Published in final edited form as:

Diabetes Obes Metab. 2012 April ; 14(4): 335–340. doi:10.1111/j.1463-1326.2011.01534.x.

Randomized Pilot Study of Cabergoline, a Dopamine Receptor Agonist: Effects on Body Weight and Glucose Tolerance in Obese Adults

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Abstract

Aim—Dopaminergic hypofunction and hyperprolactinemia have been implicated in the pathogenesis of obesity and glucose intolerance. The aim of this pilot study was to determine the efficacy of cabergoline, a dopamine receptor agonist, on body weight and glucose tolerance in obese non-diabetic persons with normal plasma prolactin levels.

Materials and Methods—This 16-week double blind, placebo-controlled pilot study randomized non-diabetic obese adults (BMI 30–42 kg/m²) to placebo or cabergoline (0.25 mg twice weekly for 4 weeks followed by 0.5 mg twice weekly for the next 12 weeks). Of 40 subjects enrolled, 29 completed 16 weeks: 16 randomized to placebo, 13 to cabergoline. All subjects were counseled on a 500 kcal/day calorie deficit diet. A 75 gm oral glucose tolerance test was performed at baseline and at 16 weeks.

Results—As expected, prolactin levels decreased after cabergoline ($P < 0.001$). Weight loss was similar after placebo compared with cabergoline treatment: 1.0 vs 1.2% body weight, respectively. Fasting glucose levels did not differ between groups after treatment, however, 90 minute post-prandial glucose and insulin decreased in the cabergoline group only ($P = 0.029$). HOMA-IR increased by 40% after placebo, and 1.5% after cabergoline treatment.

Conclusions—This pilot study suggests that cabergoline therapy may improve glucose tolerance independent of weight loss, however, a larger, longer term study of dopamine receptor agonist therapy in obese individuals is warranted to confirm this finding.

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Declaration of Interests:

None

Contributor Statements:

Gibson: data analysis and manuscript preparation

Karmally: nutrition counseling

McMahon: statistical analysis

Wardlaw: protocol design and manuscript preparation

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Introduction

In addition to the well-known effects of dopamine on prolactin secretion, central dopaminergic signaling has been implicated in the regulation of ingestive behavior, insulin sensitivity and energy partitioning. A reduction in dopamine levels and/or function has been reported in obese rodents [1, 2] and humans [3, 4]. Dopaminergic reward pathways arise from mesencephalic nuclei and project axons to brain regions involved in motivation (striatum), emotion (limbic system) and higher order functions (frontal cortex). There are five receptor subtypes classified into two main classes called D1R-like (D1 and D5) and D2R-like (D2, D3, and D4) receptors. Functional dissection of components related to eating behavior indicate that D1 agonists act to decrease meal frequency whereas D2 agonists reduce meal number in rodents [5]. Neuroimaging studies have shown that obese individuals have significantly lower D2/D3 receptor levels [4], which presumably decreases sensitivity to reward stimuli resulting in food seeking behavior. 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, in some cases in the absence of increased body weight [6, 7]. Conversely, pharmacologic agents that increase dopamine release or inhibit dopamine reuptake can reduce food intake in animals [8] and in humans [9, 10].

Dopamine deficiency also results in hyperprolactinemia which in turn appears to be a neuroendocrine cause of weight gain, impaired glucose intolerance, hyperinsulinemia and insulin resistance in animals [11] and humans [12, 13]. There a number of proposed mechanisms by which hyperprolactinemia can result in weight gain [14]. Prolactin-induced hyperphagia may be mediated by increasing hypothalamic levels of the appetite-stimulating hormones, neuropeptide Y, agouti-related protein and corticotropin releasing hormone [15, 16]. Chronically elevated prolactin levels may increase adiposity and insulin resistance by inducing lipogenesis and central leptin resistance [14, 17], inhibiting adiponectin [18], and by suppressing D2 receptor-mediated dopaminergic neural signaling to peripheral tissues promoting visceral fat storage [19].

To better understand the involvement of dopamine and prolactin in overeating, obesity and glucose homeostasis, several investigators studied the effects of pharmacological agents that target dopamine receptors. Bromocriptine, an activator of D2-R in the central nervous system reduces body fat, serum glucose, and insulin resistance in hamsters [20, 21]. Significant weight loss was associated with normalization of circulating prolactin levels after dopamine agonist therapy for prolactinomas in humans [13, 22]. Several studies have examined the effects of various formulations of bromocriptine in humans without prolactinomas [23]. Bromocriptine reduced body weight in an observational study of obese non-diabetic and diabetic subjects [24]. Bromocriptine-QR, a fast absorbing form of bromocriptine also known as Ergoset or Cycloset, modestly decreased 24 hr glucose levels in obese nondiabetic, hyperinsulinemic women on a weight maintaining diet [25], and caused greater weight loss and improved glucose tolerance compared with placebo in a mixed group of non-diabetic and diabetic subjects [26]. This quick release formulation of bromocriptine has been approved in the US as adjunctive treatment for type 2 diabetes mellitus [27].

Cabergoline is a potent long-acting dopamine agonist, that is more effective and better tolerated than bromocriptine in the treatment of hyperprolactinemia [28, 29]. Berinder *et al.* [30] observed a significant decrease in body weight in obese men with prolactinomas following 6 months of treatment with either bromocriptine or cabergoline that was not seen in obese women. Another group noted improvement in insulin resistance and triglycerides, but no change in BMI following six months of bromocriptine or cabergoline therapy [31].

We have also previously shown in a retrospective chart review that the use of cabergoline was associated with weight loss in patients treated for prolactinomas [32]. The effect of cabergoline on weight loss in obese persons with normal prolactin levels has yet to be investigated. Given the experimental evidence in animals and humans, it is plausible that cabergoline may reduce food intake, body weight and improve glucose tolerance. The current study examines the effect of cabergoline and dietary modification on body weight and glucose homeostasis in non-diabetic obese persons without hyperprolactinemia.

Materials and Methods

Participants

Eligible subjects were women and men 16 to 55 years old with a body mass index (BMI) of 30 - 42 kg/m². Women were either infertile or used appropriate contraceptive measures. Subjects were excluded if they were pregnant, lactating, or had a history of diabetes or cardiovascular, neurological, hepatic, renal, gastrointestinal, or psychiatric disease, untreated thyroid disease, alcohol or substance abuse, current smoker or recent cessation of smoking, bulimia or anorexia nervosa, weight loss of 5 kg or more within the past year, use of medications that could effect prolactin levels, body weight or glucose homeostasis, or use of weight loss medication for more than two weeks during the prior 180 day period or administration within 30 days prior to screening of opiates or glucocorticoids. A total of 61 individuals were screened to obtain 40 participants who met the qualifications for randomization. The study was approved by the Columbia University Institutional Review Board and all subjects signed informed consent.

Protocol

Out of 61 screened volunteers, 40 met inclusion criteria and were assigned to placebo or active compound using a randomized scheme generated by our research pharmacy. The active compound was cabergoline (0.25mg) given orally twice a week before bedtime for 4 weeks, and then escalated to 0.5 mg biweekly for the next 12 weeks, which is a typical dose for the treatment of hyperprolactinemia. Nutritionists from the Clinical Research Center provided a high fiber diet plan with a 500 kcal deficit calculated from the Harris Benedict formula adjusted for sex and activity, with a maximal intake of 1,800 kcal/d. The diet consisted of 25%, 55%, and 20% of energy as fat, carbohydrate, and protein, respectively, divided into 3 meals and an afternoon and evening snack. Subjects were asked to maintain a stable physical activity level and return at 4-week intervals for a total of 16 weeks. At the initial and final visits a 75 gm oral glucose tolerance test (OGTT) was performed with blood samples drawn at time 0, 60, 90, and 120 minutes. Every 4 weeks, waist circumference and weight measurements were recorded and pills counted to check compliance with study medication. Follow-up visits also included a biochemistry panel and monitoring for adverse events and medication or life-style changes. Serum prolactin levels, expected to decline in subjects receiving active compound, were also indicative of subject compliance, but were measured at study completion to avoid “unblinding” the investigator.

Materials and Methods

Serum and plasma samples in EDTA were stored at -80 C until assayed. Serum prolactin was measured by RIA (Diagnostics Products Corporation, Los Angeles, CA). Sensitivity was 1.0 ng/ml, with intra- and inter-assay coefficients of 3.1 and 7.5%, respectively. Serum insulin and leptin concentrations were measured by RIA (Linco Research, St. Charles, MO). Serum glucose was measured by the hexokinase method.

Statistical Analysis

The primary endpoint was absolute weight change from baseline to week 16. The study was designed to account for dropouts such that with 12 subjects in each group there would be 80% power at the two-tailed a level of 0.05 to detect an 8 kg difference in mean body weight assuming a standard deviation (SD) of 7 kg in initial body weight. Insulin resistance and sensitivity were calculated using the homeostasis model of assessment (HOMA-IR: (fasting insulin (mU/ml) x fasting glucose (mmol/L))/22.5). Values for the area under the curve (AUC) were calculated using the trapezoidal rule. A mixed model for repeated measures was constructed for each primary outcome with fixed effects for treatment group, time and group by time interaction with the initial baseline value of the outcome entered as a continuous covariate. All models used an ARIMA(1) covariance structure for the autocorrelation with time. Results are presented as model estimated means and SEM and within-group between time and between-group same time comparisons relied upon model estimated 95% confidence intervals. For conversion to S.I. units multiply by the following factors given in parentheses: Glucose mg/dL to mmol/L (0.0555); Insulin μ U/ml to pmol/L (6.945); Cholesterol, LDL, HDL mg/dL to mmol/L (0.0259); Triglycerides mg/dL to mmol/L (0.0113).

Results

A total of 11 subjects (27.5%) dropped out during the 16 week study period: 4 subjects from the placebo group (2 lost to follow-up; 1 removed due to unrelated medical condition; 1 removed due to protocol violation); 7 subjects from the cabergoline group (5 lost to follow-up; 1 subject preference due to lack of weight loss; 1 unrelated medical condition). Changes in clinical and biochemical characteristics are presented in Table 1. Baseline characteristics were similar between groups. As expected, prolactin levels decreased in the treatment group only.

Weight loss was apparent in both groups over time ($P = 0.019$) but did not differ between groups ($P = 0.191$). Statistically significant changes were not observed in any of the glucose homeostatic parameters analyzed (Table 1 and Fig. 1). However, in the placebo group there was a tendency for HOMA-IR and insulin AUC to increase (40% and 16%, respectively) whereas these parameters remained relatively stable or tended to decrease in the cabergoline group (1.5% increase and -22% decrease, respectively). After cabergoline treatment, post-prandial glucose and insulin decreased ($P = 0.029$ for both parameters at 90 min. At 16 weeks, 120 min values for glucose and insulin were increased in the placebo group ($P = 0.016$ and 0.072 , respectively). Results and data interpretation were similar when controlling for baseline prolactin and when analysis was restricted to include only those subjects who completed the entire 16 weeks of study (data not shown). Baseline and 16 week levels of serum lipids did not differ between groups.

Discussion

This is the first study that examines the effects of cabergoline on body weight and glucose homeostasis in healthy obese persons without hyperprolactinemia. The main impetus for this study was our observation of weight loss in patients treated with cabergoline for prolactin secreting pituitary adenomas in our Neuroendocrine unit [32]. In addition to measuring body weight, the other main objective of this study was to determine if cabergoline therapy improves insulin resistance and glucose tolerance as demonstrated in some [33, 34], but not all [25], studies with quick release bromocriptine.

Although modest weight loss was achieved over a 16-week period, we found that cabergoline treatment was not more effective than placebo in this regard. It is unlikely that

lack of efficacy with respect to body weight was due to treatment non-compliance since prolactin levels decreased in subjects randomized to drug therapy. To our knowledge, only one randomized study demonstrated weight loss with dopamine therapy in individuals without hyperprolactinemia (6.3 kg with Ergoset compared with 0.9 kg placebo) [26] while three other randomized studies did not observe an effect on body weight [34-36]. Another study reported weight loss with Ergoset in otherwise healthy obese subjects but the results are difficult to interpret due to lack of a placebo control group [24]. The reasons for discrepant results between these studies are unclear, but may be due to differences in the formulation of dopamine, duration of treatment, dietary and life-style interventions, or clinical characteristics of the subjects, such as type 2 diabetes requiring other medical therapy that could affect body weight.

Several reports have indicated that prolactinomas are associated with obesity [14, 37]. Treatment of prolactinomas with dopamine agonist therapy appears to reduce body weight [13, 14, 32, 38] although weight loss was not observed in one study [31]. Monitoring body weight after treatment for prolactinoma is complicated due to the complex hormonal deficiencies that may be altered with therapy, therefore, it is extremely difficult to decipher whether weight loss is due to dopamine agonist therapy and/or changes in growth hormone, gonadal, thyroid or adrenal function. The result of our study in healthy individuals suggests that changes in body weight noted in patients with prolactinomas may be primarily dependent on the normalization of prolactin levels and/or other hormone levels rather than an increase in dopaminergic tone independent of prolactin signaling.

Treatment with bromocriptine has been reported to improve or prevent worsening of glucose tolerance independent of changes in body weight in individuals without hyperprolactinemia and with or without diabetes [24, 25, 34, 35]. The effect of bromocriptine is most prominent in post-prandial states with reductions in AUC glucose and insulin concentrations as opposed to decreases in fasting glycaemia [25, 26]. Of interest in our study, is the tendency towards stabilization or improvement in HOMA-IR and insulin AUC in the cabergoline group with the opposite tendency occurring in the placebo group. Post-prandial glucose increased over time in the placebo group, but decreased after cabergoline treatment. These results are intriguing in their similarity to data reported on Cycloset, which has recently been approved as an adjunct to diet and exercise for type 2 diabetics [39]. For example, there were no changes in body weight (+0.2 kg), fasting glucose (0 mg/dl) or HbA1c (-0.1%) in 80 overweight subjects with diabetes treated for 24 weeks with Cycloset as monotherapy; the corresponding changes in the placebo group were +0.5 kg, +23 mg/dl, and +0.3%, respectively. Although the changes after treatment within the Cycloset group were not statistically significant, the changes from baseline in the treatment group adjusted with changes after placebo were considered both statistically and clinically significant: fasting glucose (-23 mg/dl) and HbA1c (-0.4%). Similar results were obtained in several other studies using Cycloset as add-on therapy for the treatment of type 2 diabetes suggesting that bromocriptine therapy abated the progressive worsening of glycemic control and that this effect was achieved in the absence of a change in body weight.

In retrospect, one of the limitations of our study is the enrollment of obese individuals with relatively normal glycaemic indices that are similar to the fasting glucose and HOMA-IR values reported in a population of subjects with normal glucose tolerance [40]. Since the main objective of this study was based on body weight as a primary endpoint, subjects were enrolled if they did not meet criteria for diabetes, but glucose tolerance or insulin levels were not among the inclusion criteria. Changes in this small pilot study may have been more apparent had our inclusion criteria been restricted to individuals with hyperinsulinemia and/or to parameters used to select individuals at higher risk of developing diabetes such as those in the Diabetes Prevention Program [41]. Although there was a slight reduction in body

weight in both groups, dietary compliance was clearly lacking as greater weight loss should have been achieved with the prescribed calorie deficit. While bromocriptine has been shown to reduce body fat stores in obese subjects without influencing caloric intake [24], waist circumference, as a surrogate measure of visceral adiposity in our study did not change, but perhaps more subtle changes could have been detected with radiologic assessments of visceral fat as this pilot study was powered to detect large effects on body weight. Interestingly, in a randomized trial to study safety of Cycloset in patients with T2DM fewer patients experienced a cardiovascular disease event [42]. Changes in body weight were not noted although the treatment group exhibited a small decrease in triglycerides. Another limitation of this pilot study is the possible introduction of sex bias given that 4 men were randomized to Cabergoline treatment and none to the Placebo group.

By the time the diagnosis of impaired glucose tolerance is made, a significant fraction of beta-cell function is already lost. It has been shown that life-style intervention or pharmacotherapy may alter the course towards further beta-cell failure and mitigate progression to T2DM. To date there has been an accumulation of biological evidence supporting dopaminergic regulation of glucose homeostasis. Cycloset appears to abate further deterioration of glycaemic control in individuals with T2DM. The results of this pilot study suggest that dopamine agonist therapy may also be beneficial in maintaining glucose tolerance without necessitating increased insulin secretion. The use of ergot derivatives may not be realistic for a larger population due to fibrotic-related complication [43, 44], however, non-ergot derivatives that act as dopamine receptor agonists may be a plausible option for future therapeutic considerations. Larger studies with safer and more tolerable dopaminergic agents in an appropriately selected subjects are warranted to determine if such therapy may abate progressive worsening of glucose tolerance in a diabetes-prone population.

Acknowledgments

This study was funded by a Pilot Award to J.K. from the Office of Clinical Trials, College of Physicians & Surgeons of Columbia University and Columbia University Medical Center and UL1 RR024156 from the National Center for Research Resources, a component of the National Institutes of Health.

References

- [1]. Rada P, Bocarsly ME, Barson JR, Hoebel BG, Leibowitz SF. Reduced accumbens dopamine in Sprague-Dawley rats prone to overeating a fat-rich diet. *Physiol Behav.* 2010; 101:394–400. [PubMed: 20643155]
- [2]. Levin BE, Dunn-Meynell AA. Dysregulation of arcuate nucleus preproneuropeptide Y mRNA in diet-induced obese rats. *Am J Physiol.* 1997; 272:R1365–1370. [PubMed: 9176325]
- [3]. Stice E, Yokum S, Blum K, Bohon C. Weight gain is associated with reduced striatal response to palatable food. *J Neurosci.* 2010; 30:13105–13109. [PubMed: 20881128]
- [4]. Wang GJ, Volkow ND, Logan J, et al. Brain dopamine and obesity. *Lancet.* 2001; 357:354–357. [PubMed: 11210998]
- [5]. Terry P, Gilbert DB, Cooper SJ. Dopamine receptor subtype agonists and feeding behavior. *Obes Res.* 1995; 3(Suppl 4):515S–523S. [PubMed: 8697052]
- [6]. Henderson DC. Diabetes mellitus and other metabolic disturbances induced by atypical antipsychotic agents. *Curr Diab Rep.* 2002; 2:135–140. [PubMed: 12643133]
- [7]. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry.* 2001; 62(Suppl 7):22–31. [PubMed: 11346192]
- [8]. Heffner TG, Zigmond MJ, Stricker EM. Effects of dopaminergic agonists and antagonists of feeding in intact and 6-hydroxydopamine-treated rats. *J Pharmacol Exp Ther.* 1977; 201:386–399. [PubMed: 859104]

- [9]. Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2010; 376:595–605. [PubMed: 20673995]
- [10]. Gadde KM, Yonish GM, Foust MS, Wagner HR. Combination therapy of zonisamide and bupropion for weight reduction in obese women: a preliminary, randomized, open-label study. *J Clin Psychiatry*. 2007; 68:1226–1229. [PubMed: 17854247]
- [11]. Reis FM, Reis AM, Coimbra CC. Effects of hyperprolactinaemia on glucose tolerance and insulin release in male and female rats. *J Endocrinol*. 1997; 153:423–428. [PubMed: 9203996]
- [12]. Serri O, Beauregard H, Rasio E, Hardy J. Decreased sensitivity to insulin in women with microprolactinomas. *Fertil Steril*. 1986; 45:572–574. [PubMed: 3956771]
- [13]. Greenman Y, Tordjman K, Stern N. Increased body weight associated with prolactin secreting pituitary adenomas: weight loss with normalization of prolactin levels. *Clin Endocrinol (Oxf)*. 1998; 48:547–553. [PubMed: 9666865]
- [14]. Doknic M, Pekic S, Zarkovic M, et al. Dopaminergic tone and obesity: an insight from prolactinomas treated with bromocriptine. *Eur J Endocrinol*. 2002; 147:77–84. [PubMed: 12088923]
- [15]. Strader AD, Buntin JD. Changes in agouti-related peptide during the ring dove breeding cycle in relation to prolactin and parental hyperphagia. *J Neuroendocrinol*. 2003; 15:1046–1053. [PubMed: 14622434]
- [16]. Bina KG, Cincotta AH. Dopaminergic agonists normalize elevated hypothalamic neuropeptide Y and corticotropin-releasing hormone, body weight gain, and hyperglycemia in ob/ob mice. *Neuroendocrinology*. 2000; 71:68–78. [PubMed: 10644901]
- [17]. Augustine RA, Grattan DR. Induction of central leptin resistance in hyperphagic pseudopregnant rats by chronic prolactin infusion. *Endocrinology*. 2008; 149:1049–1055. [PubMed: 18063686]
- [18]. Asai-Sato M, Okamoto M, Endo M, et al. Hypoadiponectinemia in lean lactating women: Prolactin inhibits adiponectin secretion from human adipocytes. *Endocr J*. 2006; 53:555–562. [PubMed: 16849835]
- [19]. Kok P, Roelfsema F, Frolich M, Meinders AE, Pijl H. Prolactin release is enhanced in proportion to excess visceral fat in obese women. *J Clin Endocrinol Metab*. 2004; 89:4445–4449. [PubMed: 15356045]
- [20]. Luo S, Meier AH, Cincotta AH. Bromocriptine reduces obesity, glucose intolerance and extracellular monoamine metabolite levels in the ventromedial hypothalamus of Syrian hamsters. *Neuroendocrinology*. 1998; 68:1–10. [PubMed: 9695933]
- [21]. Luo S, Liang Y, Cincotta AH. Intracerebroventricular administration of bromocriptine ameliorates the insulin-resistant/glucose-intolerant state in hamsters. *Neuroendocrinology*. 1999; 69:160–166. [PubMed: 10087448]
- [22]. Galluzzi F, Salti R, Stagi S, La Cauza F, Chiarelli F. Reversible weight gain and prolactin levels--long-term follow-up in childhood. *J Pediatr Endocrinol Metab*. 2005; 18:921–924. [PubMed: 16279371]
- [23]. 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; 3:43–48. [PubMed: 21437075]
- [24]. Meier AH, Cincotta AH, Lovell WC. Timed bromocriptine administration reduces body fat stores in obese subjects and hyperglycemia in type II diabetics. *Experientia*. 1992; 48:248–253. [PubMed: 1547854]
- [25]. Kamath V, Jones CN, Yip JC, 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; 20:1697–1701. [PubMed: 9353611]
- [26]. Cincotta AH, Meier AH. Bromocriptine (Ergoset) reduces body weight and improves glucose tolerance in obese subjects. *Diabetes Care*. 1996; 19:667–670. [PubMed: 8725871]
- [27]. Holt RI, Barnett AH, Bailey CJ. Bromocriptine: old drug, new formulation and new indication. *Diabetes Obes Metab*. 2010; 12:1048–1057. [PubMed: 20977575]

- [28]. De Rosa M, Colao A, Di Sarno A, et al. Cabergoline treatment rapidly improves gonadal function in hyperprolactinemic males: a comparison with bromocriptine. *Eur J Endocrinol*. 1998; 138:286–293. [PubMed: 9539303]
- [29]. Webster J, Piscitelli G, Polli A, Ferrari CI, Ismail I, Scanlon MF, Cabergoline Comparative Study Group. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. *N Engl J Med*. 1994; 331:904–909. [PubMed: 7915824]
- [30]. Berinder K, Nystrom T, Hoybye C, Hall K, Hulting AL. Insulin sensitivity and lipid profile in prolactinoma patients before and after normalization of prolactin by dopamine agonist therapy. *Pituitary*. 2010
- [31]. Dos Santos Silva CM, Barbosa FR, Lima GA, et al. BMI and Metabolic Profile in Patients With Prolactinoma Before and After Treatment With Dopamine Agonists. *Obesity (Silver Spring)*. 2011; 19:800–805. [PubMed: 20559294]
- [32]. Korner J, Lo J, Freda PU, Wardlaw SL. Treatment with cabergoline is associated with weight loss in patients with hyperprolactinemia. *Obes Res*. 2003; 11:311–312. [PubMed: 12582229]
- [33]. Cincotta AH, Meier AH, Cincotta M Jr. Bromocriptine improves glycaemic control and serum lipid profile in obese Type 2 diabetic subjects: a new approach in the treatment of diabetes. *Expert Opin Investig Drugs*. 1999; 8:1683–1707.
- [34]. Pijl H, Ohashi S, Matsuda M, et al. Bromocriptine: a novel approach to the treatment of type 2 diabetes. *Diabetes Care*. 2000; 23:1154–1161. [PubMed: 10937514]
- [35]. Aminorroaya A, Janghorbani M, Ramezani M, Haghighi S, Amini M. Does bromocriptine improve glycemic control of obese type-2 diabetics? *Horm Res*. 2004; 62:55–59. [PubMed: 15205563]
- [36]. Wasada T, Kawahara R, Iwamoto Y. Lack of evidence for bromocriptine effect on glucose tolerance, insulin resistance, and body fat stores in obese type 2 diabetic patients. *Diabetes Care*. 2000; 23:1039–1040. [PubMed: 10895875]
- [37]. Shibli-Rahhal A, Schlechte J. The effects of hyperprolactinemia on bone and fat. *Pituitary*. 2009; 12:96–104. [PubMed: 18338266]
- [38]. Creemers LB, Zelissen PM, van 't Verlaat JW, Koppeschaar HP. Prolactinoma and body weight: a retrospective study. *Acta Endocrinol (Copenh)*. 1991; 125:392–396. [PubMed: 1957557]
- [39]. USFDA. Cycloset Prescribing Information.
- [40]. Haffner SM, Miettinen H, Stern MP. The homeostasis model in the San Antonio Heart Study. *Diabetes Care*. 1997; 20:1087–1092. [PubMed: 9203442]
- [41]. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002; 346:393–403. [PubMed: 11832527]
- [42]. Gaziano JM, Cincotta AH, O'Connor CM, et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care*. 2010; 33:1503–1508. [PubMed: 20332352]
- [43]. Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med*. 2007; 356:29–38. [PubMed: 17202453]
- [44]. Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med*. 2007; 356:39–46. [PubMed: 17202454]

Figure 1. Serum glucose and insulin levels during OGTT at week 0 (dotted line) and week 16 (solid line) in groups treated with placebo (left column) or cabergoline (right column). * $P < 0.05$ for within group difference between week 0 vs week 16

Table 1

Baseline and week 16 characteristics

	Placebo			Cabergoline		
	Week 0	Week 16	P-value	Week 0	Week 16	P-value
N (M/F)	0/19	0/16	-	4/16	4/9	-
Age (y)	41.5 ± 2.2	-	-	38.0 ± 2.4	-	-
Weight (kg)	93.9 ± 2.9	92.8 ± 2.9	0.10	99.5 ± 2.8	98.3 ± 2.9	0.09
BMI (kg/m²)	35.2 ± 0.8	34.8 ± 0.8	0.09	35.5 ± 0.8	35.1 ± 0.8	0.11
Prolactin (μg/L)	7.6 ± 1.0	8.5 ± 1.1	0.34	4.8 ± 1.0	1.6 ± 0.4	<0.001
Glucose (mg/dL)	91.7 ± 2.7	94.6 ± 2.8	0.30	89.0 ± 2.7	91.4 ± 3.3	0.47
Insulin (μU/ml)	10.1 ± 1.9	12.8 ± 2.0	0.24	13.6 ± 1.9	13.4 ± 2.4	0.97
HOMA-IR	2.3 ± 0.5	3.1 ± 0.5	0.15	2.7 ± 0.5	2.7 ± 0.63	0.97
Glucose AUC (×10³)	14.8 ± 1.1	15.2 ± 1.0	0.69	14.6 ± 1.0	12.8 ± 1.3	0.16
Insulin AUC (×10³)	6.2 ± 1.8	7.2 ± 1.9	0.55	9.0 ± 1.8	7.0 ± 2.1	0.31
Leptin (ng/ml)	29.5 ± 3.1	27.6 ± 3.1	0.40	25.6 ± 3.4	24.4 ± 3.5	0.65
Cholesterol (mg/dL)	200 ± 8	192 ± 9	0.35	202 ± 8	196 ± 10	0.54
LDL (mg/dL)	127 ± 8	119 ± 8	0.24	131 ± 7	127 ± 9	0.63
HDL (mg/dL)	51 ± 2	52 ± 3	0.50	48 ± 2	47 ± 3	0.74
Triglycerides (mg/dL)	111 ± 11	105 ± 12	0.40	115 ± 11	111 ± 12	0.58

Values represent model estimated means ± SEM

Bold signifies statistically different between group means at specific week

P-value is for within-group average within-subject change over time