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SOCIETY OF ENDOCRINOLOGY AND METABOLISM OF TÜRKİYE

Effect of Dopamine Agonist Treatment on Glycemic Control in Patients with Lipodystrophy

SHORT REPORT
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ABSTRACT

Lipodystrophies involve the loss of subcutaneous adipose tissue, resulting in severe metabolic issues such as insulin resistance and challenging diabetes management. This case series aims to assess bromocriptine treatment response in lipodystrophy patients, offering insights into its antidiabetic effects. This retrospective analysis focused on four female lipodystrophy patients with poor glycemic control who were undergoing bromocriptine treatment. Statistical analysis used non-parametric tests. Metabolic parameters were assessed before and 3 months post-bromocriptine treatment, revealing a modest reduction in median daily insulin dose and decreased hemoglobin A1c and fasting glucose levels. Body weight remained constant, while triglyceride levels increased. Dopamine receptor expression in pancreatic β-cells and adipocytes suggests a direct impact on glucose homeostasis. While this case series hints at bromocriptine's positive influence on glycemic control and insulin requirements in lipodystrophy patients, larger studies are essential for establishing efficacy and safety.

Keywords: Insulin resistance, lipodystrophy, diabetes, dopamine, bromocriptine

Introduction

Lipodystrophies are congenital or acquired conditions characterized by the absence or loss of subcutaneous adipose tissue in a generalized or partial distribution. The dystrophy of subcutaneous adipose tissue results in severe metabolic complications and specific clinical findings such as severe insulin resistance, difficult glycemic control, and hypertriglyceridemia.[1]

Leptin replacement therapy has shown promise in ameliorating metabolic abnormalities in patients with lipodystrophy.[2] Metformin and thiazolidinediones have demonstrated some efficacy in treating hyperglycemia and hyperlipidemia in patients with lipodystrophy.[3,4] Despite metformin being the preferred first-line agent for treating insulin resistance in lipodystrophy, patients usually require high insulin doses for adequate glycemic control.

The dopamine agonists, bromocriptine and cabergoline, have long been used to treat prolactinoma.[5] Studies have demonstrated that bromocriptine treatment reduces glycated hemoglobin A1c (HbA1c), fasting plasma glucose, and body weight in patients with type 2 diabetes mellitus (T2DM), leading to its approval by the Food and Drug Administration for T2DM treatment since 2009.[6,7] The putative mechanisms of action of bromocriptine on glucose metabolism include decreasing prolactin secretion, indirectly increasing the activity of key melanocortin receptors in the central nervous system, and improving/restoring circadian rhythms.[8,9] Moreover, studies have demonstrated that beta cells express type 2 dopamine receptors (D2R), and bromocriptine decreases central sympathetic activity. Therefore, regulating pancreatic circadian rhythm and decreasing hepatic glucose production may be the key mechanism of action of bromocriptine.[10,11]

Given the severe metabolic complications caused by leptin deficiency in lipodystrophy, it is crucial to explore new therapeutic options for managing diabetic complications aggravated by hyperglycemia. This case series aims to evaluate the response to bromocriptine treatment in lipodystrophy patients and present new insights into the anti-diabetic effects of this treatment in the literature.

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Materials and Methods

We conducted a retrospective cohort study of patients diagnosed with lipodystrophy receiving treatment at our clinic. We analyzed the records of patients undergoing bromocriptine treatment. Four female patients on bromocriptine based on poor glycemic control were identified. Patients were administered bromocriptine at a dose of 1 × 1.25 mg/day for the first week, followed by 1 × 2.5 mg/day. The drug was taken within the first 2 hours after waking up.

This case series was approved by the Ege University Faculty of Medicine Ethics Committee with the decision dated June 13, 2023, and numbered 23-6T/5. Verbal and written informed consent was obtained from the patients who agreed to take part in the study.

Results

In total, the results of 4 patients were evaluated. The median age of the patients was 54 years, the youngest being 48 years old and the oldest 72 years old. All patients (100%) were female. Regarding lipodystrophy subtypes, 2 (50%) patients had congenital generalized lipodystrophy, and the other 2 (50%) patients had familial partial lipodystrophy. Parental consanguinity was present in 2 (50%) of the patients. Three patients (75%) had pancreatitis in their medical history, and 1 patient (25%) underwent plasmapheresis. All patients (100%) received combined therapy with insulin, metformin, thiazolidinedione, and sodium-glucose co-transporter 2 inhibitor therapy. No patient was using dipeptidyl peptidase-4 (DPP-4) inhibitor. One patient was taking statins, and 3 patients were using fibrates. Additionally, 1 patient was on angiotensin-converting enzyme inhibitor therapy (Table 1).

Table 2 presents the evaluation of metabolic parameters before and 3 months after bromocriptine treatment. One patient had elevated transaminases after bromocriptine treatment, while the transaminases of the other 3 patients remained unchanged.

Table 1. Baseline Characteristics of Patients

	Patient #1	Patient #2	Patient #3	Patient #4
Age (years)	30	19	70	21
Gender	Female	Female	Female	Female
Lipodystrophy subtype	CGL	CGL	FPLD	FPLD
Consanguinity	Yes	Yes	None	None
Pancreatitis	Yes	None	Yes	Yes
Plasmapheresis	Yes	None	None	None
Insulin use	Yes	Yes	Yes	Yes
Metformin use	Yes	Yes	Yes	Yes
Thiazolidinedione use	Yes	Yes	Yes	Yes
SGLT2 inhibitor use	Yes	Yes	Yes	Yes
DPP-4 inhibitor use	None	None	None	None
Statin use	Yes	None	None	None
Fibrate use	Yes	Yes	None	Yes
ACE inhibitor use	Yes	None	None	None

ACE, angiotensin converting enzyme; CGL, congenital generalized lipodystrophy; DPP-4, dipeptidyl peptidase-4; FPLD, familial partial lipodystrophy; SGLT2, sodium-glucose co-transporter 2.

Table 2. Metabolic Parameters Before and 3 Months After Bromocriptine Treatment

	Patient #1		Patient #2		Patient #3		Patient #4	
Variable	Before	After	Before	After	Before	After	Before	After
Daily total insulin dose (IU)	26	26	8	14	66	54	142	112
HbA1c (%)	9.2	7.5	10.4	6.9	8.3	7.3	11.0	7.8
Fasting plasma glucose (mg/dL)	129	133	308	111	104	91	376	123
Weight (kg)	50	51.8	48	46.7	72	65.5	58	58.2
TG (mg/dL)	221	267	1143	950	83	68	204	312
Total-C (mg/dL)	171	150	359	186	127	121	206	222
HDL-C (mg/dL)	31	33	17	18	35	33	31	40
Non-HDL-C (mg/dL)	140	117	342	168	92	88	175	182
eGFR (mL/min/1.73 m^2)	91	96	148	142	74	82	137	135
Spot urine albumin/creatinine ratio (mg/g)	3069.1	3343.0	120	64.1	7	3.1	6	9.7
AST (U/L)	13	12	27	31	26	23	12	530
ALT (U/L)	11	16	32	43	15	14	23	795
PRL (µg/L)	16.63	4.49	6.12	0.05	12.79	0.62	31.25	12.97

ALT, alanine aminotransferase; AST, aspartate aminotransferase; C, cholesterol; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; PRL, prolactin; TG, triglyceride.

Discussion

The understanding of brain insulin resistance emerged as the pathophysiology of diabetes expanded from the "ominous triumvirate" in 1987 to the "ominous octet" in 2009.[12,13] Early morning hypothalamic dopamine levels are decreased in diabetic patients, which in turn increases central sympathetic activity; therefore, hepatic glucose production, lipolysis (increase in free fatty acid level), and lipogenesis (increase in TG level) increase, and dopamine levels are restored with early morning bromocriptine administration.[10] Moreover, studies have demonstrated that activation of D2R in adipocytes leads to upregulation of leptin and IL-6 and may have a tissue-specific proinflammatory effect.[14] These observations led us to evaluate the efficacy and safety of bromocriptine in lipodystrophy.

In this cohort, we evaluated the response to bromocriptine treatment in a small group of lipodystrophy patients with poor glycemic control. Although the results did not reach statistical significance, notable trends were observed in several metabolic parameters. The median daily total insulin dose showed a slight reduction after bromocriptine treatment, suggesting a potential beneficial effect on insulin requirements. HbA1c and glucose levels also improved, indicating improved glycemic control, which further supports the potential of bromocriptine in managing hyperglycemia. However, it is important to note that these findings did not reach statistical significance, possibly due to the lack of clusters for analysis caused by the small sample size. In addition, the absence of a significant change in body weight after bromocriptine treatment may be due to the short time interval of the case series. However, it is necessary to evaluate whether there is a change in fat distribution rather than weight loss in this group, which was one of the limitations of our case series.

While the number of cases to support our findings is insufficient, these findings suggest that modulating dopamine activity in the brain may have a beneficial effect on metabolic parameters, including glycemic control.[15]

The most commonly reported adverse events associated with bromocriptine in clinical trials have included nausea, vomiting, dizziness, headache, somnolence, and fatigue. Still, these effects have been primarily transient and have resolved within days of dosage decreases or discontinuation of the drug. No side effects other than mild dizziness were reported in the patient files.

It is essential to acknowledge the limitations of this case series presentation, which includes only four cases, due to its small sample size, retrospective design, and the absence of a control group. Therefore, to draw definitive conclusions and establish the efficacy of bromocriptine in lipodystrophy-related insulin-resistant diabetes, larger randomized and prospective studies with well-defined patient cohorts are warranted.

In conclusion, our preliminary findings suggest that bromocriptine treatment in patients with lipodystrophy may have a potential positive impact on glycemic control and insulin requirements. However, the limited sample size and absence of statistical significance call for further research. Such investigations will provide valuable insights for developing new strategies to improve metabolic outcomes in this challenging patient population.

Data availability statement: Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Ethics Committee Approval: The study was approved by the Ege University Faculty of Medicine Ethics Committee with the decision dated June 13, 2023, and numbered 23-6T/5.

Informed Consent: Verbal and written informed consent was obtained from the patients who agreed to take part in the study.

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References

1. Garg A. Lipodystrophies. *Am J Med*. 2000;108(2):143-152. [CrossRef]
2. Akinci B, Sahinoz M, Oral E. Lipodystrophy syndromes: presentation and treatment. In: *Endotext. South Dartmouth (MA)*. Feingold KR, Anawalt B, Boyce A, et al. eds. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29989768
3. Vantyghem MC, Vigouroux C, Magré J, et al. Late-onset lipoatrophic diabetes. Phenotypic and genotypic familial studies and effect of treatment with metformin and lispro insulin analog. *Diabetes Care*. 1999;22(8):1374-1376. [CrossRef]
4. Moreau F, Boullu-Sanchis S, Vigouroux C, et al. Efficacy of pioglitazone in familial partial lipodystrophy of the Dunnigan type: a case report. *Diabetes Metab*. 2007;33(5):385-389. [CrossRef]
5. Casanueva FF, Molitch ME, Schlechte JA, et al. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. *Clin Endocrinol (Oxf)*. 2006;65(2):265-273. [CrossRef]
6. Pijl H, Ohashi S, Matsuda M, et al. Bromocriptine: a novel approach to the treatment of type 2 diabetes. *Diabetes Care*. 2000;23(8):1154-1161. [CrossRef]
7. Mahajan R. Bromocriptine mesylate: FDA-approved novel treatment for type-2 diabetes. *Indian J Pharmacol*. 2009;41(4):197-198. [CrossRef]
8. Framnes-DeBoer SN, Bakke E, Yalamanchili S, et al. Bromocriptine improves glucose tolerance independent of circadian timing, prolactin, or the melanocortin-4 receptor. *Am J Physiol Endocrinol Metab*. 2020;318(1):E62-E71. [CrossRef]
9. Tong Y, Pelletier G. Role of dopamine in the regulation of proopiomelanocortin (POMC) mRNA levels in the arcuate nucleus and pituitary gland of the female rat as studied by in situ hybridization. *Brain Res Mol Brain Res*. 1992;15(1-2):27-32. [CrossRef]
10. DeFronzo RA. Bromocriptine: a sympatholytic, d2-dopamine agonist for the treatment of type 2 diabetes. *Diabetes Care*. 2011;34(4):789-794. [CrossRef]
11. Wei H, Zapata RC, Lopez-Valencia M, et al. Dopamine D2 receptor signaling modulates pancreatic beta cell circadian rhythms. *Psychoneuroendocrinology*. 2020;113:104551. [CrossRef]
12. Defronzo RA. Banting lecture. from the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58(4):773-795. [CrossRef]
13. Cetinkalp S, Simsir IY, Ertek S. Insulin resistance in brain and possible therapeutic approaches. *Curr Vasc Pharmacol*. 2014;12(4):553-564. [CrossRef]
14. Wang X, Villar VA, Tiu A, Upadhyay KK, Cuevas S. Dopamine D2 receptor upregulates leptin and IL-6 in adipocytes. *J Lipid Res*. 2018;59(4):607-614. [CrossRef]
15. Shivaprasad C, Kalra S. Bromocriptine in type 2 diabetes mellitus. *Indian J Endocrinol Metab*. 2011;15:S17-S24. [CrossRef]