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Belančić, Andrej; Krpina, Marija; Klobučar Majanović, Sanja; Merlak, Maja

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• Letter to the Editor •

Ocular hypertension secondary to obesity: cortisol, the missing piece of the pathophysiological puzzle?

Andrej Belančić[1], Marija Krpina[1], Sanja Klobučar Majanović[1,2], Maja Merlak[1,3]

[1]University of Rijeka, Faculty of Medicine, Rijeka 51000, Croatia

[2]Department of Endocrinology, Diabetes and Metabolic Diseases, Clinical Hospital Centre Rijeka, Rijeka 51000, Croatia

[3]Department of Ophthalmology, Clinical Hospital Centre Rijeka, Rijeka 51000, Croatia

Correspondence to: Andrej Belančić. University of Rijeka, Faculty of Medicine, Braće Branchetta 20, Rijeka 51000, Croatia. a.belancic93@gmail.com

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Dear Editor,

Obesity has nowadays become a global public health challenge due to its rapidly growing prevalence and interconnection with a wide spectrum of comorbidities. A positive association of obesity with intraocular pressure (IOP) and glaucoma status has been confirmed in majority of studies[1]. Several etiology theories have been proposed: 1) excess in intraorbital adipose tissue, an increase in episcleral venous pressure and consequent impairment of aqueous outflow facility; 2) increased blood viscosity (red cell count, hemoglobin, hematocrit) and consequent increase in outflow resistance of episcleral veins; 3) increased ciliary artery pressure and aqueous humor ultrafiltration secondary to elevated blood pressure; 4) osmotic fluid shift into the intraocular space due to hyperglycemia. However, clear pathophysiological explanation for the association between obesity and ocular hypertension is currently lacking[1]. Hence, that provoked us to try to solve the pathophysiological puzzle.

Steroid-induced ocular hypertension was first described by McLean in 1950, who documented IOP elevation after systemic administration of adrenocorticotrophic hormone (ACTH). Side-effect of local corticosteroid administration was reported four years later by Francois. Nowadays it is well known that ocular hypertension can occur as a side-effect of both intravenous, topical, oral, inhaled, periocular and intravitreal corticosteroid therapy[2]. Furthermore, cases of increased IOP and open-angle glaucoma secondary to endogenous hypercortisolism (Cushing's syndrome/disease) are also well-documented[3]. It has also been reported that IOP in normal healthy subjects fluctuates diurnally with its peak at around 7 a.m. and trough during the early evening, which positively correlates with serum cortisol levels. On top of that, there is no diurnal IOP variation in patients with Cushing's syndrome/disease, patients with adrenal insufficiency maintained on daily divided doses of corticosteroids and adrenalectomysed patients[2].

Results of our preliminary cross-sectional study, conducted on 50 obese adults (80.0% female, median age of 44 years, body mass index 42.0±7.4 kg/m^2, waist circumference 124.2±16.5 cm), revealed that IOP is significantly positively correlated with morning basal serum cortisol (r=0.28, P=0.049), whilst no significant correlation was found between IOP and red blood cell count (r=0.01, P=0.966), hemoglobin (r=0,09, P=0.550) or hematocrit (r=0.14, P=0.329). Moreover, there was no significant difference in IOP based on diabetes mellitus (DM+ 17.0±2.0 *vs* DM- 15.9±2.0 mm Hg; P=0.339, Mann-Whitney U test) and arterial hypertension (AH+ 16.3±1.7 *vs* AH- 15.9±2.2 mm Hg; P=0.470, Mann-Whitney U test) status. Hence, that provoked us to question ourselves: Is cortisol the missing piece of the obesity-related ocular hypertension/open-angle glaucoma pathophysiological puzzle?

To clarify, abdominal/visceral obesity phenotype is associated with chronic hypothalamic-pituitary-adrenal axis hyperactivity, which leads to a condition of functional hypercortisolism[4]. 11β-hydroxysteroid dehydrogenase (11β-HSD) type 1 is overexpressed in adipose tissue of obese individuals and what is more, it positively correlates with measures of total (body mass index, body fat percentage) and central (waist circumference) adiposity, fasting glucose, insulin and insulin resistance[5]. 11β-HSD1 is a microsomal enzyme, expressed mainly in adipose tissue and liver, acting primarily as a nicotinamide adenine dinucleotide phosphate-dependent reductase *in vivo* interconverting inactive cortisone to active cortisol, thereby amplifying glucocorticoid receptor activation. The contrasting isoform, 11β-HSD2 is predominantly expressed in mineralocorticoid target tissues, where it inactivates

cortisol to cortisone thus excluding cortisol from exerting effects on non-selective mineralocorticoid receptors[6]. At this point it is of high importance to highlight that the presence of glucocorticoid and mineralocorticoid receptors and 11β-HSD in human and mammalian ocular tissues has been demonstrated in several studies[7]. Cortisol/cortisone ratio in the aqueous humour of 14:1 is suggested for predominant 11β-HSD1 activity[7]. Consequently, it is plausible that cortisol generation by overexpressed 11β-HSD1 (cortisone reductase) stimulates serum and glucocorticoid-regulated kinase isoform 1 to increase epithelium Na^+ transport and aqueous humor production[8]. On top of that, there is also a simultaneous decrease in aqueous humor outflow facility, since glucocorticoids are connected with miscellaneous effects on trabecular meshwork cells causing changes in trabecular meshwork protein expression, cytoskeletal organization, extracellular matrix deposition, cell shape and cell function, *etc*[2,9]. Finally, inhibition of 11β-HSD1 in the ocular ciliary epithelium lowers IOP in patients with ocular hypertension, which also upholds the latter hypothesis[8].

Last but not least, it is very interesting to highlight that cortisol is even a common link/denominator between the previously published (inidicated above as 1-4) obesity-related ocular hypertension theories. Cortisol, through its erythropoietic effects, may slightly increase blood viscosity[10]. Second, cortisol increases arterial blood pressure through interplay between several pathophysiological mechanisms: intrinsic mineralocorticoid activity; activation of the renin-angiotensin system; enhancement of cardiovascular reactivity to vasoconstrictors (catecholamines, vasopressin, angiotensin II); increased β-adrenergic receptor sensitivity to catecholamines; supression of the vasodilatory systems (NO synthase, prostacyclin, kinin-kallikrein); increased cardiac output, total peripheral resistance and renovascular resistance[11]. Furthermore, increased blood pressure is accompanied by increased ciliary artery pressure and aqueous humor ultrafiltration. Third, glucocorticoids enhance muscle protein breakdown, adipose tissue lipolysis, and hepatic tissue gluconeogenesis, and reduce glucose utilization, effects that elevate circulating glucose concentrations (whole-body insulin resistance), which may result in osmotic fluid shift into the intraocular space[12].

To deduce, we hypothesize that cortisol is the missing link between obesity and ocular hypertension and we propose the "cortisol" etiology theory.

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