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# BROMOCRIPTINE IN THE TREATMENT OF DIABETIC RETINOPATHY

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## Introduction

The role of growth hormone (GH) in the pathogenesis of diabetic retinopathy (DR) is still under debate. But, although not essential for the development of retinopathy GH may still be important in modifying its course. The aim of our work was to test, in a double-blind study, the effects of bromocriptine (Parlodel®), a central dopamine agonist with GH suppressing activity on the metabolic control, GH levels and evolution of pre-proliferative DR in a group of insulin-dependent diabetics.

## Material and methods

The subjects were 12 insulin dependent diabetics-7 males and five females-with a mean age of 31 years (range, 24—45) and a mean duration of diabetes of 15 years (range, 9—26). They were all affected by advanced background DR (pre-proliferative) characterized by microaneurisms, hemorrages, hard exudates and cotton-wool spots (not present in all the patients) and numerous retinal ischemic areas, demonstrated by a previously performed fluorescein angiography. We chose this form of DR because of its evolution in a relatively brief period. The patients were randomly assigned in equal number to a placebo group and to a bromocriptine group (2.5 mg of bromocriptine three times a day) and treated for 12 months. Of the six patients receiving bromocriptine three were males and three females with a mean age of 30 years and mean duration of diabetes of 14 years. Of the six patients receiving placebo four were males and two females with a mean age of 31 years and mean duration of diabetes of 17 years. The following principal metabolic parameters were evaluated-at intervals of three months-: glycemia and GH profiles (8, 10, 14, 20 hrs), HbA1; we also assessed: cholesterol, tryglicerides, lactate, pyruvate, alanine, glycerol, acetoacetate, 3-hydroxybuthyrate, blood urea nitrogen and creatinine clearance. Every six months we evaluated the GH response after arginine infusion (25 g) and an electromyography was performed. From the ophthalmologic point of view all the patients were studied as follows: visual acuity, intraocular pressure, anterior segment biomicroscopy, ophthalmoscopy and fundus photography of both eyes were performed every 3 months. The fundus photography considered 5 fields in each eye. At the time 0, 6 and 12 months a fluorescein angiography of both eyes (with an interval of at least 72 hrs between the two eyes) was carried out: posterior pole and peripheral retina were analyzed. The metabolic parameters were statistically analyzed with the T unpaired test; GH profiles were evaluated with a non parametric test (Wilcoxon test). The retinopathy was assessed as follows: the ophthalmologists of the research group individually evaluated fundus photographies and fluorescein angiongraphies of each patient and reported a final judgement — particularly considering fluorescein angiography — : unchanged, worsened, improved. We considered unchanged a patient whose ischemic areas extension, qualitatively assessed, was unmodified; improved a situation of revascularization of ischemic areas; worsened a subject whose retinopathy demonstrated an evident extension of ischemic areas and/or the appearance of new vessels.

## Results

The metabolic control of diabetes, considered as glycemia areas and HbA1, between the two groups was not significantly modified neither between basal and 12 months values nor between bromocriptine and placebo subjects (Fig. 1). The

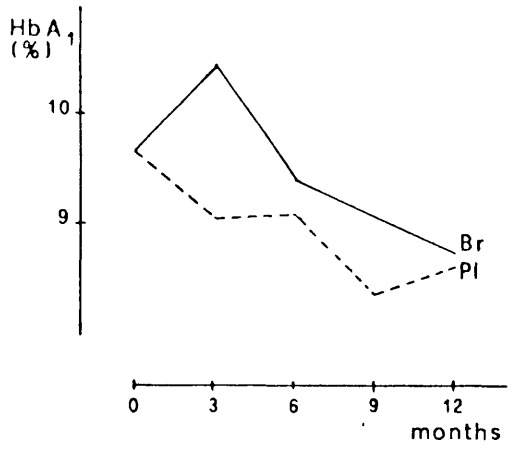


Fig. 1: Glycosilated hemoglobin in the two groups of patients.

other metabolic parameters and electromyography evidenced the same tendency. The GH profiles of placebo group during the 12 months are superimposable; the GH profiles of bromocriptine patients demonstrated a significant increase after 9 months of therapy compared to basal values (p 0.05 vs basal) (Fig. 2). Of the six placebo treated patients one evidenced an improvement of DR, one was unchanged and four worsened. Of the six bromocriptine treated patients four were unchanged and two worsened. No difference in the evaluation of the patients was evident among the examinators. Nobody of the patients reported side effects, and we were not able to evidence any complication due to the therapy.

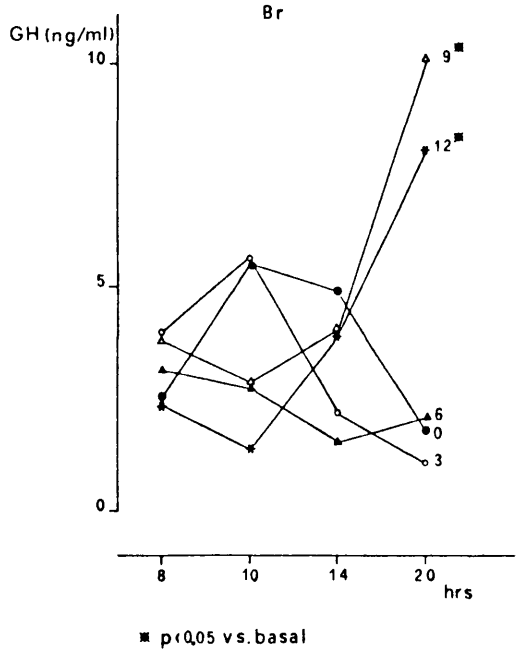


Fig. 2: GH levels in the bromocriptine-treated subjects (Br=bromocriptine)

## Discussion

In 1953 Poulsen first suggested an influence of the pituitary on the course of diabetic retinopathy. Subsequent studies in diabetic patients indicated a relation between the pituitary, especially GH, and the thickness of capillary basement membranes in many tissues, and a relation between GH and abnormalities of coagulation and fibrinolysis. Moreover, patients with diabetes and retinopathy appear to have higher levels of GH and GH-dependent insulin-like growth factors than do patients without DR (Merimee, 1984). In addition, hypophysectomy can arrest or slow the progression of proliferative DR. Furthermore, GH deficient dwarfs with diabetes usually, even not always, lack microvascular complications. Finally, GH or insulin-like growth factors may directly affect vascular smooth muscle and endothelium metabolism. All this data seems consistent with the hypothesis that GH has a role in the pathogenesis of DR. As a consequence some authors proposed the use of GH suppressors to modify the evolution of DR: none of these agents were effective (Lundbaek and Hansen, 1980). Zavala et al. (1979) reported some interesting, but questionable, data about the use of bromocriptine in the treatment of DR. We were not able, in our double-blind study, to confirm their positive data: we only evidenced a slight tendency — in the bromocriptine treated group —to a better course of pre-proliferative DR. Moreover, our study allows us to state that bromocriptine (7.5 mg daily) neither modifies the metabolic control of diabetes nor dignificantly influences the intermediate metabolites, and that this drug significantly increases GH levels after 9 months of therapy (a brief rise of GH is reported in normal subject after a dose of bromocriptine (Parkes, 1979) without a significant corresponding derangement of metabolic control. In agreement with Gerich (1984) considerations we suggest that the possible permissive role of GH on the course of DR needs particular attention and pharmacologic intervention aimed at suppressing GH secretion may be beneficial "not only in improving glycemia but also in preventing severe retinopathy".

## Summary

A double-blind clinical study was performed on a group of 12 insulin-dependent diabetics affected by pre-proliferative DR with bromocriptine, a dopamine agonist with GH suppressing activity. The authors evidenced that bromocriptine does not influence the course of pre-proliferative DR; does not modify the metabolic control of diabetes; increases plasma GH levels after 9 months of therapy. The — at least — permissive role of GH on the cource of diabetic retinopathy must be considered with attention and, if safely possible, it is better to suppress ist activity.

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