

Study of Serum Cortisol Levels In type 2 Diabetes and Its Correlation with Severity of Diabetic Retinopathy in South India

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ABSTRACT

Background: Diabetes is a chronic disease involving pancreases. Prevention of the complication among the diabetic patients is through prompt and aggressive treatment aimed at maintaining normal blood sugar levels. One of the most common complication of diabetes is diabetic retinopathy, which is one of the leading cause of blindness. Objective: To prove the hyperactivity of HPA axis in uncontrolled diabetes and hypercortisolism fasten the progression of diabetic retinopathy.

Methods: A Cross Sectional study was conducted in a Government Tertiary care hospital in Mysuru city between November 2020 to October 2022. The study population were known case of Type 2 Diabetes Mellitus. Sample size was estimated to be 100. Purposive sampling was used.

Results: The study conducted on type 2 diabetic patients. The mean age was 56.8. themale:female ratio in the study was 47:53. The study showed significant correlation between serum cortisol with duration of diabetes, FBS, PPBS, HbA1c. The also showed a positive association between serum cortisol levels with diabetic retinopathy severity.

Conclusion: Serum Cortisol levels are High in uncontrolled Diabetes and it implies the risk of faster progression of diabetic retinopathy.

Keywords: Diabetes Mellitus, Cortisol Levels, Diabetic Retinopathy, Mysuru

INTRODUCTION

Diabetes mellitus refers to a group of common metabolic diseases that shares the phenotype of hyperglycemia. Diabetes is a common comorbidity which is rising in prevalence in the modern era Between 2000 and 2016, there was a premature mortality of 5 % from diabetes. In 2019 According to WHO, diabetes was the 9th leading cause of death with 1.5 million deaths. 8.5% of adults aged 18 years and older has diabetes worldwide.^[1] NFHS 4 in 2015-2016 showed that prevalence of women with blood sugars more than 140mg/dl is 5.8% and men with blood sugars more than 140 mg/dl is 8%.^[2] 1 out of every 6 persons with diabetes in the world is from India. India stands 2nd place when it comes to number of diabetic persons in a country.^[3] There were estimated 72.96 million cases of diabetes in adult population of India in comparison to 26.0 million (23.4–28.6) in 1990.^[4] The prevalence in urban areas ranges between 10.9% and 14.2% and prevalence in rural India was 3.0 -7.8%. Among population aged 20 years and above with a much higher prevalence among individuals aged over 50 years (INDIAB Study).^{[2][5]}

Hyperglycaemia, as a result of uncontrolled diabetes, over time leads to serious damage to many of the bodily organsystems, especially the nerves and blood vessels. Uncontrolled diabetic adults have higher risk of various diseases like heart attacks, strokes and infection and blindness. Adults with diabetes have a 3 fold increased risk of heart attacks and strokes. Combined with reduced blood flow, neuropathy in the feet increases the chance of foot ulcers, infection and eventual leads to limb amputation.^[6,7] Diabetic retinopathy is an important cause of blindness, and occurs as a result of long-term accumulated damage to the small blood vessels in the retina.

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. Close to 1 million people are blind due to diabetes. Diabetic retinopathy has many risk factors which aggravate the progression of the disease.^[8,9]

Diabetic retinopathy accounts for 41.5% prevalence as a diabetic complication. And it is one of the early complication of diabetes. 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. Out of the many known risk factors there are some less studied ones like Cortisol.^[10,11,12] Cortisol is produced from adrenal gland from zona fasciculata. Cortisol increases gluconeogenesis and decreases glycogen synthesis in liver. It also decreases insulin secretion. It also increases lipolysis in adipose. And decreases glycolysis in muscles.^[13,14,15] Serum cortisol is a easily available test. Its level normally reflect with that of corticotropin hormone, there by is fluctuating with circadian rhythm normally the serum concentrations are higher in early morning (about 6 AM), ranging from 10-20 mcg / dl. And concentration is lowest (less than 5 mcg/ dl) at around one hour after sleep. Cortisol is turned in to inactive metabolite cortisone by 11-beta hydroxysteroid dehydrogenase type 1 in the liver. Its high level promote atherogenesis and hence increase cardiovascular risk.^[16,17,18,19]

Hence this study was conducted to prove the hyperactivity of HPA axis in uncontrolled diabetes and hypercortisolism fasten the progression of diabetic retinopathy.

MATERIALS AND METHODS

This Cross sectional-Observational study was conducted among patients visiting the OPD /or admitted in Department of General Medicine, KR Hospital, MMCRI, Mysore.

Sample size was 100.

Inclusion Criteria:

- Known case of type 2 diabetes diagnosed by ADA 2019 .

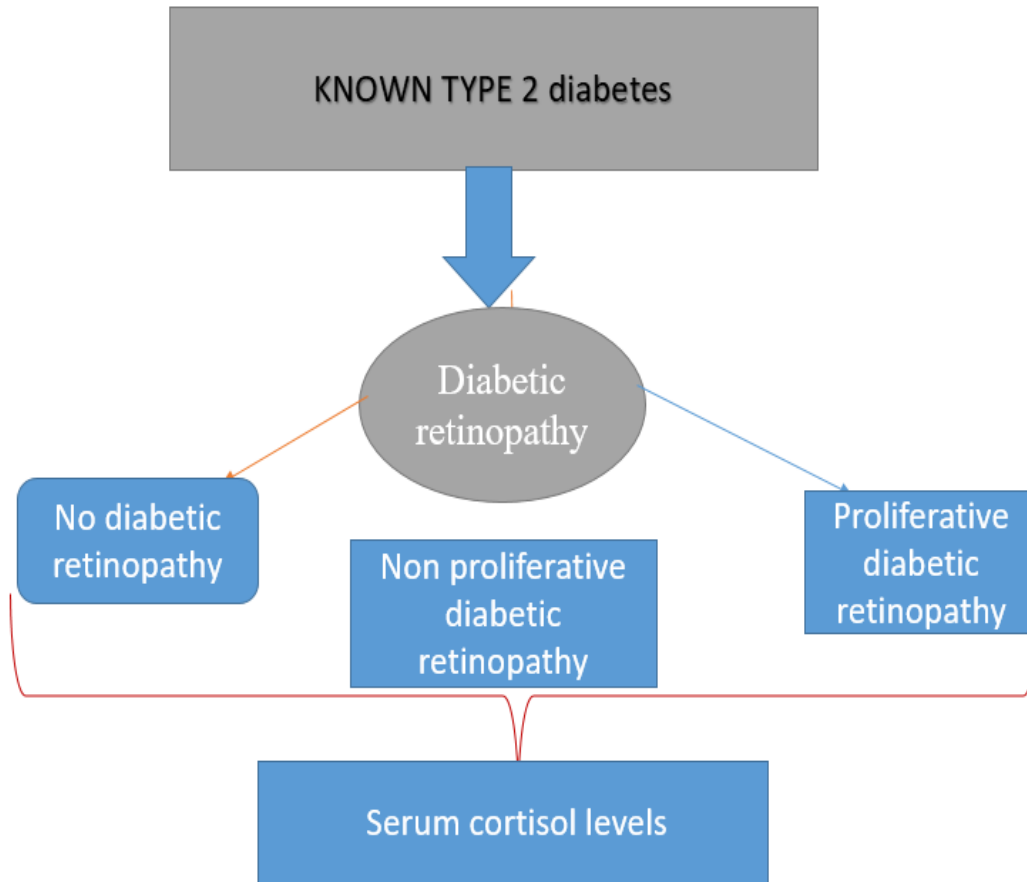
Exclusion Criteria:

- Patients with cushings syndrome.
- Patients on long duration corticosteroid medications.
- Patient with retinopathy due to any other causes than diabetes.
- Patients admitted in sepsis.
- Patient admitted for some systemic infectious etiology.

- Patient admitted for DKA or HHS.
- Patient with CLD.
- Patient with CKD.

Methods

After taking the institutional ethical clearance for the study purpose of the study will be explained to the patient and attenders. Written informed consent will be taken from the subjects. Relevant history and clinical examination will be done.



Statistical Analysis

Data obtained from the study will be entered in excel sheets and it will be double checked. Data analyzed using SPSS software version 22.0 and it will be presented as descriptive statistics in form of frequency table, figures and graphs. Association between variables will be done using chi-square test and unpaired t test for qualitative and quantitative variables. Result will be expressed as mean+/-SD. Correlation of parameters is done by Pearson’s correlation formula. A p value of <0.05 is considered statistically significant.

RESULT

Majority patients where in the age group of 40 – 70. Male: female participation was approximately equal. Patients included in the study was more in the group of no retinopathy.

Table 1 – diabetic retinopathy grading distribution

RETINOPATHY GRADING	PERCENTAGE
NO RETINOPATHY	43
MILD NPDR	20
MODERATE NPDR	10
SEVERE NPDR	16
PDR	11

Table 2- distribution of study subjects

Sex	n (%)
Female	53(53%)
Male	47(47%)
Total	100(100%)
Diabetic Retinopathy Grading	n (%)
No Retinopathy	43(43%)
Mild NPDR	20(20%)
Moderate NPDR	10(10%)
Severe NPDR	16(16%)
PDR	11(11%)
Total	100(100%)
Age category	n (%)
27 to 30	3(3%)
31 to 40	11(11%)
41 to 50	19(19%)
51 to 60	25(25%)
61 to 70	30(30%)
71 and above	12(12%)
Total	100(100%)

Cortisol and FBS correlation

There is a positive correlation of serum cortisol and FBS levels with a Pearson coefficient of 0.694 and satisfying a p value <0.001

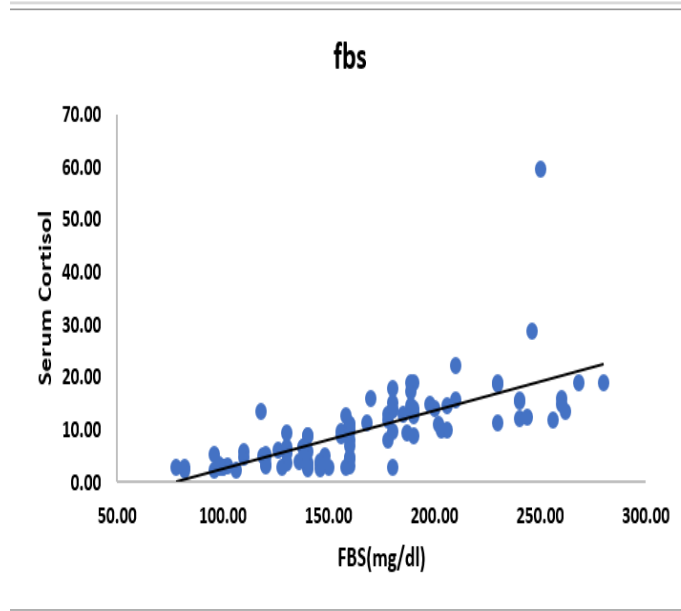


Figure 2– FBS with Serum cortisol

Cortisol and PPBS correlation: There is a positive correlation between PPBS and cortisol levels with a Pearson’s coefficient of 0.746 and satisfying a p value <0.001

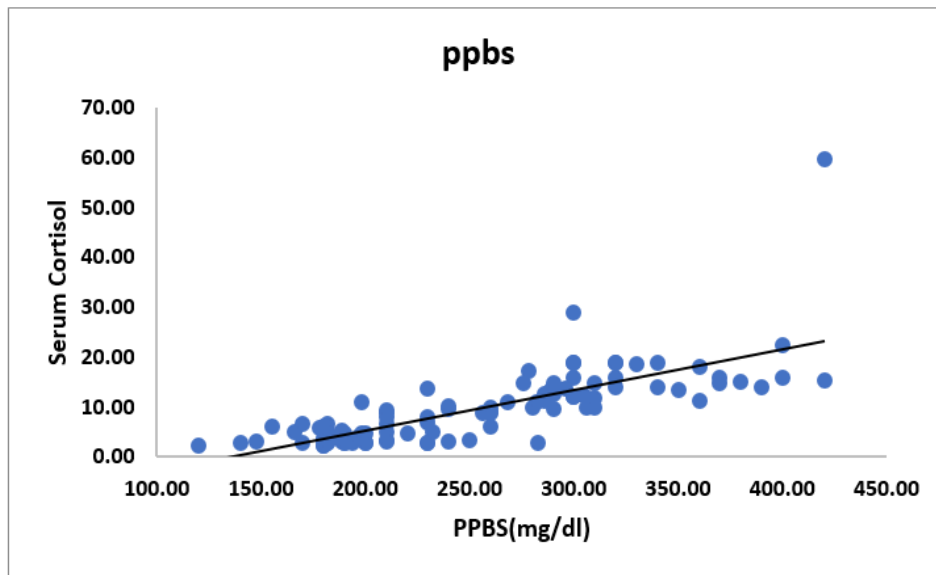


Figure3 – cortisol with PPBS

Cortisol and HbA1c correlation: There is a positive correlation between cortisol and HbA1c with a Pearson’s coefficient of 0.834 and satisfying a p value < 0.001.

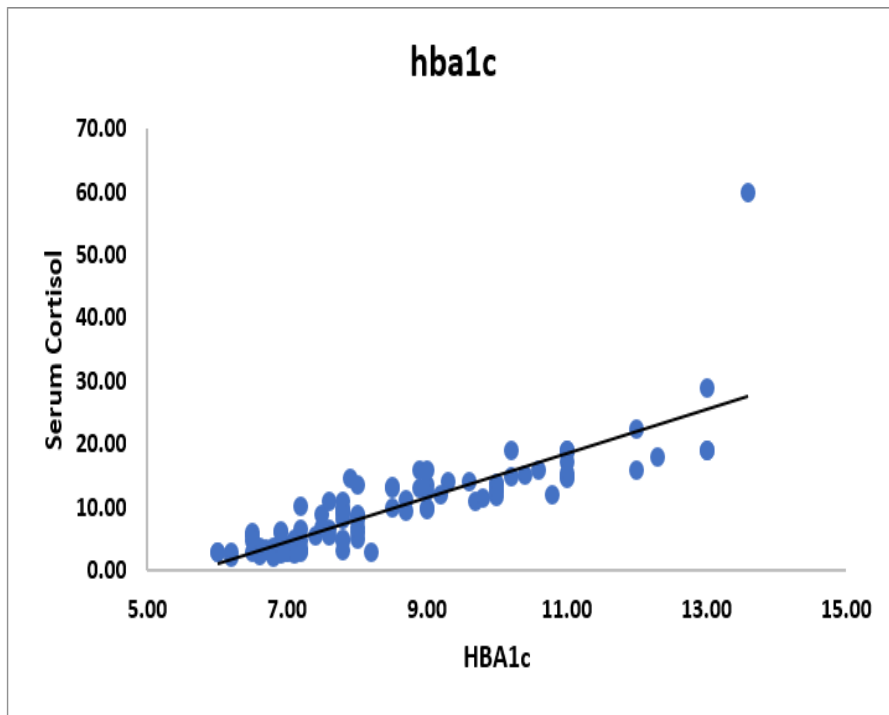


Fig 4 – serum cortisol with HbA1c

Table 3– correlation of diabetic parameters to serum Cortisol

The Pearson correlation coefficient between Age & Serum Cortisol is 0.119 and it was not statistically significant with a p value of 0.239
The Pearson correlation coefficient between Duration of Diabetes & Serum Cortisol is 0.743 and it was statistically significant with a p value of 0
The Pearson correlation coefficient between FBS(mg/dl) & Serum Cortisol is 0.694 and it was statistically significant with a p value of 0
The Pearson correlation coefficient between PPBS(mg/dl) & Serum Cortisol is 0.746 and it was statistically significant with a p value of 0
The Pearson correlation coefficient between HbA1c & Serum Cortisol is 0.835 and it was statistically significant with a p value of 0

Table 4 -diabetic retinopathy with duration of diabetes

Diabetic Retinopathy grading	MEAN Duration of diabetes to retinopathy grading	Standard deviation of duration of diabetes to retinopathy grading
No retinopathy	6.12	2.64
Mild NPDR	9.15	1.95
Moderate NPDR	11.7	3.13
Severe NPDR	13.56	2.25
PDR	18.82	6.16

Diabetic retinopathy severity shows a higher grade with more duration of diabetes. There is association between age and severity of diabetic retinopathy.

Diabetic retinopathy severity was higher in patients with higher HbA1c values. They are associated.

Table 5 – HbA1c Association with Diabetic Retinopathy

Diabetic retinopathy grading	Mean HbA1c to retinopathy severity	Standard deviation of HbA1c to retinopathy severity
No retinopathy	7.04	0.51
Mild NPDR	7.99	0.77
Moderate NPDR	9.25	0.74
Severe NPDR	10.05	1
PDR	11.92	1.13

Table 6– Diabetic retinopathy severity association with Serum Cortisol

Diabetic retinopathy grading	Mean serum cortisol to severity of retinopathy (microg/dl)	Standard deviation of serum cortisol to severity of retinopathy
No retinopathy	4.16	1.63
Mild NPDR	9.07	2.24
Moderate NPDR	12.7	0.93
Severe NPDR	14.66	1.78
PDR	23.31	12.59

Diabetic retinopathy severity showed higher severity in patients with higher values of cortisol. They are associated
 There was a significant association between diabetic retinopathy severity grading and the duration of diabetes, serum cortisol and serum HbA1c.

DISCUSSION

In the groups studied 53 patients were female and 47 were male. Majority of the patient was in the age group of 40 – 70 years.

	Study population	Mean age
Present study	100 cases	56.8
Study conducted by Bhatia and Adarsh Singh	53	54
Study by Akshay Kumar et al	46	55.93
Study by Roy M S et al	67	58
Study by Xiaodan Zhang et	211	56

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The study conducted by Xiaodan Zhang et al had a sample size of 211 with the mean age of 56 . Except this study all other studies had a sample size smaller than the present study. The mean age was nearly same for the present study with Xiaodan Zhang et al study and Akshay Kumar et al study.^[13,14,16]

Among 100 cases, males were 47 and females were 53 with a slight female predominance with female : male ratio of 1.12:1.

	Male to female percentage
Present study	47% male 53% female
Bhatia and Adarsh Singh	49.1% male 50.9% female
Akshay Kumar et al	43.4% male 56.6% female
Roy M S et al.,	40.3% males 59.7% females
Xiaodan Zhang et al.,	47% males 53% females

All the studies had a female predominance. The present study had a Male : Female ratio comparable with study conducted by Xiaodan Zhang et al.,

The present study focused on serum cortisol levels in patient who are known case of DM type 2 . The study took random serum cortisol of all patients as the parameter for comparison.

Patient’s serum cortisol were measured which had a mean of 9.78 +/- 7.587. This parameter was showing a positive correlation with other parameters of diabetes like Duration of Diabetes , FBS, PPBS , HbA1c.

The present study also tried to prove an association between diabetic retinopathy severity with Serum Cortisol levels.

	Investigation Done
Present study	Random Serum Cortisol
Bhatia and Adarsh Singh	Serum Cortisol and 17-hydroxycorticosteroid
Akshay Kumar et al	Serum Cortisol and Serum Prolactin
Roy M S et al	24 hr Urine free cortisol
Xiaodan Zhang et al	3 samples of serum cortisol and ACTH at 3 different times

The present study was comparing random serum cortisol value in type 2 DM patients and diabetic retinopathy severity. The present study is comparable with Bhatia and Adarsh Singh’s study, both studies compare the same parameter with diabetic retinopathy severity.^[13]

Other studies used other parameter to prove a increase in HPA axis secretion in Diabetic patients and they also associated the parameter with microvascular complications of Diabetes like Diabetic retinopathy, nephropathy, cardiovascular dysfunction.

Comparison To Other Studies

	Present study	Study conducted by Bhatia and Adarsh Singh	Study by Akshay Kumar et al	Study by Roy M S et al	Study by Xiaodan Zhang et al
Sample size	100	53	46	67	211
Male : female	47:53	26:27	20:26	27:40	99:112
Mean age	56.8	54	55.93	58	56
Investigation done	Serum cortisol	Serum cortisol and 17-hydroxycorticosteroid	Serum cortisol and serum prolactin	24 hr urine free cortisol	3 samples of serum cortisol and ACTH at 3 different times (8, 16 , 0 hr)
Conclusion	Positive correlation of cortisol with diabetes and associated with diabetic retinopathy	Diabetic retinopathy severity has positive association with serum cortisol and 17-hydroxycorticosteroid	Increase in severity of diabetic retinopathy with higher cortisol values	Higher urine free cortisol for patients with diabetic retinopathy or cardiovascular dysfunction	Serum cortisol associated with <u>microalbuminurea</u> in diabetic and <u>prediabetic</u>

Table – comparison with other similar studies.^[13,14,15]

The present study was able to prove that there is an HPA axis hyperactivity in uncontrolled diabetic cases and also that cortisol it self can act as a secondary precipitating factor for diabetic microvascular complications like diabetic retinopathy.

CONCLUSION

The study showed a significant correlation between serum cortisol and diabetic parameters. It also showed that there is a association between serum cortisol and diabetic retinopathy severity. Serum cortisol plays a part as precipitating factor for diabetic vascular complication. So screening of serum cortisol in diabetic will give an idea on overseeing the vascular complications.

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