IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 10 Ser.13 (October. 2020), PP 47-52
www.iosrjournals.org

Role of endogenousglucocorticoid levels in patients with Central Serous Chorioretinopathy

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Abstract
Background: *To study the levels of endogenous cortisolin patients with Central Serous Chorioretinopathy (CSCR).*
Methods:*This was a Case control Study which included patients of CSCR presenting to the Eye OPD at a Tertiary care centre in Western India. Serum cortisol levels were evaluated in 30 such patients and compared with 30 age and sex matched controlswho were on oral steroids.*
Results*:The mean(SD) of the 8 am serum cortisol values at presentation in the patients with CSCR was 23.15 (10.34)µg/dl while in controls was 13.05 (0.05)µg/dl, revealing statistically significant higher cortisol values in CSCR patients (p<0.001).The mean (SD) of the 8 am serum cortisol values in the cases with CSCR at follow up after 12 weeks reduced to 20.53(6.59) µg/dl. This difference was statistically significant (p=0.007). The mean cortisol levels were found to be higher in bilateral cases compared to unilateral cases, and in cases with multifocal leaks as compared to ones with single focus of leak, however these differences were not statistically significant.*
Conclusions*:Significantly higher levels of serum cortisol are seen in patients with CSCR.*
Keywords: *endogenous cortisol, central serous chorio-retinopathy, serum cortisol*

Date of Submission: 17-10-2020 Date of Acceptance: 02-11-2020

I. Introduction

Central serous chorioretinopathy (CSCR) is a condition with multi-factorial etiology and is characterized by serous neurosensory detachment (NSD) of the retina at the posterior pole, most widely hypothesised to be the result of choroidal hyperpermeability with resultant defects in retinal pigment epithelium (RPE). This condition was well described by Von Graefe in 1866[1] while the definition, clinical picture and coinage of term 'Central serous retinopathy' was given by George Bennet in 1955.[2] It is a poorly understood disorder and has been reported as the fourth most common non-surgical retinopathy[3] which typically affects middle aged men who present with acute onset blurring of vision with metamorphopsia, micropsia and central scotoma.[4]

Classic or Acute CSCR is frequently self-limiting with spontaneous resolution within 3-4 months and a favourable visual prognosis in 90-95 % cases.[5] The chronic form which was earlier termed as 'diffuse retinal epitheliopathy'[6] is characterized by diffuse decompensation of RPE,[7] irregular RPE detachments (PEDs) and a duration longer than 5 years.[8]

The widespread choroidal circulatory abnormality which is central to the pathophysiology of CSCR is thought to stem from various mechanisms.[9] A myriad of psychological associations have been described in literature including the observation of definite association with 'Type-A' personality pattern by Yannuzi,[10]psychotropic medication use, depression, stress and narcissistic personality.[11,12,13] Pregnancy,[14] hypertension, obstructive sleep apnoea,[15] smoking, alcohol consumption, allergic respiratory diseases[11] and Helicobacter pyroli infection[16] have been reported as independent risk factors.

Positive association with causation of CSCR have been studied and reported with exogenous as well as endogenous corticosteroids. However, the exact mechanism which might elucidate this association is yet to be confirmed. One explanation could be the corticosteroid induced alteration of RPE standing potential and choroid metabolic functions leading to reduced RPE fluid absorption.[17]Another explanation could be corticosteroid induced increase in adrenergic sensitivity and resultant susceptibility of catecholamine receptorsto sympathetically mediated vasoconstriction.[18]

Precipitation of CSCR has been reported after administration of exogenous corticosteroids through different routes, most prominently after systemic administration.[19]Garg et al found increased levels of endogenous cortisol in patients with CSCR.[20]

A limited number of studies in the Indian population have evaluated endogenous cortisol levels in patients with CSCR.Furthermore, to our knowledge, no studies have compared the impact of endogenous with exogenous steroids on the causation of CSCR. Therefore, this study was undertaken to investigate serum cortisol levels in patients with CSCR and controls on oral steroids. Establishing an association between endogenous cortisol level and the risk of CSCR may pave the path for interventions that may prevent or treat this visually debilitating condition among young population.

II. Material and Methods

The general study design was a case control, non interventional study which was conducted at a tertiary care teaching hospital between July 2011 and July 2013.Thirty patients with CSCR who presented to the Eye OPD were included in the study.

Inclusion criteria were:20–50 years of age, documentation of characteristic leak on fluorescein angiography, and presentation within 2 weeks of onset of symptoms.

Exclusion criteria were: Patients receiving any topical or systemic steroids, with any history of ocular surgery or trauma to eye 2 weeks prior to entering the study, obesity with body mass index (BMI) more than $30Kg/m^2$, alcohol or substance abuse or dependence, patients with psychiatric disorder requiring therapy. Thirty age and sex matched patients on oral steroids (Tab Prednisolone 1 mg/kg day) of more than 4 weeks duration for any systemic disease and with no ocular findings were included as controls.

The enrolled patients in the study were then subjected to detailed ocular examination in the form of best corrected visual acuity on Snellen's chart, Slit lamp biomicroscopic evaluation of the anterior segment,dilated fundus examination with direct ophthalmoscopy, slit lamp biomicroscopy with 78 & 90 D lens and by indirect ophthalmoscopy; and Intra Ocular Pressure by Applanation tonometry.The diagnosis of CSCR was based on clinical findings, Optical coherence tomography (OCT) macula and Fundus fluorescein angiography(FFA). The cases were defined as localized NSD caused by one or several discrete isolated leaks at the level of the RPE, which were termed "focal leaks" in case of single and multifocal in case of two or more leaks. These leaks typically were quite evident during FFA.[11]

For serum cortisol estimation, 3 ml of venous blood sample was obtained at 8 am after overnight fasting and the sample was analyzedusing radioimmunoassay.The normal range of fasting plasma cortisol morning 8 am sample was taken as 05-27 µg/dl.[21]

The study was approved by the Institutional ethical committee and informed written consent was taken from all patients. All patients were subsequently followed up at 04, 08 and after 12 weeks, with detailed ocular evaluation on each visit. After 12 weeks the serum cortisol levels were repeated and OCT for the macular thickness was performed for all cases.

The results were presented as mean $\pm$ standard deviation. Statistical analyses were conducted using SPSS (IBM, version 25). Serum cortisol levels were compared between CSCR patients and controls with independent sample *t*-test. P values < 0.05 were considered statistically significant

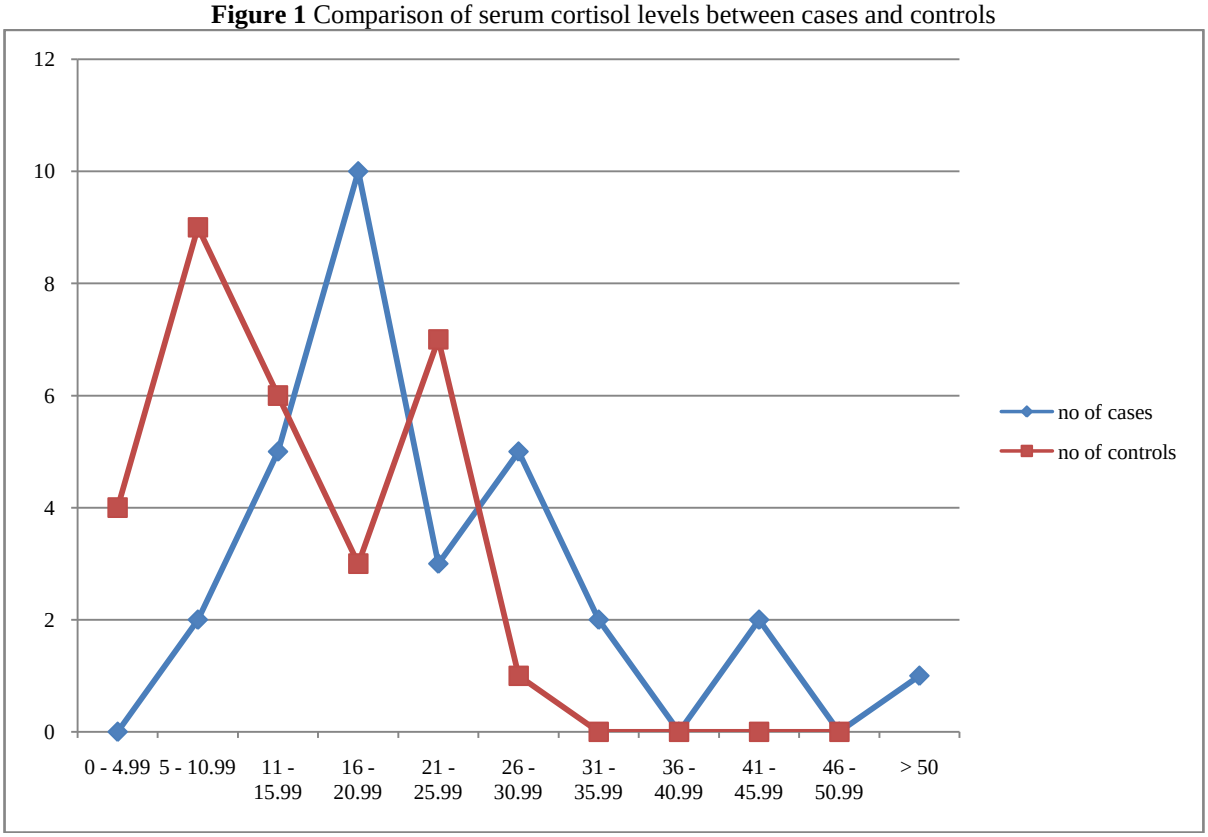
III. Results

The study group comprised of 36 eyes of 30 cases with CSCR, of whom 26 (86.7 %) were males and 04 (13.3 %) were females. The control group had 20 (66.7 %) males and 10 (33.3 %) females. The mean age was 39.3 $\pm$ 8.3 years in patients with CSCR and 35.8 $\pm$ 7.6 years in controls, which was not significantly different. On presentation 6 (20 %) patients had bilateral CSCR while 24 (80 %)had unilateral CSCR. Out of the 36 eyes with CSCR, 34 (94.4 %) had inkblot pattern and 02 (5.6 %)had smokestack type of leak on Fundus Fluorescein Angiography (FFA).The percentage of smokestack type of leak in this study was less than the expected incidence of 10-15 %.[22]

24 (66.7 %) eyes had multifocal leaks and 12 (33.3 %) eyes had single focus of leakage. This high proportion of multifocal leaks was a surprising finding as classic CSCR rarely presents with two or more leaks.

The mean$\pm$ SD of the 8 am serum cortisol values in the patients with CSCR was 23.15 $\pm$ 10.34 µg/dl and in controls was13.05 $\pm$0.05 µg/dl, revealing statistically significant higher cortisol values in CSCR patients (unpaired *t*test, $p<0.001$). Figure 1 depicts the comparison of cortisol levels between cases and controls.

Figure 1 Comparison of serum cortisol levels between cases and controls

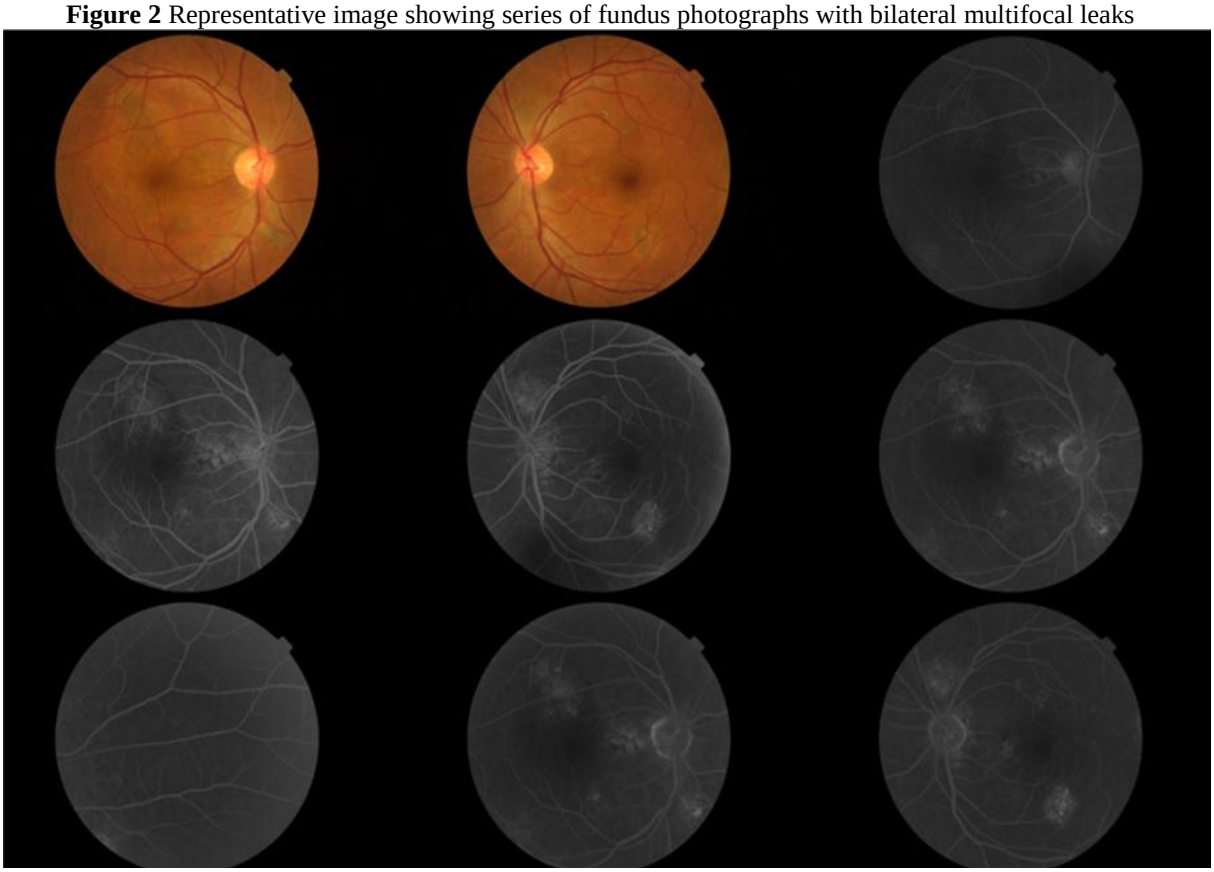


The mean ± SD of the 8 am serum cortisol values at presentation in the cases with CSCR was 23.15± 10.34 µg/dl and at follow up after 12 weeks was 20.53±6.59 µg/dl.This difference was statistically significant (paired *t* test, p=0.007). The mean ± SD of the 8 am serum cortisol values at presentation in the controls was 13.05 ±0.05 µg/dl and at follow up after 12 weeks was 12.28± 6.7 µg/dl.This difference was not statistically significant (paired *t* test, p=0.08).

The mean central macular thickness (CMT) on OCT was higher in cases with multifocal leaks (305.42 µm) than in cases with single focus of leak (275.75 µm), though this difference was not statistically different. The overall mean CMT was 295.52 µm at presentation and 236.03 µm on 12 weeks follow up, indicating statistically significant reduction (paired *t*test, p< 0.001).

The mean± SD of the 8 am serum cortisol values was higher in patients with multifocal leaks(24.71 ± 11.45µg/dl) than in the patients with single focus of leak (20.82 ± 7.26 µg/dl). However, this difference was not statistically significant.

Figure 2 Representative image showing series of fundus photographs with bilateral multifocal leaks



Similarly, the mean± SD of the 8 am serum cortisol values was higher in patients with bilateral CSCR(26.34 ± 13.47 µg/dl) than in the patients with unilateral CSCR (22.35 ± 8.9 µg/dl). This difference was also not statistically significant. Table 1 summarizes the distribution of cortisol levels in different CSCR varieties and controls.

Table no 1 Summary of distribution of serum cortisol values among different comparison groups of CSCR (Normal range 05-27 µg/dl[21])

	Comparison groups		P value
	Cases(at presentation)	Controls(at presentation)	
Mean (SD) serum cortisol level (µg/dl)	23.15(10.34)	13.05(0.05)	< 0.001 (Statistically significant)
Number within normal limits	20 (66.7 %)	30 (100 %)	
Number above normal limits	10 (33.3 %)	0 (0 %)	
	Cases (at presentation)	Cases (at 12 week follow-up)	
Mean (SD) serum cortisol level (µg/dl)	23.15(10.34)	20.53 (6.59)	0.007 (Statistically significant)
Number within normal limits	20 (66.7 %)	22 (73.3 %)	
Number above normal limits	10 (33.3 %)	8 (26.7 %)	
	Controls (at presentation)	Controls (at 12 week follow-up)	
Mean (SD) serum cortisol level (µg/dl)	13.05(0.05)	12.28(6.7)	0.08 (Statistically not significant)
Number within normal limits	30 (100 %)	30 (100 %)	
Number above normal limits	0 (0 %)	0 (0 %)	
	Cases with Multifocal leaks(at presentation)	Cases with single focus of leak(at presentation)	
Mean (SD) serum cortisol level (µg/dl)	24.71(11.45)	20.82(7.26)	0.16 (Statistically not significant)
Number within normal limits	12 (66.7 %)	8 (66.7 %)	
Number above normal limits	6 (33.3 %)	4 (33.3 %)	
	Bilateral cases	Unilateral cases	
Mean (SD) serum cortisol level	26.34(13.47)	22.35(8.9)	0.2

(µg/dl)			(Statistically not significant)
Number within normal limits	4 (66.7 %)	16 (66.7 %)	
Number above normal limits	2 (33.3 %)	8 (33.3 %)	

IV. Discussion

The exact etiology of CSCR has always eluded clinicians and researchers in spite of existence of extensive published literature. One particular area of interest has been the endogenous corticosteroids and their possible role in the causative mechanism. This interest stemmed from the potential association of the well-established risk factors like male gender, Type A personality, psychological stress and pregnancywith steroid hormone dysregulation.[23]

Zakir et al evaluated 23 cases of idiopathic CSCR and age-matched controls for levels of cortisol and testosterone. They found mean 8 am serum cortisol levels to be significantly higher in the cases as compared to the controls.[24]Garg et al reported higher values of 8 am, 11 pm and 24 hour urine cortisol in their sample of 30 patients with CSCR as compared to controls.[20]Schellevis et al most recently concluded in their study evaluating steroid hormone levels in active CSCR that there was an alteration in steroid hormone balance in cases of CSCR.[25] A meta-analysis of 5 studies published between March 1994 and December 2009 also concluded that the 8 am serum cortisol levels and 24 hour urine steroid levels were higher in patients with CSCR compared to controls.[26]

In concordance with the above-mentioned studies, our study demonstrated a positive association between serum cortisol levels and CSCR. We reported a significantly higher levels of serum cortisol in patients with CSCR compared to the age-matched controls who were on oral steroids ($p < 0.001$). In addition, we documented a reduction in the serum cortisol levels on 12-week follow-up compared to the levels on presentation, which was statistically significant.

We also tried to evaluate any possible correlation between the cortisol levels and the occurrence of multifocal leakage on FFA and while the mean levels were higher in cases with multifocal leaks (24.71 ± 11.45µg/dl) than in cases with single focus of leak (20.82 ± 7.26 µg/dl), the difference was not found to be statistically significant. Similarly, the cortisol levels were higher in bilateral cases (26.34 ± 13.47 µg/dl) compared to unilateral cases (22.35 ± 8.9 µg/dl), butthis difference was not statistically significant. The controls in our study were age-matched individuals with no ocular findings, who were on oral steroids for more than 4 weeks for systemic condition.This aspect of the study serves to highlight a possible greater role of endogenous steroids compared to exogenous steroids in the causation of CSCR.A surprising observation was that two-thirds of the eyes had two or more points of leakage on FFA, as classic CSCR usually presents with single leakage site.

A number of hypotheses have been put forth regarding the mechanism by which corticosteroids contribute to the pathogenesis of CSCR. Firstly, by virtue of its anti-fibroblastic activity and inhibition of extracellular matrix synthesis, cortisol may lead to direct damage to RPE cells or the outer blood-retinal barrier formed by RPE tight junctions and may affect the reparative function of the RPE layer as well.[27]Secondly, choroidal hyperpermeability leading to increased tissue hydrostatic pressure, formation of PEDs and subsequent leakage of fluid into subretinal space, may be induced by capillary fragility as a result of cortisol excess. Moreover, corticosteroid induced immune-suppression may make the individual susceptible to infection, which may in turn affect the RPE function.[28]

One of the limitations of the study was that the serum cortisol levels were evaluated at presentation, which might have differed from the levels at actual onset of symptoms. Another limitation was the sample size.

V. Conclusion

Our study demonstrates higher levels of serum cortisol in a significant percentage of the patients of CSCR providing additional evidence in favour of possible role of endogenous steroids in the pathogenesis of CSCR. Mean serum cortisol levels were higher in bilateral cases (as compared to unilateral) and cases with multifocal leaks (as compared to cases with single focus of leak), however the difference was not statistically significant. We also found that the cortisol levels had reduced significantly 12 weeks after presentation, with a possible implication ofan episodic spike in cortisol levels rather than persistently high levels. In conclusion, this study strengthens the existing belief that endogenous steroids play an important role in the pathogenesis of CSCR.

References

[1]. Von Graefe A. Uebercentralerecidivierenderetinitis.Graefes Arch ClinExpOphthalmol.1866; 12: 211-215.
[2]. Bennet G. Central serous retinopathy. Br J Ophthalmol.1955; 39: 605–618.
[3]. Wang M, Munch IC, Hasler PW, Prünte C, Larsen M. Central serous chorioretinopathy. *ActaOphthalmol (Copenh)*. 2008; 86(2): 126–145.
[4]. Ryan SJ, Schachat AP, Murphy RP, Paty A Spitznas M. Central serous retinopathy. Retina.1989, 2: 217–227.

[5]. Semeraro F, Morescalchi F, Russo A, Gambicorti E, Pilotto A, Parmeggiani F, et al.Central Serous Chorioretinopathy: Pathogenesis and Management. ClinOphthalmol. 2019, 13: 2341-2352.
[6]. Yannuzzi LA, Slakter JS, Kaufman SR, et al. Laser treatment of diffuse retinal pigment epitheliopathy. Eur J Ophthalmol. 1992; 2: 103–114.
[7]. Imamura Y, Fujiwara T, Spaide RF. Fundus autofluorescence and visual acuity in central serous chorioretinopathy. Ophthalmology 2011;118:700–705.
[8]. Iida T, Yannuzzi LA, Spaide RF, et al. Cystoid macular degeneration in chronic central serous chorioretinopathy. Retina.2003; 23: 1–7.
[9]. Spaide RF, Goldbaum M, Wong DWK, et al. Serous detachment of the retina. Retina.2003; 23:820–846.
[10]. Yannuzzi LA. Type Abehavior and central serous chorioretinopathy. Trans Am Ophthalmol Soc. 1986; 84:799–845.
[11]. Tittl MK, Spaide RF, Wong D, et al. Systemic findings associated with central serous chorioretinopathy. Am J Ophthalmol.1999; 128: 63–68.
[12]. Fok AC, Chan PPM, Lam DSC, et al. Risk factors for recurrence of serous macular detachment in untreated patients with central serous chorioretinopathy. Ophthalmic Res. 2011; 46:160–163.
[13]. Carlesimo SC, Piazzi G, Leone C, et al. Masuda's central serous chorioretinopathy (CSCR) and its somatic investment in narcissism: our observations on new psychiatric nosography. ClinTer 2014; 165:27–30.
[14]. Haimovici R, Koh S, Gagnon DR, et al. Risk factors for central serous chorioretinopathy: a case–control study. Ophthalmology.2004; 111:244–249.
[15]. Eom Y, Oh J, Kim S, et al. Systemic factors associated with central serous chorioretinopathy in Koreans. Korean J Ophthalmol.2012; 26:260–264.
[16]. Mansuetta CC, Mason JO, Swanner J, et al. An association between central serous chorioretinopathy and gastroesophageal reflux disease. Am J Ophthalmol.2004; 137:1096–1100.
[17]. Arndt C, Sari A, Ferre M, et al. Electrophysiological effects of corticosteroids on the retinal pigment epithelium. Invest Ophthalmol Vis Sci. 2001; 42:472–475.
[18]. Wakakura M, Suzuki H. Urinary excretion of catecholamines in central serous chorioretinopathy. Jpn J ClinOphthalmol. 1979; 33:1237–1240.
[19]. Tsai DC, Chen SJ, Huang CC, Chou P, Chung CM, Chan WL, Huang PH, Lin SJ, Chen JW, Chen TJ, Leu HB. Risk of central serous chorioretinopathy in adults prescribed oral corticosteroids: a population-based study in Taiwan. Retina. 2014; 34(9): 1867–1874.
[20]. Garg SP, Dada T, Talwar D, Biswas NR. Endogenous cortisol profile in patients with central serous chorioretinopathy. Br J Ophthalmol. 1997; 81(11):962–964.
[21]. Rotman-Pikielny P, Rouach V, Chen O, Gur HG, Limor R, Stern N. Serum cortisol levels in patients admitted to the department of medicine: Prognostic correlations and effects of age, infection, and comorbidity. Am J Med Sci. 2006; 332(2):61-67.
[22]. Daruich A, Matet A, Dirani A, et al. Central serous chorioretinopathy: Recent findings and new physiopathology hypothesis. *ProgRetin Eye Res*. 2015; 48:82-118.
[23]. Haimovici R, Rumelt S, Melby J. Endocrine abnormalities in patients with central serous chorioretinopathy. Ophthalmology. 2003; 110(4):698–703.
[24]. Zakir SM, Shukla M, Simi ZU, Ahmad J, Sajid M. Serum cortisol and testosterone levels in idiopathic central serous chorioretinopathy. Indian J Ophthalmol. 2009; 57(6):419–422.
[25]. Schellevis RL, Altay L, Kalisingh A, Mulders T.W.F, Sitnilska V, Hoyng CB, et al. Elevated Steroid Hormone Levels in Active Chronic Central Serous Chorioretinopathy. Invest. Ophthalmol. Vis. Sci. 2019; 60(10):3407-3413.
[26]. Liang ZQ, Huang LZ, Qu JF, Zhao MW. Association between endogenous cortisol level and the risk of central serous chorioretinopathy: a Meta-analysis. Int J Ophthalmol. 2018; 11(2):296-300.
[27]. Smith TJ. Dexamethasone regulation of glycosaminoglycan synthesis in cultured human skin fibroblasts. J Clin Invest.1984; 74:2157–2163.
[28]. Rinehart JJ, Wuest O, Ackerman GA. Corticosteroid alteration of human monocyte to macophage differentiation. N Engl J Med. 1975; 292:236–241.

Shabnam Bhalla, et. al. "Role of endogenousglucocorticoid levels in patients with Central Serous Chorioretinopathy." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(10), 2020, pp. 47-52.