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CLINICAL UTILITY OF C-PEPTIDE AND HbA1C MEASUREMENT IN THE MANAGEMENT OF TYPE-II DIABETES.

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Abstract:

Background*: The global prevalence of diabetes mellitus has more than doubled since 1980 and is expected to continue to rise at alarming rates . An estimated 336 million people worldwide now have T2DM. T2DM results from an interaction between genetic and environmental factors that impair β-cell function and insulin action. Diabetes is diagnosed clinically by elevated plasma glucose levels, however, loss of β-cell function is progressive over time and β-cell dysfunction is far advanced by the time diabetes is diagnosed clinically. Therefore, methods for preserving or restoring β-cell function are important in our attempts to prevent and treat T2DM. In this project, we discuss current evidence for causes of the progressive loss of β-cell function in T2DM, and the effects of current therapeutic strategies on preservation of β-cell function and the prevention and treatment of T2DM.*

Objectives: *To measure beta cell function mass and metabolic control in patients with type 2 diabetes mellitus which can serve as an effective index for selecting a diabetic treatment. It has been shown that basal serum C-peptide levels are useful indicators for determining the proper timing to introduce the intensive insulin therapy into DM patients. They were, also, of greater value in identifying patients suitable for oral therapy than any single clinical criterion, and thus may help in identifying insulin-treated diabetic patients who may be treated with oral therapy without deterioration in metabolic control.*

Methods: *Fasting serum c-peptide levels and metabolic control (HbA1C) are measured in patients enrolled in the study, the statistical analysis of mean data was done by using Paired T-test of the before and after values of test results at $p<0.05$*

Conclusion: *Interventions that reduce body fat and increases physical functioning such as diet and exercise, or that change fat biology through different therapies in lowering blood glucose provide the best evidence for slowing or arresting the deterioration of β-cell function that causes T2DM. These interventions should form the basis of interventions to prevent and treat T2DM, particularly early in its course.*

Keywords: *C-Peptide, HbA1C, β-cell function, Insulin Resistance, Type 2 diabetes, Oral hypoglycemic therapy, Insulin therapy, Micro and Macrovascular Diseases.*

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INTRODUCTION:

The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss.[1]. In its most severe forms, ketoacidosis or a non–ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment, death. The first widely accepted classification of diabetes mellitus was published by WHO in 1980 and, in modified form, in 1985. The 1980 Expert Committee proposed two major classes of diabetes mellitus and named them, IDDM or Type 1, and NIDDM or Type 2. In the 1985 Study Group Report the terms Type 1 and Type 2 were omitted, but the classes IDDM and NIDDM were retained[2,3].

The long–term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, and features of autonomic dysfunction, including sexual dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease[4].

Several pathogenetic processes are involved in the development of diabetes. These include processes which destroy the beta cells of the pancreas with consequent insulin deficiency, and others that result in resistance to insulin action. The aetiological type named Type 1 encompasses the majority of cases which are primarily due to pancreatic islet beta–cell destruction and are prone to ketoacidosis. Type 1 includes those cases attributable to an autoimmune process, as well as those with beta– cell destruction and who are prone to ketoacidosis for which neither an aetiology nor a pathogenesis is known (idiopathic) [5].

The type named Type 2 includes the common major form of diabetes which results from defect(s) in insulin secretion, almost always with a major contribution from insulin resistance.

C-Peptide and Its Significance in Type-II DM: C-peptide is a substance produced by the beta cells in the pancreas when proinsulin splits apart and forms one molecule of C-peptide and one molecule of insulin. Insulin is the hormone that is vital for the body to use its main energy source, glucose. Since C-peptide and insulin are produced at the same rate, C-peptide is a useful marker of insulin production. In type 2 diabetes, the body is resistant to the effects of insulin (insulin resistance) and it compensates by producing and releasing more insulin, which can also lead to beta cell damage [6].

Therefore, the C-peptide test can be used to monitor beta cell activity and capability over time and to help a health practitioner determine when to modify insulin treatment. C-peptide measurement is a useful alternative to testing for insulin in insulin resistant diabetes. The normal range of C-peptide is 1.1-4.4 ng/ml [7].

HBA1C:

The term HbA1c refers to glycated haemoglobin. It develops when haemoglobin, a protein within red blood cells that carries oxygen throughout your body, joins with glucose in the blood, becoming 'glycated' [8].

By measuring glycated haemoglobin (HbA1c), clinicians are able to get an overall picture of what our average blood sugar levels have been over a period of weeks/months.

METHODOLOGY:

The main scope of the study is to have better patient care based on the two parameters, C-Peptide and HbA1c:

Around 80 Diabetic patients who visited Owaisi hospital (both IP & OP), were counselled regarding the utility of c-peptide and HbA1c measurements in their Diabetic management and care. Out of 80 people, 50 people gave written and signed consent to participate in the study.

The C-Peptide and HbA1c tests were performed during the initial and final visit of the patients with a gap interval of 3 months between the visits. The reports were reviewed and ,endogenous insulin level (c-peptide) and metabolic control (HbA1c) were observed closely to modify treatment regimen(if necessary), accordingly to get better results thus improving the quality of life.

A. STUDY SITE: Owaisi Hospital and Research centre, Hyderabad.

B. STUDY DESIGN:Single centered, Observational, Prospective and Interventional Study.

C. SAMPLE SIZE: A total of 50 patients.

D. STUDY PERIOD: Six Months (6 Months).

E. SELECTION CRITERIA:

Inclusion criteria:

- 1. Patients of both the genders (male and Female).
- 2.Patients who are diagnosed with Type II DM
- 3. Patients of ages between 25 – 85 years of age suffering from DM.

- 5. Patients who are voluntarily willing to participate in the study.

Exclusion criteria

- 1.Patients with Type I DM
- 2. Pregnant women (Gestational diabetes).

F.Source of Data:

Patient's data relevant to the study was obtained

G.Plan of Work:

- To get the Ethical Committee approval for the study.
- Design a data collection form.
- To assess the Clinical condition of patient, management based upon insulin levels and metabolic control interpreted by C-peptide and HbA1c measurements respectively.
- Report the data collected.

H. Statistical Analysis:

- Student paired t-test is used for the data analysis

TREATMENT CHART OF SUBJECTS DURING THE STUDY:

Pt No:	Previous Drug Therapy	Modification	Current drug therapy
1	Human mixtard insulin 30/70 (25U-20U)	YES	Increased the dose of Insulin to(30U 20U)
2	DENOVO	-	Metformin 500mg BD
3	Human mixtard insulin 50/50 (18U-12U)*****	YES	Increased the dose of insulin to (25U-20U)
4	1.Metformin 500 mg+voglibose0.3mg ½ BD 2. Metformin 500 mg+glipizide 50mg BD	YES	+ vildagliptin 50mg OD
5	DENOVO	-	1.Human mixtard insulin 30/70(26U-14U) 2.Metformin 500mg+sitagliptin 50mg OD
6	1.Metformin500mg BD 2.Human mixtard 50/50 (22U-20U)	YES	+ Metformin 500mg+ sitagliptin 50mg OD
7	1.Human mixtard insulin 30/70 (40U-20U) 2.metformin 500mg+voglibose0.3mg BD	NO	
8	Human mixtard 30/70 (30U-30U)	YES	+ pioglitazone 15mg BD
9	Metformin500mg+ pioglitazone 15mg+ glimipride 1mg TID	NO	
10	1.Inj.Lantus 35U HS 2.metformin 500mg+glipizide 2mg BD 3.metformin 500mg+ voglibose 0.3 mg ½ BD	YES	+pioglitazone 7.5 mg BD +Inj. Lupinsulin(18U-12U)
11	Metformin500mg+ glibenclamide 5mgTID	NO	
12	1.Human mixtard 50/50 (24U-20U) 2.Vildagliptin 50 mg OD	YES	Increased insulin dose to 40U-25U
13	Metformin 500mg+ glipizide 5mg TID	NO	
14	Metformin 500mg+ glipizide 5mg BD	NO	
15	Metformin500mg+ glimipride 2mg TID	YES	+Pioglitazone 7.5 mg TID
16	Metformin1000 mg+ glimipride 2mg ½ BD	NO	
17	DENOVO	-	Metformin 250mg TID
18	Metformin 500mg+ pioglitazone 15mg BD	YES	+ Vildagliptin 50mg OD +H mixtard 20U-18U
19	Human mixtard 30/70 (40U-25U)	YES	+Inj.Lantus 20U HS
20	DENOVO	-	Metformin 500mg+pioglitazone 7.5mg BD

Continue…….

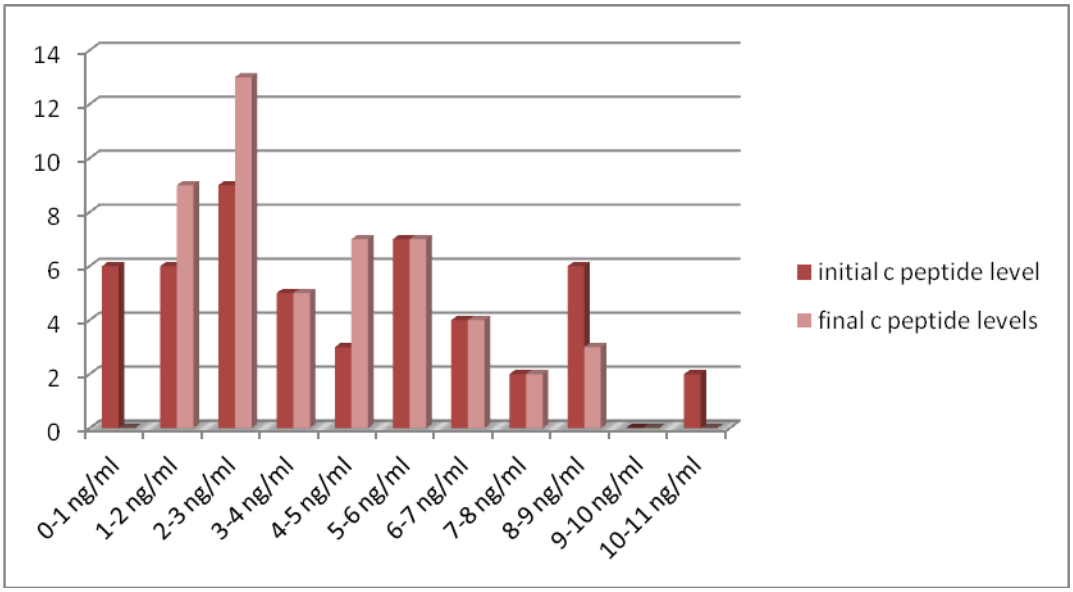
21	1.Inj.Lantus 25U HS 2.Glimipride 1mg+metformin 500mg BD	YES	+Human mixtard 25U before breakfast
22	1.metformin 500mg+ glimipride 2mg BD 2.Human mixtard 30/70 30U	YES	+ metformin+ glimipride to TID +pioglitazone 7.5 mg TID
23	Metformin 500 mg+ glimipride 2 mg TID	YES	+ vildagliptin 25 mg BD
24	Metformin 500 mg + glimipride 2 mg TID	YES	+ Pioglitazone 15 mg BD
25	Metformin 500 mg+ voglibose 0.2 mg TID	YES	Changed the drugs to metformin 500 mg+ glimipride 2mg+ pioglitazone 7.5 mg TID
26	1.Huminsulin N(12U-12U) 2. Huminsulin R acc to GRBS	YES	+ Inj.Lantus 25U HS
27	Lupinsulin 50/50(18U-12U-12U)	NO	
28	Metformin 500 mg+ glimipride 2 mg BD	YES	Changed to metformin 500 mg+ glimipride 2 mg + pioglitazone 15mg BD
29	1.Inj. Lantus 30U HS 2.H mixtard 50/50 (25U-20U)	NO	
30	DENOVO	-	Metformin 500mg+ Sitagliptin50 mg ½ BD
31	1.Metformin 500 mg+glimipride 2 mg TID 2. Huminsulin N (15U-15U)	YES	+Huminsulin R 18 U before major meals BD
32	1.H mixtard 30/70 (35U-30U) 2. Pioglitazone 15 mg BD	NO	-
33	Pioglitazone hcl 30 mg+ glimipride 2 mg BD	YES	+ metformin 500 mg TID
34	Metformin 500 mg+ glibenclamide 5 mg BD	NO	-
35	Metformin 500 mg+ glipizide 5 mg BD	YES	+ Pioglitazone 15 mg BD + Voglibose 0.2 mg OD
36	DENOVO	-	Metformin 500mg+ voglibose 0.3 mg ½ BD
37	DENOVO	-	Metformin 500 mg + sitagliptin 50 mg ½ BD
38	H mixtard 50/50 (25U-18 U)	NO	-
39	DENOVO	-	Metformin 500 mg ½ BD
40	1.Metformin 500 mg ½ BD 2.H mixtard 8 U BD	NO	-
41	DENOVO	-	Metformin 500 mg ½ BD
42	Metformin 1000 mg + glimipride 2 mg BD	NO	-
43	Metformin 500 mg+ gliclazide 80m	YES	+ Rosiglitazone 2 mg BD
44	H mixtard 30/70 (20U-18U)	NO	-
45	Metformin 500 mg+ glipizide 5 mg TID	NO	-
46	H mixtard(30U25U)	NO	-
47	1.H mixtard 20U-20U 2.Metformin 500 mg+glipizide 5mg BD	NO	-
48	Lupinsulin 50/50 18-13-13 U	YES	+ Vildagliptin 50 mg OD
49	1.H mixtard 30/70 (20U-10U) 2.Metformin 500 mg+ glimipride 1 mg BD	YES	OHA changed to metformin 500 mg+ gimipride 2 mg + pioglitazone 15 mg BD
50	Metformin 500 mg+ glibenclamide 5 mg	YES	+ Pioglitazone 15 mg OD

Summary: Out of 50 patients,there were 9 Denovo patients. Among the rest 41 DM history patients 20 patients were on only Oral hypoglycemic agents, 14 patients were on both Insulin & OHAs and 7 patients were on only Insulin.
Treatment was started for Denovo patients.
The treatment modality was changed in 24 patients (among 41) either by increasing the dose/frequency of their Insulin or OHAs or by adding new combination drugs to their already existing regimen. Strict diabetic diet and exercise was recommended for all the patients including Denovo (9 patients) t hose for whom there was no treatment modification (18 patients) and 24 patients for whom drug regimen was altered.

RESULTS:

Fig 1: RANGES of C-Peptide Levels of Subjects During Initial And Final Visits :
The Normal Levels of C-peptide is 1.1 – 4.4 ng/ml

C-PEPTIDE RANGE	NO.OF PATIENTS(Initial)	NO.OF PATIENTS(Final)
0-1ng/ml	6	0
1-2ng/ml	6	9
2-3ng/ml	9	13
3-4ng/ml	5	5
4-5ng/ml	3	7
5-6ng/ml	7	7
6-7ng/ml	4	4
7-8ng/ml	2	2
8-9ng/ml	6	3
9-10ng/ml	0	0
10-11ng/ml	2	0
TOTAL	50	50

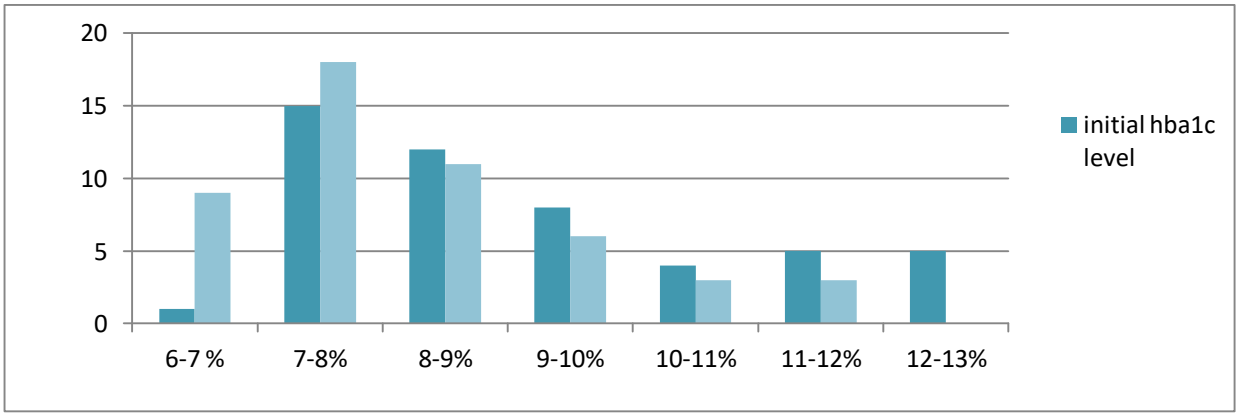


Out of 50 patients, 25 patients (50%) were bought in a range of 2-5 ng/ml (normal range) of serum C-peptide.

Fig 2: ranges of HBA1c of patients during the initial and final visit:

The Normal level of HbA1c is upto 6.5%

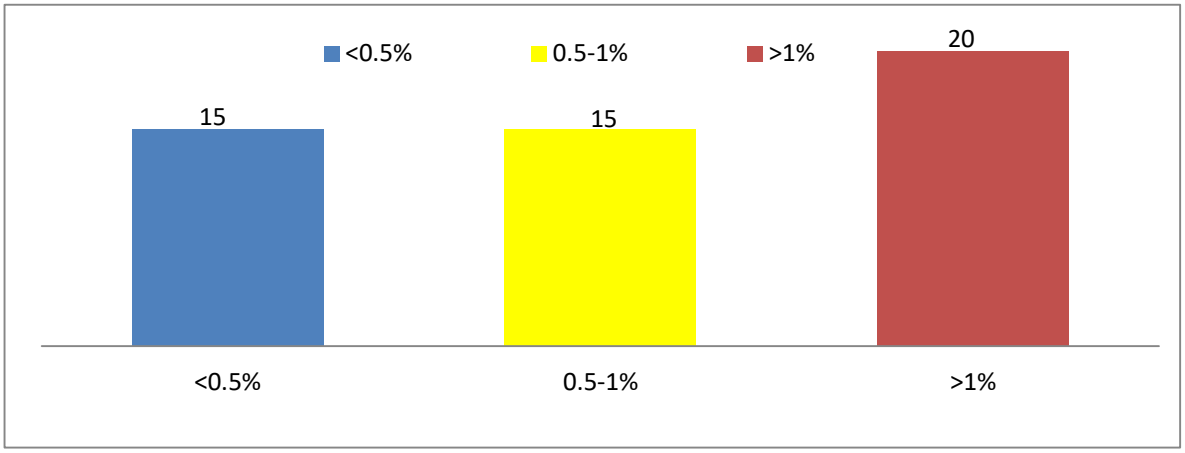
HbA1c RANGE	NO.OF PATIENTS(Initial)	NO OF PATIENTS(Final)
6-7%	1	9
7-8%	15	18
8-9%	12	11
9-10%	8	6
10-11%	4	3
11-12%	5	3
12-13%	5	0
TOTAL	50	50



Out of 50 patients 33 patients (66%) were bought in a range of 6-8 % (normal) HbA1c levels.

Fig 3: Percentage Improvement in HBA1c Values among the Subjects after 3 Months of Study:

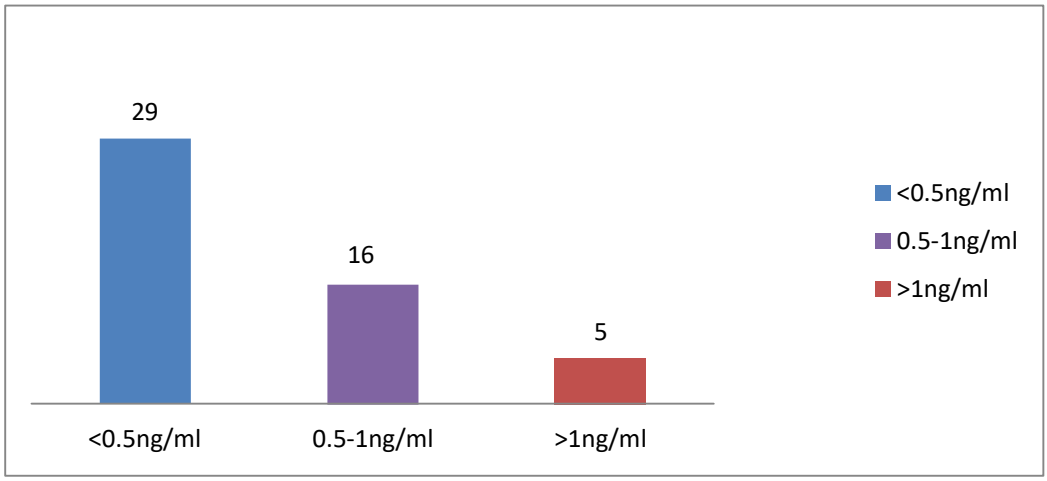
PERCENTAGE IMPROVEMENT IN HbA1c	NO.OF PATIENTS
<0.5%	15
0.5-1%	15
>1%	20
TOTAL NUMBER OF PATIENTS=50	



Among 50 subjects, 20 showed improvement range of 1% in their HbA1C since the initial visit to the final visit whereas15 subjects had improvement of 0.5-1% and another 15 had 0.5% improvement (since HbA1c is measured in percentages).

Fig 4: Units Improvement in C-Peptide Levels among the Subjects after 3 Months of Study:

UNITS IMPROVEMENT IN C-PEPTIDE	NO.OF PATIENTS
<0.5ng/	29
0.5-1ng/ml	16
>1ng/ml	5
Total number of patients= 50	



Among 50 subjects, 29 patients showed an average improvement of <0.5 ng/ml in their C-Peptide levels whereas 16 patients showed an improvement range of 0.5-1 ng/ml and another 5 patients showed an improvement of >1 ng/ml in C-Peptide values.

The improvement in the C-peptide as well as HbA1C levels are based on the comparision of the initial and final test values of the subjects enrolled in the study for a period of 3 months.

Statistical analysis:

C Peptide:

The means of Group 1 and Group 2 significantly different at $p < 0.05$.

Summary		
	Initial c peptide	Final c peptide
Mean	4.3302	4.1476
Variance	7.8621	5.0874
Stand. Dev.	2.8039	2.2555
N	50	50
T	2.3424	
degrees of freedom	49	
critical value	2.011	

- After substituting these values into the formula for t we have:
- t=XD¯¯¯¯¯SDn√=0.18260.700850√≈2.3424
- The degrees of freedom is n-1=49
- Determine critical value for t with degrees of freedom = 49 and α=0.05.
- In this example the critical value is 2.011
- The calculated t value is smaller than critical value (2.3424>2.011), so the means significantly different.

HbA1C:

The means of Group 1 and Group 2 are significantly different at $p < 0.05$.

Summary		
	Initial hba1c	Final hba1c
Mean	9.3046	8.397
Variance	3.1404	1.9071
Stand. Dev.	1.7721	1.381
N	50	50
T 2.2405		
degrees of freedom	49	
critical value	2.011	

- After substituting these values into the formula for t we have:
- t=XD¯¯¯¯¯SDn√=0.90760.778850√≈2.2405
- The degrees of freedom is: d.o.f=n−1=49
- The calculated t exceeds the critical value (2.2405>2.011), so the means are significantly different. Thus the test is statistically significant

Note: TABLE VALUE:

48	**2.011**	**2.682**	**3.505**

CONCLUSION:

Diabetes mellitus is now a common disorder prevalent over the world. It is a clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin. There is a estimation that every month around the world some billions are spent for the treatment of DM and by this we can understand the severity of the DM prevailing all over the world. According to WHO by 2030, 200 million people are going to be affected and the worst part in the news is that affected age group from 35-55 years will be higher due to the lifestyle followed by the group.[9]

Generally DM is diagnosed by GRBS screening test and this test should be done 3times/ day to get exact severity of DM in patients. Moreover GRBS values may vary from home screening to hospital screening due to technique errors (patient errors) and thus cannot be relied upon for the management of DM.

To overcome this we opted for C-peptide and HbA1c tests.:-

C-peptide is a substance produced by the beta cells in the pancreas when proinsulin splits apart and forms one molecule of C-peptide and one molecule of insulin. Since C-peptide ad insulin are produced at the same rate,C-peptide is a useful marker of insulin production. C-peptide test can be used to monitor beta cell activity and capability over the time and help health practitioner when to modify insulin treatment.[10,11]

Whereas Glycated haemoglobin (HbA1c) gives an accurate and objective measure of glycemic control over period of weeks to months. The rate of formation of HbA1c is proportional to ambient blood glucose concentration. A rise of 1% in HbA1c is approx. average increase of 2mmol/lit in blood glucose.

As GRBS was only accepted test present in early days and there are chances of getting errors by patients in fasting and other technical errors So we have created awareness about C-peptide and HbA1c tests and advised patients to go for that, so that exact endogenous insulin level (through C-peptide test) and blood glucose level (through HbA1c test) is known.

The patients were counseled regarding:

- the importance of diet, exercise and medication adherence in their diabetic care
- importance of screening tests in their diabetic management (C-peptide should be done atleast twice a year & HbA1C once in three months)
- the long term complications and management of DM

Awareness about the new parameter C-peptide was brought among the physicians and other health care professionals.

We identified insulin resistant patients (14) based on their high C-peptide values (>6ng/ml) ***The overall result was approx. 60% significant improvement in patient condition.*** We got modified result in C-peptide and satisfactory results in HbA1c. If another 2-3 months the treatment would have been continued the rest 40% patients would have achieved normal levels

The Quality of life was improved aiming the main scope of the study and thus concluding the study.

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Conflict of Interests: Declared none

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