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EFFECT OF SERUM CORTISOL AND PROLACTIN ON DIABETIC RETINOPATHY

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ABSTRACT

Diabetes mellitus[DM] is a group of metabolic disorders with various complications that include Nephropathy, Neuropathy and Retinopathy. Diabetic retinopathy refers to retinal changes seen in patients with diabetes mellitus which may lead to marked disability. Eye changes in Diabetes may lead to various hormonal changes and vice versa hormonal changes may increase the progression of diabetic retinopathy. Degree of cortisol secretion is related to the presence and number of diabetic complications (Diabetes care 30:83-88, 2007). The hormone prolactin is proteolytically processed to vasoinhibins, a family of peptides that inhibit the excessive retinal vasopermeability related to diabetic retinopathy after its intraocular conversion to vasoinhibins (Diabetes 59:3192-3197, 2010). The Research aims to find out whether serum cortisol and prolactin levels in patients could lead to progression of diabetic retinopathy.

KEYWORDS: Diabetic Retinopathy, Cortisol, Prolactin, Microvascular complications.

INTRODUCTION

Diabetic retinopathy (DR) is a leading cause of vision loss globally. Diabetic retinopathy refers to retinal changes seen in patients with diabetes mellitus. Of an estimated 285 million people with diabetes mellitus worldwide, approximately one third have sign of DR and of these, further one third of DR is vision- threatening DR, including diabetic macular edema (DME). With increase in life expectancy the incidence of diabetic retinopathy [DR] has increased. The identification of established modifiable risk factors for DR such as hyperglycemia and hypertension has provided the basis for risk factor control in preventing onset and progression of diabetic retinopathy (Lee R etal, 2015).[1] Diabetes in India is rapidly gaining the status of an Epidemic. Diabetes is a chronic disease and is associated with a number of ocular complications –diabetic retinopathy, neovascular glaucoma, cataract, refractory deviations, ptosis, palsy of oculomotor nerve and neurotrophic keratitis. Some of these even result in blindness.

Diabetic retinopathy has many risk factors which aggravate the progression of the disease. The well known risk factors are Duration of diabetes, Glycemic control, Pregnancy, Hypertension, Nephropathy, Hyperlipidemia, anaemia, obesity, Smoking.[2] Out of the many known risk factors there are some less studied ones. Cortisol which is a steroid hormone, in the glucocorticoid class of hormones is released in response to stress and low glucose concentrations. It functions to increase blood sugar through gluconeogenesis, to suppress the immune system, and to aid in the metabolism of fat, protein, and carbohydrates. It also decreases bone formation.[3] Prolactin which is a protein hormone stimulates the mammary glands for milk production and so plays important role in lactation.[3] Our research involves the measurement of the serum levels of these two hormones and the status of retinopathy in the eye to find the correlation between the hormones and retinopathy.

Relation With Cortisol

Bhatia RP and Adarsh Singh[4] undertook a study in which Plasma cortisol levels and its metabolite-17-hydroxycorticosteroids were evaluated from the urine of 53 patients. These 53 patients had early and late stages of diabetic retinopathy. Values were compared with 30 cases of a control group. Plasma cortisol was found to be raised significantly in early as well as in advanced stages of retinopathy, while 17-hydroxycorticosteroid was significantly raised in earlier stages of diabetic retinopathy only. The findings suggest that increased plasma cortisol levels may take some part in the production of diabetic retinopathy.

Roy MS et al[5] conducted a study in which they measured urinary free cortisol output in diabetic patients.

They compared a group of 35 insulin dependent diabetic outpatients with a group of 32 normal controls for 24 hr urinary free cortisol. They found out that diabetic patients had significantly greater 24 hr UFC outputs than control. There were trends for patients for patients with either diabetic retinopathy or diabetic cardiovascular complications to have higher 24 hr UFC outputs than patients without these complications.

Iacopo chiodini et al[6] conducted a study in which cortisol level relationship with chronic complications of diabetes were studied. They enrolled 294 type 2 diabetic patients to evaluate the presence of subclinical hypercortisolism in diabetes, biochemical parameters of HPA axis secretionand the presence of diabetic complications. In all subjects the following determinants were performed: serum cortisol levels at 12 p. m. [F 24], 24 hr urinary free cortisol and plasma ACTH. They found out that parameters of HPA were not associated with the presence of diabetic complications whereas F 24 was significantly related to retinopathy[P=0. 010]and neuropathy[P=0. 039].

In type 2 diabetes subjects, hypothalamic – pituitary adrenal activity is enhanced in patients with diabetic complications and the degree of cortisol secretion is related to the presence and number of diabetic complications. (Diabetes care 30: 83-88, 2007).

In patients with type 2 diabetes, glucocorticoid secretion has been suggested to be a possible link between insulin resistance and the features of the metabolic syndrome (hypertension, obesity, coronary heart disease, hyperlipidemia and type 2 diabetes).[7-10]

Glucocorticoid excess has been demonstrated to lead to diabetes or to worsen metabolic control.[11-13]

Cortisol Level Range

20 ug/dL-5ug/dL[14]

The secretory rates of cortisol are high in the morning, but low in the late evening. The plasma cortisol level ranges between a high of about 20 ug/dL in the morning to a low of about 5ug/dL around midnight.[14] Therefore the measurements of blood cortisol levels of all patients are to be made at a similar time to minimize error due to diurnal variation.

Relation with Prolactin

Pan H et al[15] conducted a study in which he examined the role of 16 kDA N-terminal fragment of human prolactin[16K hPRL] in the inhibition of abnormal retinal neovascularisation. Intravitreal injections of 16K hPRL inhibited neovascularisation in the mouse model of oxygen induced retinopathy, suggesting a role for 16K hPRL in the treatment of proliferative retinopathies.

Aranda J et[16] al also conducted a similar study in rats and concluded that Prolactin is cleaved to antiangiogenic 16K-PRL by retinal tissue and that these molecules play a key role in preventing angiogenesis in the healthy retina.

Edith Arnold et al[17] conducted a study in which serum prolactin was evaluated in 40 nondiabetic and 181 diabetic men at various stages of Diabetic retinopathy. They found out that serum prolactin levels were higher in diabetic patients with no retinopathy than in those with proliferative diabetic retinopathy. All diabetic patients showed higher levels of PRL than the control subjects[P<0. 005]. However, patients with PDR had a reduced concentration of PRL[P<0. 05] compared with diabetic patients without retinopathy. The pattern of circulating PRL levels did not depend on the type of diabetes or on other systemic complications associated with diabetes [hypertension and nephropathy].

Triebel J etal[18] conducted a study to investigate prolactin related vasoinhibin in sera from patients with diabetic retinopathy. They performed a case control study and semi quantitatively determined Prolactin related vasoinhibin [PRL-V]in serum samples from 48 male subjects. The case group consisted of 21 patients with diabetes mellitus and proliferative or non proliferative diabetic retinopathy. The control group consisted of 27 healthy subjects with no history of diabetes mellitus. They found out that the case group had significantly lower PRL-V serum concentrations than the control group[P=0. 041]. There was no significant difference between patients with proliferative and those with non proliferative diabetic retinopathy.

Bonakdaran Shokoofeh etal[19] in a study enrolled 212 type 2 diabetics. The case group consisted of 70 patients with type 2 diabetes mellitus who suffered either proliferative [n=24] or non proliferative [n=46]diabetic retinopathy. The control group consisted of 142 type 2 diabetics without retinopathy. The serum 23KD prolactin levels were estimated. They found out that there was no difference in serum 23 KD prolactin level between retinopathic and non-retinopathic diabetics. The association between PRL and diabetic retinopathy has always been a matter of controversy.

The hormone prolactin is proteolytically processed to vasoinhibins, a family of peptides that inhibit the excessive retinal vasopermeability related to diabetic retinopathy after its intraocular conversation to vasoinhibins. Inducing hyperprolactinemia may represent a novel therapy against diabetic retinopathy. (Diabetes 59: 3192 - 3197, 2010).

Vasoinhibins are a family of antiangiogenic prolactin fragments that inhibit ischaemia induced retinal angiogenesis and prevent excessive retinal vasopermeability associated with diabetes [20, 21]. Proclactin is an important systemic inhibitor of diabetes induced retinal hypervasopermeability after its intraocular conversion to vasoinhibins, which act directly

on endothelial cells to block blood vessel growth, dilatation and permeability and to promote apoptosis mediated vascular regression.[21]

Prolactin level range

For Women= 10ug/dL – 25ug/dL
For Men= 10ug/dL-20ug/dL [14]

CONCLUSIONS

Diabetes mellitus is the most important complication of diabetes mellitus that impairs the individual functioning and diminishes the quality of life. It ultimately imposes severe health burden on society and can cause significant morbidity if not addressed appropriately. Increase in cortisol levels lead to increase in blood sugar levels causing worsening of diabetic control. Due to this reason increased cortisol levels lead to increase in all diabetic related vasculopathy including retinopathy. Serum prolactin derived vasoinhibins which are proteins obtained after proteolytic cleavage of prolactin have been shown to be protective in diabetic retinopathy. These vasoinhibins may be utilized in the future for their protective effect. Through Genetic engineering if these vasoinhibins are produced they might be used as intravitreal injections similar to anti vascular endothelial growth factor, for treatment of diabetic retinopathy complications. The direct role of prolactin levels in diabetic retinopathy however is not clear and a matter of further research. The treatment modalities for management of diabetic retinopathy are available and found to be efficacious in different in different controlled studies, but the best treatment is prevention and strict control of the risk factors.

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