Serum Cortisol Response in Acute Hypoglycemic Diabetic/Non Diabetic Patients Arriving through Emergency Department – A Comparative Study

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Abstract Background and objectives: Hypoglycemia in the body is controlled by counter regulatory hormones. Serum cortisol is one among them not subjected to extensive study, in Type 2 diabetes mellitus cases. Cortisol responses among non diabetics and type 1 diabetics have been studied to a certain extent. The primary objective of our study was to identify the serum cortisol levels in hypoglycemic patients with or without type 2 diabetes and to find out the correlation between the mean cortisol responses in the two groups. Methodology: A total population of 51 symptomatic hypoglycemic patients meeting Whipple's criteria were studied in the ER of a medical college hospital at Kochi. Forty patients were diabetic and 11 non diabetic. Previous history, present illness, comorbidities, medical history and reasons for hypoglycemia were considered. Laboratory investigations on RFT, 7 AM serum cortisol and RBS were made and the results analysed applying standard statistical methods and SPSS II software. Results and discussion: Male female ratio in the diabetic and non diabetic groups was 3:1 and 10:1 respectively. Hypoglycemia was more among males, especially in the diabetic group due to decreased food intake(49%) or concurrent illness(51%), the mean age being 65.7 years in these cases. Hypoglycemia was more frequent in those on sulfonylurea (61.9%), and in habitual insulin users (42.5%). In non diabetic patients, hypoglycemia was caused by renal failure(27.27%), insulinoma(27.27%) or sepsis(18.18%). The mean serum cortisol among the diabetic group was subnormal(17.47), and in the non diabetic group it was 28.56. Age, sex, serum creatinine, GCS, period of stay and condition at discharge showed no correlation with serum cortisol levels. RBS, period of stay and condition at discharge showed no correlation with diabetic status. Conclusion: Diabetic patients with acute symptomatic hypoglycemia demonstrated a subnormal serum cortisol response as compared to non diabetic hypoglycemic patients.

Keywords Serum Cortisol, Hypoglycemia, Type 2 Diabetes Mellitus, Sulfonylurea, Insulin

1. Introduction

Hypoglycemia is a major cause of mortality/morbidity all over the world, drug induced in patients with diabetes, or may be due to other reasons in the non diabetic populations. Glucose homeostasis in the body is maintained by the HPA axis through hormones. Serum cortisol is one among them. Various studies have been made on hypoglycemia among type 1 diabetics and non diabetics, where such information on type 2 diabetes are lacking. Serum cortisol response in type 2 diabetics has not been properly studied. Previous studies have demonstrated that glucose counter regulatory mechanisms are abnormal in insulin treated and non insulin treated type 2 diabetics. Serum cortisol increased in response to prolonged hypoglycemia in normal individuals [1] and in patients with chronic diabetic complications[2]. It limits glucose utilization and enhance hepatic glucose production as per the requirement. In diabetic patients with hypoglycemia, there exists a subnormal response with resultant prolonged hypoglycemia. The objective of this study was to estimate the serum cortisol levels in hypoglycemic diabetic/non diabetic patients after a single cortisol response at the time of hypoglycemia, and to find out the correlation between the mean cortisol responses in both these groups.

2. Methodology

A non interventional observational study of patients

presenting to the ER of a medical college hospital at Kochi with hypoglycemia was undertaken from December 2008 to December 2010. Based on a previous study[3] on the serum cortisol levels in diabetic/non diabetic patients with hypoglycemia, a mean of 2.2 mcg/dl $\pm$ 0.5 was obtained in diabetic cases and a mean of 4 mcg/dl $\pm$ 0.7 was obtained in the non diabetic cases [3]. With 99% confidence and 10% allowable error, minimum sample size computed for diabetic patients was 35 whereas for the non diabetic patients, the sample size was 5.

Though the minimum sample size computed was 35, and 5 respectively in both these groups, we have selected 42 diabetics and 11 non diabetics for this study. Two patients were eliminated from this group as they violated the inclusion or exclusion criteria on subsequent evaluation. So, the total population subjected to the study was 51 (40 diabetics and 11 non diabetics).

Patients with symptoms of hypoglycemia later on confirmed by blood glucose value less than 60 mg/dl (as per ADA 2010 guidelines), showing relief of symptoms when plasma glucose concentration was brought to normal, were included in the study. Patients on steroid therapy and those having adrenal insufficiency were excluded.

Each selected patient was subjected to thorough examination. History regarding previous illness, present illness, co morbidities, medications, diabetic history and reasons for hypoglycemia were collected. Laboratory investigations on RFT, 7 am serum cortisol and RBS were made in the hospital laboratory.

For the comparison of values of different variables on an

average between the two groups, and for testing the statistical significance of the values of the variables such as serum cortisol, RBS, period of stay, age group, sex distribution, GCS, co morbidities, serum creatinine level and condition at discharge, Wilcoxon rank sum test was applied because of the small sample size in one of the groups and high variation in the values in both these groups. Probability values less than 0.05 was considered as statistically significant. Statistical analysis was done using SPSS 2 software..

3. Results

The study population consisted of 51 patients (diabetic and non diabetic), with hypoglycemia, satisfying the Whipple's criteria. 78 % were diabetic and 22 % non diabetic, comprising both males and females[Table 1].

Sex distribution in diabetic and non diabetic patients (both gender) showed no correlation with each other, as the p value obtained was not significant (p=0.418).

We obtained a mean age of 65.7 in the diabetic group and 45.36 in the non diabetic group[Table 1].

Drowsiness, sweating, general weakness and seizures were the common symptoms in most cases, whereas some of the patients were asymptomatic [Table 1].

No significant relationship was noticed between diabetic and non diabetic patients as far as presenting symptoms are concerned.

Table 1. Characteristics of the population(n=51)

	Characteristics	Diabetic(n=40)	Percentage	Non diabetic	Percentage	P value
1	Subjects	40	78	11	22	
2	Sex					0.418 Not significant
	Male	30	75	10	90.9	
	Female	10	25	1	9.1	
	Total	40	100	11	100	
	Male:Female	3:1		10:1		
3	Age(years)					
	Mean	65.7		45.36		
4	Presenting symptoms					0.866 Not significant
	Drowsiness & sweating	16	40	4	36.36	
	General weakness & seizures	16	40	5	45.45	
	Others	8	20	2	18.18	
	Total	40	100	11	99.99	

Table 2. Distribution of hypoglycemic incidence among patients on diet control, oral hypoglycemic agents and insulin(n=40)

Diet control	2	5%
Medications		
Only OHA	8	20%
Only insulin	17	42.5%
OHA+insulin	13	32.5%
Total	40	100%

Hypoglycemic incidence was more in those patients exclusively on insulin (42.5%) as compared with patients on OHA(20%) or OHA plus insulin(32.5%) [Table 2].

Table 3. Profile of comorbidities in diabetic and non diabetic cases(n=51)

DM	13	25.5%
DM/DLP	2	3.9%
DM/HTN/DLP	12	23.5%
DM/HTN	13	25.5%
DLP	4	7.8%
HTN/DLP	2	3.9%
HTN	2	3.9%
No comorbidities	3	5.9%
Total	51	100%

The major comorbidities which contributed to hypoglycemia were diabetes mellitus alone(25.5%), diabetes mellitus/ hypertension combination (25.5%) and diabetes/hypertension/dyslipidemia combination (23.5%)[Table 3].

Table 4. Reason for hypoglycemia in diabetic and non diabetic cases(n=51)

Decreased food intake	25	49%
Concurrent illness	26	51%
Total	51	100%

Table 5. Causes of hypoglycemia among non diabetic patients(n=11)

Liver failure	1	9.09%
Cardiac failure	1	9.09%
Renal failure	3	27.27%
Sepsis	2	18.18%
Hypopituitarism	1	9.09%
Insulinoma	3	27.27%
Total	11	100%

Decreased food intake/ concurrent illness caused hypoglycemia in the diabetic group[Table 4], whereas insulinoma/diseases caused hypoglycemia in the non diabetic group[Table 5].

Table 6. Comparison of frequency of hypoglycemia among OHA

Metformin	8	38.09%
Sulfonylureas	13	61.90%
Total	21	100%

The intake of drugs like sulfonylure caused higher incidence of hypoglycemia in the diabetic group [Table 6].

Table 7. Diabetic status and age distribution

Age(years)	Diabetic	%	Non diabetic	%	P value
20 to 59	12	30	10	90.9	<0.001 Significant
60 & above	28	70	1	9.1	
Total	40	100	11	100	

The incidence of hypoglycemia increased with age showing a significant correlation in the diabetic group, and the maximum number of patients were in the age group 60 and above(70%). The maximum number of patients with hypoglycemia in the non diabetic group were below 60 years(90.9%) [Table 7].

Table 8. Mean serum cortisol response in diabetic and non diabetic patients with hypoglycemia

Serum cortisol	Diabetic(n=40)	Non diabetic(n=11)	p value
Mean	17.47	28.56	<0.001 Significant
Standard deviation	8.969	9.487	
Median	15	31	

A mean cortisol value of 17.47 ± 8.9 mcg/dl was obtained in the diabetic group, as against 28.56 ± 9.48 in the non diabetic group[Table 8], showing statistically significant correlation. Based on a previous study[1], the cut off value for serum cortisol was taken as 18 mcg/dL. 67.5% (27) patients in the diabetic group exhibited a subnormal response, and 36.5 % (13) showed a normal response, proving that serum cortisol response got impaired in the diabetic group[Table 13].

Table 9. Diabetic status and RBS values(mg/dL)

Diabetic status	Number	Mean RBS	Standard deviation	Median	P value
Diabetic	40	42.69	11.799	44	0.869 Not significant
Non diabetic	11	42.18	8.727	40	
Total	51				

Table 10. Diabetic status and period of stay

Diabetic status	Number	Mean period of stay	Standard deviation	Median	P value
Diabetic	40	5.53	8.083	3	0.140 Not significant
Non diabetic	11	6.27	4.221	5	
Total	51				

Table 11. Serum cortisol and age distribution

Age(years)	Number	Mean serum cortisol level	Standard deviation	Median	P value
20 to 59	22	20.31	11.352	22	0.785 Not significant
60 and above	20	19.52	9.229	17	

Table 12. Serum cortisol level and sex distribution (n=51)

Serum cortisol	Male(n=40)	Female(n=11)	P value
Mean	20.25	18.44	0.801 Not significant
Standard deviation	10.887	6.691	
Median	17.15	19.00	

Table 13. Serum cortisol response in diabetic patients(n=40)

Subnormal(<18 mcg/dl)	27	67.5 %
Normal(>18 mcg/dl)	13	32.5 %
Total	40	100 %

Table 14. Serum cortisol and GCS

GCS	Number	Mean serum cortisol level	Standard deviation	Median	P value
Mild(13 to 15)	39	19.17	11.062	15	0.331 Not significant
Moderate and severe (3 to 12)	12	21.75	7.606	22	

Table 15. Serum cortisol and creatinine level

Creatinine (mg/dL)	Number(n=51)	Mean serum cortisol level(mcg/dL)	Standard deviation	Median	P value
<1.4	42	19.91	9.865	19	0.551 Not significant
>1.4	9	19.63	11.772	14.70	

Table 16. Serum cortisol and period of stay

Serum cortisol(mcg/dL)	Number(n=51)	Mean serum cortisol level(mcg/dL)	Standard deviation	Median	P value
<18 mcg/dL	28	6.36	8.586	4.50	0.407 Not significant
>18 mcg/dL	23	4.87	5.691	3.00	

Table 17. Serum cortisol and condition at discharge

Serum cortisol(mcg/dL)	Number(n=51)	Mean serum cortisol level(mcg/dL)	Standard deviation	Median	P value
Better	46	19.84	10.220	17.30	0.966 Not significant
Expired	6	20.02	10.028	18.10	

Serum cortisol levels showed no significant correlation with age[Table 11], sex[Table 12], GCS[Table 14], serum creatinine[Table 15], period of stay[Table 16] or condition at discharge[Table 17]. RBS[Table 9] and period of stay[Table 10] showed no correlation with diabetic status.

3. Discussion

The study population consisted of 40 diabetic and 11 non diabetic patients with hypoglycemia satisfying the Whipple's criteria, comprising both males and females. An increased incidence of hypoglycemia was noticed among the males, probably due to decreased drug compliance or increased incidence of concurrent illness.

The mean age for diabetic patients was 65.7 years and for

non diabetic patients 45.36 years. The incidence of hypoglycemia increased with age in the diabetic population and the maximum number(70%) of hypoglycemic patients belonged to the age group 60 years and above. Various comorbidities other than diabetes might have predisposed the elderly to hypoglycemia also. The mean age obtained as per a previous study was 46±3 and 42±3 respectively in each group.

The patients presented themselves with neurogenic or neuroglycopenic symptoms of hypoglycemia. Majority of the patients came with drowsiness and sweating (40%), general weakness and seizures(40%). Some of the patients were asymptomatic, probably due to hypoglycemia unawareness resultant to sympatho adrenal, sympathetic neural responses to a given degree of hypoglycemia caused by recent antecedent hypoglycemia, prior exercise, or sleep

in patients with diabetes [4,1].

The reason for hypoglycemia in the diabetic group was decreased food intake(49%), as well as concurrent illness(51%). In the non diabetic group, the causes were insulinoma and concurrent illness, and mainly due to renal failure (27.3%).

Some of the diabetic patients had dyslipidemia and hypotension when majority of the population had diabetes, hypertension and dyslipidemia (23.5%).

Among the patients on OHA, those taking sulfonylurea had a higher prevalence of hypoglycemia(61.9%). High incidence of hypoglycemia was obtained in patients exclusively on subcutaneous insulin(42%). Improper use or overdose of insulin might have caused this phenomenon. The overall event rate for severe hypoglycemia in insulin treated type 2 diabetics was approximately 30% of that of type 1 diabetes, as per earlier studies [5]. The prevalence rate of mild hypoglycemic symptoms has been reported as 16 to 20% in patients using sulfonylurea agents, and 30 to 50 % in patients treated with subcutaneous insulin [6].

Regarding serum cortisol levels among hypoglycemic diabetic/non diabetic patients arriving through the ER, no studies hitherto have attempted to adjudge the serum cortisol response after a single blood test at the time of a hypoglycemic incidence. We have done this, and obtained mean serum cortisol values of 17.47 ± 8.9 mcg/dl and 28.56 ± 9.48 mcg/dl respectively, in the diabetic vs non diabetic population. In a previous study on hyperinsulinemic hypoglycemia, mean serum cortisol value obtained in the diabetic group was 2.2 ± 0.5 mcg/dl as against 4 ± 0.7 mcg/dl (p value <0.05) in the non diabetic group[3]. Both studies revealed a decreased cortisol response among the hypoglycemic diabetic patients as compared to the non diabetic patients with hypoglycemia.

Age and sex distribution showed no correlation with serum cortisol levels.

Based on a previous study[7], the cut off value for serum cortisol was taken as 18 mcg/dl. It was found that about 67.5%(27) of the diabetic patients were having a subnormal response whereas 32.5%(13) was having a normal response, clearly indicating that serum cortisol response got impaired in the diabetic patients.

No significant correlation was obtained between GCS and serum cortisol levels.

Long standing diabetic patients are prone to diabetic nephropathy, depending on the duration of the illness. So, serum cortisol levels were correlated with serum creatinine levels, but no significant correlation was obtained between the two. Similarly, the period of stay and the condition at discharge (survived/expired) showed no correlation with serum cortisol levels.

4. Limitations

Cortisol secretion increases on physical and psychological stress, both of which were not taken into consideration in this

study. Cortisol levels show diurnal variation, with peak levels during early morning and low levels during evening hours. Even though 7 AM cortisol was taken for study, the levels depend on the circadian sleep pattern of each patient, which can be a major confounding factor in the judgement. Immunoassays in the institution measured total serum cortisol, most of which exist in a protein bound state. Unbound cortisol is the biologically active product. Hence factors that raise the levels of binding proteins can show falsely elevated cortisol levels in the blood.

5. Suggestions and Recommendations

Further studies involving large populations of hypoglycemic diabetic/non diabetic patients are required to establish a cut off value for diagnosing hypocortisolism in both these groups.

The reason for the subnormal cortisol response among the hypoglycemic diabetic patients is a curious finding, requiring further investigation. The clinical significance of reduced cortisol levels among the diabetic group and the role of steroids in such patients have to be subjected to further studies. Studies on serum cortisol levels in both these groups at different intervals have to be undertaken to ascertain whether the subnormal response seen among the diabetic group was showing a uniform pattern throughout the day.

6. Conclusions

Hypoglycemia was more common among the males and the elderly diabetic population, caused due to decreased food intake (49%) and concurrent illness(51%). The incidence of hypoglycemia was more in sulfonyl urea takers and habitual subcutaneous insulin users. Hypoglycemic incidence increased with age in the diabetic group, the majority of the patients belonged to the age group 60 and above. Among the non diabetic group, the maximum number of patients were below 60 years. A subnormal serum cortisol response was clearly visible among hypoglycemic diabetic patients, with a mean cortisol level of 17.47 ± 8.9 mcg/dl, as against a response of 28.56 ± 9.48 mcg/dl in the non diabetic hypoglycemic patients. Serum cortisol levels showed no correlation with age, sex, serum creatinine, GCS, period of stay and condition at discharge. Similarly RBS, period of stay and condition at discharge showed no correlation with the diabetic status.

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