of prediabetic patients and also their insulin resistance index, HOMA-IR.

Bromocriptine considered as one of the novel antidiabetic agents with its effectiveness for both glycemic and metabolic control of patients with T2DM has been reported in several studies.^[17,18]

It is reported that in T2DM, bromocriptine reduces HbA1c level by 0.4-0.7%.^[21] Some pharmacological advantages of bromocriptine, such as lower side effects, safety, tolerability and good adherence to treatment, have made it as one of the favorable antidiabetic agents.^[22]

According to the report of FDA in 2009, bromocriptine could be used in the treatment of T2DM as an adjunct to diet and exercise to obtain more appropriate glycemic control.^[19]

Before that time Aminorroaya, *et al.*, in Iran, had investigated the effect of bromocriptine on glycemic control among obese type 2 diabetic patients in 2004. They showed that bromocriptine improved glycemic control in obese type-2 diabetic patients.^[23]

Ramteke *et al.*, in India, have evaluated both monotherapy and combination therapy of bromocriptine with metformin in three groups of patients with T2DM for 12 weeks and they observed that all the studied treatment strategies were effective and safe for achieving optimal glycemic control.^[24]

Via *et al.*, in the USA, have reviewed different studies regarding the effectiveness of bromocriptine in glycemic control of T2DM and they concluded that its efficacy is more significant if it can be used early in the course of the disease and preferably with other antidiabetic agents.^[14]

Considering the fact that proper management of prediabetic patients as the target group which are at higher risk for developing T2DM is crucial for prevention of T2DM and the superiority of bromocriptine than other antidiabetic agents this study was designed among this group of patients in Isfahan.

The results of current study indicated that bromocriptine was not effective for reducing FPG, HbA1c and other glycemic factors, but area under the curve of glucose during OGTT [Table 2]. However, the decrease in the area under the curve of glucose is just marginally significant ($P = 0.045$). It is recommended to do a study with bigger sample size and with higher dosage of bromocriptine to show a probably more effect on glycemic factors in prediabetic patients.

Table 1: Baseline characteristics (mean \pm SD) of bromocriptine and placebo treated prediabetic patients

Variables	Bromocriptine n=27	Placebo n=26	P value
Age (years)	46.8 \pm 5.5	49.5 \pm 5.9	NS
Sex (female/male)	21/6	18/8	NS
Body mass index (BMI) (kg/m ²)	29.4 \pm 4.4	30.3 \pm 3.3	NS
Blood pressure			
Systolic (mmHg)	119.1 \pm 15.3	123.8 \pm 16.8	NS
Diastolic (mmHg)	85.5 \pm 10.5	85.9 \pm 12.8	NS
Glycemic factors			
Plasma glucose (mg/dl)	102.1 \pm 12.1	105.6 \pm 9.8	NS
Fasting	143.9 \pm 31.4	158.2 \pm 36.8	NS
30 min post OGTT	166.6 \pm 52.1	176.0 \pm 35.8	NS
60 min post OGTT	135.3 \pm 34.1	140.0 \pm 33.6	NS
120 min post OGTT			
HbA1c (%)	5.2 \pm 0.5	5.3 \pm 0.5	NS
Insulin (μ U/ml)	9.5 \pm 7.7	8.8 \pm 3.9	NS
HOMA-IR (mmol/l/ μ U/ml)	11.8 \pm 3.3	13.1 \pm 4.0	NS
AUC of glucose	966.8 \pm 182.5	1024.6 \pm 161.1	NS
Lipid profile			
Cholesterol (mg/dl)	187.6 \pm 29.9	180.3 \pm 28.0	NS
Triglyceride (mg/dl)	129.7 \pm 70.5	128.1 \pm 58.1	NS
HDL-C (mg/dl)	44.3 \pm 8.6	41.3 \pm 8.7	NS
LDL-C (mg/dl)	117.3 \pm 26.7	113.4 \pm 26.0	NS

OGTT: Glucose tolerance test, HOMA-IR: Homeostasis model assessment of insulin resistance, SD: Standard deviation, AUC: Area under the curve, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol

Table 2: Mean±SD of data in bromocriptine and placebo treated prediabetic patients before and after intervention

	Bromocriptine n=27			P value*	Placebo n=26			P value*
	Before	After	Mean differences		Before	After	Mean differences	
Body mass index (kg/m ²)	29.0±4.4	28.7±4.2	0.13±0.32	0.75	30.3±3.3	30.3±3.5	0.13±0.45	0.99
Blood pressure								
Systolic (mmHg)	119.1±15.3	113.1±16.1	6.8±7.16.00	0.18	123.8±16.8	115.9±26.9	8.20±21.76	0.21
Diastolic (mmHg)	85.5±10.5	79.0±7.7	7.20±11.74	0.02	85.9±12.8	77.9±17.2	8.52±19.53	0.06
Glycemic factors:								
Fasting plasma glucose (mg/dl)	102.1±12.2	99.2±16.8	3.58±16.24	0.48	105.6±9.8	101.5±8.0	4.80±8.52	0.11
30 min post OGTT	143.9±31.4	133.1±29.6	13.84±34.34	0.24	158.2±36.8	145.3±31.9	11.16±37.97	0.24
60 min post OGTT	166.6±52.1	145.3±29.5	28.95±52.08	0.08	176.0±35.8	167.0±33.6	15.50±28.84	0.88
120 min post OGTT	135.3±34.1	125.2±27.8	11.70±39.36	0.25	140.0±33.6	134.2±30.3	2.13±34.06	0.53
HbA1c (%)	5.2±0.5	5.4±0.7	-0.18±30.56	0.42	5.3±0.5	5.6±0.8	-0.23±0.70	0.10
Insulin (μU/ml)	9.5±7.7	8.1±5.2	0.07±5.06	0.49	8.8±3.9	9.2±4.4	0.23±2.80	0.11
HOMA-IR (mmol/l/μU/ml)	11.8±3.3	12.1±3.0	-0.13±1.82	0.78	13.1±4.0	14.3±6.3	-0.71±2.83	0.44
AUC of glucose	966.8±182.5	867.7±121.5	156.44±147.20 [‡]	0.045	1024.6±161.1	972.9±139.4	56.15±145.54 [‡]	0.28
Lipids								
Cholesterol (mg/dl)	187.6±29.9	179.2±37.3	11.75±26.40 [‡]	0.38	180.3±28.0	186.1±31.4	-4.95±30.55 [‡]	0.49
Triglyceride (mg/dl)	129.7±70.5	145.4±56.7	-11.91±13.54	0.39	128.1±58.1	149.1±61.8	-20.69±58.99	0.23
HDL-C (mg/dl)	44.3±8.6	45.3±7.2	-0.6±6.49	0.65	41.3±8.7	42.3±14.2	-1.26±10.6	0.75
LDL-C (mg/dl)	117.3±26.7	106.6±30.9	14.36±26.18	0.20	113.4±26.0	114.0±30.6	-0.44±29.4	0.94

*P value between before and after. [‡]P<0.05 between mean differences of the two studied groups. OGTT: Glucose tolerance test, HOMA-IR: Homeostasis model assessment of insulin resistance, SD: Standard deviation, AUC: Area under the curve, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol

In literature review, there was not any similar study in this regard. At our best knowledge, this is the first study, which has been conducted to investigate the effect of bromocriptine in prediabetic patients.

Although many studies have confirmed the effectiveness of monotherapy of bromocriptine on glycemic control on T2DM, but it seems that its conjunction with lifestyle modification including diet, exercise and other anti diabetic agents would be more useful as mentioned in previous studies.^[14,19,24]

Another explanation is based on the pathophysiology of prediabetes. Our study populations are the patients with IFG and or IGT which are classified as prediabetics. However, the response of patients with IFG and IGT to bromocriptine was not similar to overt diabetes.

IFG and IGT are associated, predominantly, with hepatic insulin and muscle insulin resistance, respectively. Those with IFG and IGT have both muscle and hepatic insulin resistance. The risk of diabetes development is higher in patients with both IFG and IGT.^[25,26] On the other hand, DeFronzo *et al.* have reported that bromocriptine could not increase insulin sensitivity or augment its secretion in peripheral tissue, that is, in muscles. Moreover, they indicated that it could not enhance insulin action in the physiologic range of hyperinsulinemia.^[27]

Though above mentioned mechanisms of bromocriptine needs further clarification, it seems that in prediabetic

patients the severity of hyperinsulinemia is not much higher than the physiologic range.

We analyzed the data of our patients with IFG or IGT or those with IFG and IGT, separately (data were not shown). However, the findings were not conclusive. Probably, the sample size was small.

The period of our study was 12 weeks; it seems that longer duration of trial would provide us more concise results. The durations of trial in many studies which have reported the favorable effect of bromocriptine on glycemic control were longer.^[28,29]

There are controversies regarding the effectiveness of bromocriptine on cardiovascular risk factors and its effectiveness in this field have not confirmed, yet.^[30]

Garber and colleagues in Houston have reported that bromocriptine effect on CVD risk factors is more favorable in T2DM with history of CVD disease or those with significant CVD risk factors.^[30] Gaziano *et al.* conducted two studies regarding the safety and efficacy of bromocriptine on major adverse cardiovascular events among patients with T2DM. They showed a 52% and 42% reduction in the relative risk of major adverse cardiovascular events in the two studies.^[31,32]

In this study, it had a significant effect on diastolic blood pressure and not lipid profile [Table 2]. It seems that its usefulness on other CVD risk factors would be observed by continuing the period of study, increasing

the dose of bromocriptine or by combination of the agent with life style modification.

CONCLUSION

In this study which designed as a primary trial to investigate the therapeutic effect of bromocriptine on glycemic and metabolic factors of prediabetic patients, we found no significant effect on glycemic control, insulin resistance index and lipid profile, but diastolic blood pressure and area under the curve of glucose during OGTT. However, a decrease in mean of diastolic blood pressure may show its beneficial effect on cardiovascular risk factors.

Future study with bigger sample size and longer duration of trial is suggested to achieve more conclusive results.

ACKNOWLEDGEMENT

The authors would like to thank Ms. Karim Abadi and Ms. Zareh for their help in collecting the data, Mr. Abyar for his assistance in computer technical affairs and Dr. Awat Feizi for his statistical consult.

REFERENCES

- Ginter E, Simko V. Type 2 diabetes mellitus, pandemic in 21st century. *Adv Exp Med Biol* 2012;771:42-50.
- Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: A high-risk state for diabetes development. *Lancet* 2012;379:2279-90.
- WHO, International Diabetes Foundation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: Report of a WHO/IDF consultation. Geneva: World Health Organization; 2006.
- The DECODE Study Group. Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. *Diabetes Care* 2003;26:61-9.
- Qiao Q, Hu G, Tuomilehto J, Nakagami T, Balkau B, Borch-Johnsen K, *et al.* Age and sex-specific prevalence of diabetes and impaired glucose regulation in 11 Asian cohorts. *Diabetes Care* 2003;26:1770-80.
- National Screening Committee. The Handbook for Vascular Risk Assessment, Risk Reduction and Risk Management. A report prepared for the UK National Screening Committee. England, UK: University of Leicester; 2008.
- Santaguida PL, Balion C, Hunt D, Morrison K, Gerstein H, Raina P, *et al.* Diagnosis, prognosis, and treatment of impaired glucose tolerance and impaired fasting glucose. *Evid Rep Technol Assess (Summ)* 2005;128:1-11.
- International Diabetes Federation. *IDF Diabetes Atlas, 5th edn.* Brussels: International Diabetes Federation, 2011.
- Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V; Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 2006;49:289-97.
- Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009;374:1677-86.
- Kitabchi AE, Tempresa M, Knowler WC, Kahn SE, Fowler SE, Haffner SM, *et al.* Role of insulin secretion and sensitivity in the evolution of type 2 diabetes in the diabetes prevention program: Effects of lifestyle intervention and metformin. *Diabetes* 2005;54:2404-14.
- Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, *et al.* Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: Systematic review and meta-analysis. *BMJ* 2007;334:299.
- Kerr JL, Timpe EM, Petkewicz KA. Bromocriptine mesylate for glycemic management in type 2 diabetes mellitus. *Ann Pharmacother* 2010;44:1777-85.
- 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 Metab Syndr Obes* 2010;3:43-8.
- Tan EK, Jankovic J. Choosing dopamine agonists in Parkinson's disease. *Clin Neuropharmacol* 2001;24:247-53.
- Jahnichen S, Horowski R, Pertz HH. Agonism at 5-HT_{2B} receptors is not a class effect of the ergolines. *Eur J Pharmacol* 2005;513:225-8.
- 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;23:1154-61.
- Holt RI, Barnett AH, Bailey CJ. Bromocriptine: Old drug, new formulation and new indication. *Diabetes Obes Metab* 2010;12:1048-57.
- Cycloset. Silver Spring, Maryland: U.S. Food and Drug Administration. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search DrugDetails> [Last cited on 2012 Jan 30].
- American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2013;36(Suppl 1):S67-74.
- Quianzon CC, Cheikh IE. History of current non-insulin medications for diabetes mellitus. *J Community Hosp Intern Med Perspect* 2012;2(3).
- Shivaprasad C, Kalra S. Bromocriptine in type 2 diabetes mellitus. *Indian J Endocrinol Metab* 2011;15(Suppl 1):S17-24.
- Aminorroaya A, Janghorbani M, Ramezani M, Haghighi S, Amini M. Does bromocriptine improve glycemic control of obese type-2 diabetics? *Horm Res* 2004;62:55-9.
- Ramteke KB, Ramanand SJ, Ramanand JB, Jain SS, Raparti GT, Patwardhan MH, *et al.* Evaluation of the efficacy and safety of bromocriptine QR in type 2 diabetes. *Indian J Endocrinol Metab* 2011;15(Suppl 1):S33-9.
- Ferrannini E, Gastaldelli A, Iozzo P. Pathophysiology of prediabetes. *Med Clin North Am* 2011;95:327-39.
- DeFronzo RA, Abdul-Ghani MA. Preservation of beta-cell function: The key to diabetes prevention. *J Clin Endocrinol Metab* 2011;96:2354-66.
- DeFronzo RA. Bromocriptine: A sympatholytic, d₂-dopamine agonist for the treatment of type 2 diabetes. *Diabetes Care* 2011;34:789-94.
- 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 Metab Syndr Obes* 2010;3:43-8.
- Scranton RE, Gaziano JM, Ruddy D, Ezrokhi M, Cincotta A. A randomized, double-blind, placebo-controlled trial to assess safety and Tolerability during treatment of type 2 diabetes with usual diabetes therapy and either Cycloset or placebo. *BMC Endocr Disord* 2007;7:3.
- 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. *Endocr Pract* 2013;19:100-6.
- Gaziano JM, Cincotta AH, O'Connor CM, Ezrokhi M, Ruddy D, Ma ZJ, *et al.* Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care* 2010;33:1503-8.
- Gaziano JM, Cincotta AH, Vinik A, Blonde L, Bohannon N, Scranton R. Effect of bromocriptine-QR (a quick-release formulation of bromocriptinemesylate) on major adverse cardiovascular events in type 2 diabetes subjects. *J Am Heart Assoc* 2012;1:e002279.

Source of Support: Isfahan University of Medical Sciences, **Conflict of Interest:** None declared.