

**Research Article****A Study of Residual C-Peptide Level (Fasting and Post OGTT) in Type –1 Diabetes Population & It's Correlation with duration of Diabetes and Antibody Status in a Tertiary Care Centre in Eastern India**

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Dr Animesh Maiti**Abstract**

Introduction: Type 1 diabetes is a disorder of chronic autoimmune destruction of pancreatic beta cells. Current model of type 1 diabetes shows that varying proportion of functioning beta cells persist even after symptomatic disease onset. This residual beta cell function can be assessed by measurement of fasting and stimulated C-peptide level. This residual proportion of beta cell mass could be associated with improved metabolic outcome.

Objectives: Measurement of fasting and post OGTT (oral glucose tolerance test) C-peptide level in type 1 diabetes population and it's correlation with duration of diabetes and antibody status.

Methods: Observational, cross-sectional study carried out in the department of Endocrinology and metabolism, Medical College, Kolkata from march 2017 to January 2019. Total number of study subjects were 100 consecutive type 1 diabetes patients of 10 – 30 years of age.

Results: Diagnosis of diabetes in majority of cases done by 12-18 years of age. Male to female ratio was 0.78: 1. Fasting C-peptide was detectable in 75 % of cases and after stimulation detectable C-peptide increased to 89 %. Stimulated C-peptide values were significantly negatively correlated with duration of diabetes [$\rho = (-0.260)$; $p = 0.03$]. Antibody positivity were found in 77 % of cases and out of that majority (47 %) cases were GAD-65 positive. Fasting and stimulated C-peptide values are significantly higher in antibody negative groups than antibody positive groups ($p < 0.001$). Lowest mean fasting and stimulated C-peptide level were found in GAD-65 antibody positive groups. We found a significant negative correlation of stimulated C-peptide level with GAD-65 antibody titre in antibody positive groups ($p = 0.017$).

Conclusion: It can be concluded that progressive decline in C-peptide level was observed with increasing duration of diabetes. Antibody negative groups had higher residual beta cell mass than antibody positive groups.

Keywords: Type 1 diabetes, C-peptide, Post OGTT, Duration of diabetes, GAD-65 antibody, IA-2 antibody, Beta cell mass.

Introduction

Type 1 diabetes is a disorder resulting from chronic autoimmune destruction of pancreatic beta cells. As far as the conventional understanding of

Type 1 diabetes goes, beta cells of pancreas are destroyed almost completely at the symptomatic disease onset. Only 10% of beta cells remain in the stage of overt diabetes during pre-symptomatic

period and thereafter these beta cells are destroyed within one year of symptomatic disease onset⁽¹⁾. In contrary, the current model of Type 1 diabetes shows that certain amount of functioning beta cells remain in varying proportion in all individuals with Type 1 diabetes, even as long as for 40 years duration⁽²⁻⁵⁾. The amount of residual beta cells is indirectly measured by measuring serum C- peptide level in fasting state as well as after stimulation either by OGTT or mixed meal or Glucagon injection⁽⁶⁻⁸⁾. The studies have shown that this proportion of residual beta cell activity could be associated with improved metabolic outcome, reduced insulin dose requirements and reduced incidence of diabetes related complications⁽⁹⁻¹⁶⁾. However, the studies are less in our country.

So, in this study we want to re-establish the fact that varying proportion of residual beta cell activity may be present in symptomatic type 1 diabetes individuals. We also want to evaluate the relation of residual beta cell activity with insulin dose requirement, disease duration, age at onset, so that we can identify the population of Type 1 diabetes, where beta cell preservation therapy can be tried in addition to insulin therapy.

Objectives

Primary Objectives

- To measure fasting and post OGTT serum C- peptide level in young (<30 years) Type 1 diabetes population.
- To study the correlation of fasting and post OGTT C- peptide level separately with the duration of the disease and antibody status

Secondary Objectives

- To study the correlation between fasting and post OGTT C- peptide level with age at diagnosis, insulin dose requirement.

Materials & Methods

This was a single centre observational cross-sectional study carried out in the department of Endocrinology and metabolism, Medical College, Kolkata from March 2017 to January 2019.

100 consecutive Type 1 diabetic patients from our diabetic OPD were included in this study. The selected patients were in the age group between 10 – 30 years. Type 1 diabetes was diagnosed by ADA 2017 criteria for diagnosis of diabetes along with history of osmotic symptoms, documented ketoacidosis, insulin requirement from disease onset and low C-peptide level in the absence of history suggesting other forms of diabetes.

Inclusion Criteria

- Diabetic patients (ADA diagnostic criteria) of 10 - 30 years of age.
- Stimulated C-Peptide (post OGTT) level <0.6 ng/dl.
- Patients with documentation of one or more episode of DKA.
- Patients with history of osmotic symptoms & weight loss at the onset of Diabetes
- Patient requiring insulin to achieve euglycemia from the disease onset.
- Patient's blood glucose level should be <200 mg/dl with therapy for last 1 months.

Exclusion Criteria

- Patient with any suggestion of secondary diabetes (long term steroid intake, endocrine or genetic disease)
- Patient having known pancreatic diseases that can cause diabetes
- Patient having significant family history of diabetes.
- Patient with chronic kidney disease, chronic liver disease.
- Pregnant women.

Statistical Analysis

- Descriptive statistical analysis were carried out with SAS (Statistical Analysis System) version 9.2 for windows, SAS Institute Inc. Cary, NC, USA and Statistical Package for Social Sciences (SPSS Complex Samples) Version 21.0 for windows, SPSS, Inc., Chicago, IL, USA, with Microsoft Word and Excel being used to generate graphs and tables. Results on continuous measurements were presented as Mean \pm SD and results on categorical measurements were presented in Number (%).

Significance was assessed at a level of 5%. Unpaired t-test was used to find the significance of the study parameters between two groups of patients namely type 1 antibody positive and type 1 antibody negative, retinopathy present or absent and proteinuria or no proteinuria group. Chi-square test was used to find the significance of study parameters on categorical scale between two or more groups namely type 1 antibody positive and type 1 antibody negative, retinopathy present or absent and proteinuria/no proteinuria group. Spearman Correlation test was used to draw a correlation between c-peptide levels and duration of disease as well as insulin dose requirement. Adjustment of confounders was done by partial correlation test.

- Kruskal Wallis test & post hoc Dunnett T test were used to find the significance of study parameters on categorical scale between two or more groups. This was used to find out the significance of differences of C-Peptide levels in different antibody groups.

- Multiple regression analysis were further performed to find out the causal relationship between c-peptide levels and other predictors and to compute change of the c-peptide levels with unit change in the other predictor levels.

Result & Analysis

This study included consecutive 100 Type 1 Diabetes subjects, of which 56 were female & 44 were male. Age of the study participants was spanned from 10 to 30 years.

We found that Diabetes have been diagnosed at <12 years of age in 29% of population, though majority (47%) of the study subjects were diagnosed at 12-18 years age. On the other hand 19% of the patients were diagnosed at 19-24 years age and 5% were at 24-30 years age.

In 25% of the patients fasting C-Peptide was undetectable (<0.01ng/ml) whereas stimulated C-Peptide was undetectable (<0.01ng/ml) in 11% patients.

Detectable fasting & Stimulated C-Peptide levels were divided into tertiles:

Table 1: Distribution of C- Peptide values in different tertiles

	Fasting C-Peptide	Stimulated C-Peptide
1 st Tertile	<0.1ng/ml (28%) Mean= 0.08	<0.2 ng/ml (24%) Mean= 0.06
2 nd Tertile	0.1-0.3 ng/ml (36%) Mean = 0.23	0.2-0.4 ng/ml (35%) Mean= 0.29
3 rd Tertile	>0.3 ng/ml (11%) Mean = 0.49	>0.4 ng/ml (30%) Mean= 0.68

Differences of mean of fasting C-Peptide levels ($p < 0.001$) & stimulated C-Peptide levels ($p < 0.001$) between each tertile as assessed by ANNOVA were statistically significant.

Out of 75% cases of detectable fasting c-peptide level, 28% had fasting C-Peptide value <0.1

ng/ml, 36% had 0.1-0.3 ng/ml and 11% had >0.3 ng/ml. Out of 89% cases of stimulated c-peptide level, 24% had value <0.2 ng/ml, 35% had 0.2-0.4 ng/ml and 30% had >0.4ng/ml.

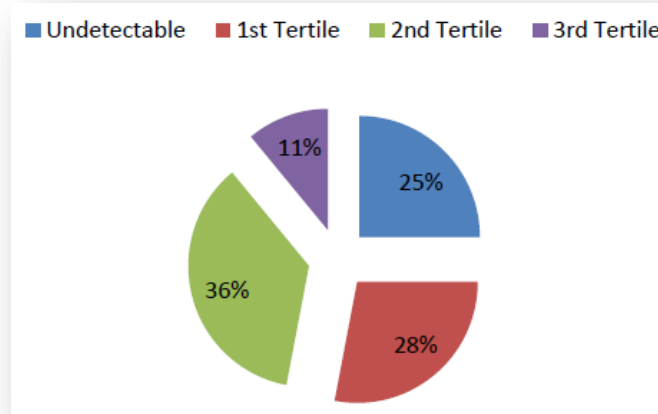


Fig - 1: Pie Diagram showing Distribution of Fasting C-Peptide values in study population

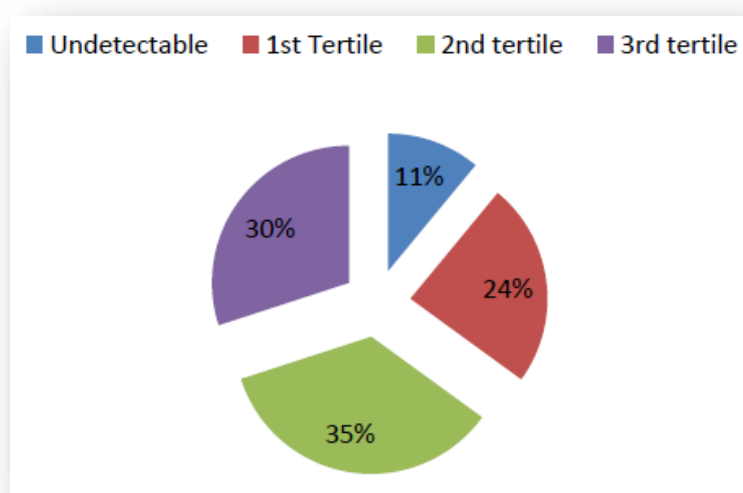


Fig - 2: Pie Diagram showing Distribution of Stimulated C-Peptide values in study population

Statistically significant negative correlation was found between duration of diabetes with stimulated C-Peptide level which suggest that

with increasing duration of diabetes there was significant reduction of stimulated C-Peptide levels ($r = -0.26$; $p = 0.030$).

Table - 2: Spearman’s Correlation of Fasting C-Peptide & Stimulated C-Peptide with Duration of Diabetes

Correlations			Fasting C-PEP	Stimulated C-PEP
Spearman's rho	DOD (YRS)	Correlation Coefficient	-.204	-.260*
		p. (2-tailed)	.079	.030
		N	75	89
*. Correlation is significant at the 0.05 level (2-tailed).				
**. Correlation is significant at the 0.01 level (2-tailed).				

Mean duration of diabetes in 1sttertile, 2ndtertile&3rdtertile of fasting C-peptide levels were 3.68, 1.33, 2.18 years respectively. By ANOVA difference between means were

significant ($p = 0.003$).In multiple comparisons by Dunnett T test, difference between mean duration in 1st&2ndtertile of fasting C-peptide was significant ($p = 0.004$).

Mean duration of diabetes in 1st tertile, 2nd tertile & 3rd tertile of stimulated C-peptide level were 3.96, 1.49, 1.75 years respectively. By ANOVA difference between means were

significant ($p < 0.001$). In multiple comparisons by Dunnett T test, difference between mean duration in 1st & 2nd tertile of stimulated C-peptide was significant ($p = 0.007$).

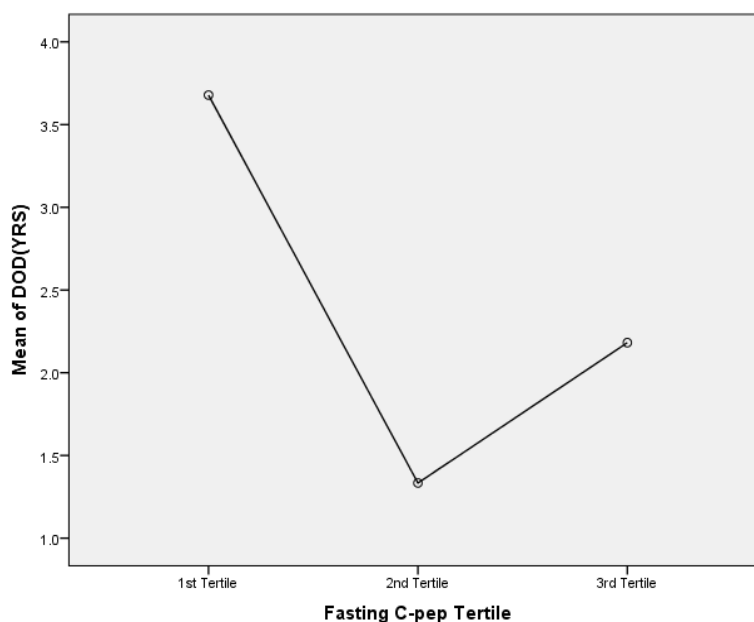


Fig 3: Line Diagram Showing Distribution of Duration of Diabetes in Different Tertiles of Fasting C-Peptide Level

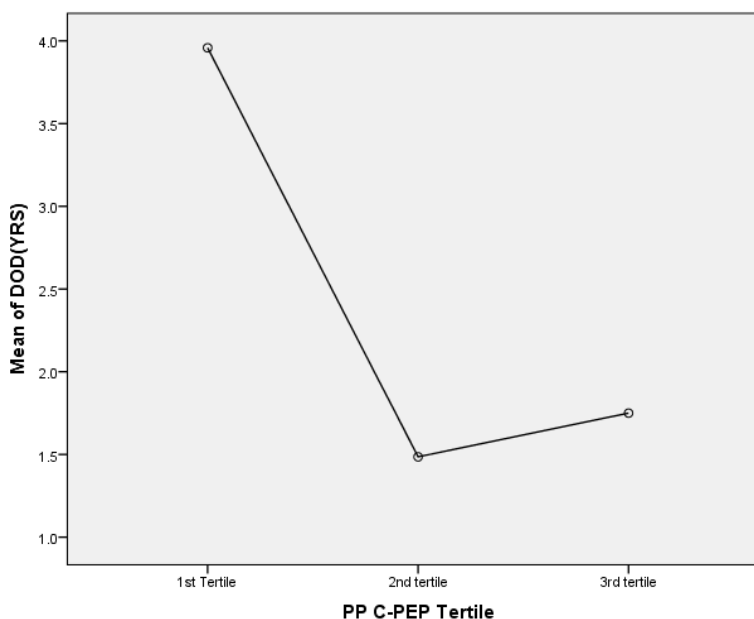


Fig 4: Line Diagram Showing Distribution of Duration of Diabetes in Different Tertiles of stimulated C-Peptide Level

Out of total 100 Type 1 Diabetes subjects, 77% were antibody positive & rest 23% were negative for both the antibodies. Out of antibody positive group, 47% were only GAD-65 antibody positive,

14% were only IA-2 antibody positive & rest 16% were both IA-2 antibody & GAD-65 antibody positive.

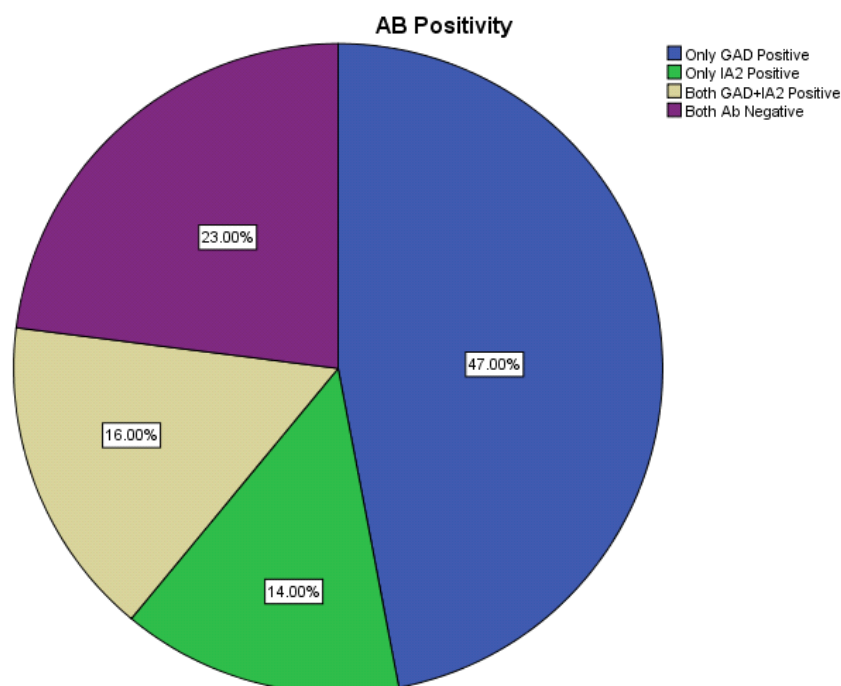


Fig 5: Pie Diagram Showing Distribution of Antibody Positivity

Differences of the fasting C-peptide level & stimulated C-peptide levels between the 4 antibody groups were statistically significant ($p < 0.001$). Higher fasting C-peptide level (0.30 ± 0.10) were found in both IA-2 & GAD-65 antibody negative groups as compared to other groups. Both IA-2 & GAD-65 antibody negative groups had higher stimulated C-peptide (0.62 ± 0.13), lowest stimulated C-peptide level (0.14 ± 0.10) were found Only in GAD-65 Antibody positive group. Significant difference between each group as estimated by Post-hoc Dunnet's T test was at a level of $p = < 0.05$.

Statistically significant negative correlation was found between stimulated C-peptide level & GAD-65 antibody titre in both IA-2 & GAD-65 antibody positive groups ($r = -0.587$; $p = 0.017$). So, increasing GAD-65 Antibody titre was associated with decreasing stimulated C-peptide level.

No statistically significant correlation was found between fasting & stimulated C-peptide level and total daily insulin dose and age at diagnosis of diabetes.

Discussion

This study was a hospital based, cross-sectional observational study done in a tertiary care hospital of Eastern India. This study included randomly taken 100 consecutive Type 1 Diabetes patients of 10- 30 years of age.

Diagnosis of Type 1 Diabetes was done mostly on clinical ground like patients with history of weight loss & osmotic symptoms at disease onset, with one or more documented DKA episode, with requirement of insulin therapy from the beginning (that effectively rules out Latent Autoimmune Diabetes) and after excluding the possibilities of secondary diabetes, pancreatic diabetes as well as Maturity Onset Diabetes of Young (as patients with family history of diabetes were excluded). Age group of our study population were between 10-30 years.

Diagnosis of Diabetes of majority (47%) of our study population were made at 12-18 years of age, 29% of subjects were diagnosed at < 12 years of age & 24% of population were diagnosed at 24-30 years of age. This finding was consistent with previous Indian data by Prasanna et al. They concluded that peak age of onset of Type 1

Diabetes was 12 years⁽¹⁷⁾. SEARCH International data for Type 1 Diabetes also showed that maximum incidence of Type 1 Diabetes observed between 10-14 years of age in both Hispanic & non-Hispanic groups⁽¹⁸⁾. In other studies, the incidence rate started increasing from birth and peaked between the ages of 10–14 years during puberty. The increasing incidence of type 1 diabetes throughout the world is especially marked in young children⁽¹⁹⁾. Incidence rates decline after puberty and appear to stabilize in young adulthood (15–29 years)&approximately one fourth of persons with type 1 diabetes are diagnosed in adults⁽²⁰⁾.

Male and female ratio of our study population was 0.78:1. It was similar to previous literature⁽¹³⁾. In contrast, male preponderance was observed in some European studies⁽²¹⁾. Mirella et al study⁽¹²⁾, observed male preponderance in childhood & adolescent onset Type 1 Diabetes & female preponderance in adult onset Type 1 Diabetes.

In our study, fasting C-peptide values were found to be undetectable in 25% of population. Stimulated C-peptide values were found to be undetectable in 11% of population. Detectable fasting C-peptide level was found in 75% of patients, but it was increased to 89% in case of stimulated C-peptide level. It signifies that beta cell mass is not totally burnt out at the onset of Type 1 diabetes. In majority of the patients significant amount of beta cell mass persisted especially in the initial years. This is in contrary to our popular belief that only 10% of beta cell mass remain when subjects move from pre-diabetes to overt diabetes stage in Type 1 diabetes and those remaining beta cells are also destroyed within one year of symptomatic disease onset⁽¹⁾. But current model of Type 1 diabetes shows that certain amount of functioning beta cells may remain in varying proportions in all individuals with Type 1 diabetes, even as long as up to 40 years duration⁽²⁻⁵⁾. Our results were in favour of this model. It was also shown in older studies that young children with classical ketosis prone insulin dependent diabetes had residual insulin secretion⁽²²⁾. Katz et

al⁽²³⁾ reported that fasting C-peptide levels of 0.38 ± 0.37 ng/ml can distinguish T1DM from T2DM with 83% sensitivity. In Mirella et al study which included⁽¹²⁾ 88 type 1 diabetes subjects, detectable fasting C-Peptide was found in 21.6% cases and detectable post glucagon stimulated C-peptide was found in 31.8% cases. This low value might be due to their higher detection limit (≥ 0.5 ng/ml) than our study (< 0.01 ng/ml).

Values of stimulated C-peptide levels were significantly negatively correlated with duration of diabetes ($r = -0.260$; $p = 0.030$). Fasting C-peptide values were also negatively correlated with duration of diabetes though not statistically significant. It suggests with increasing duration of diabetes there is decrement of C-peptide level & more so in cases of stimulated C-Peptide. It indicates stimulated C-peptide levels may be the better predictor of beta cell mass. Limei et al⁽¹³⁾ studied 182 Type 1 Diabetic patients and observed the similar relation of C-peptide level with duration of diabetes. Davis et al⁽²⁴⁾ studied 819 Type 1 Diabetic patients with detection limit of C-Peptide > 0.017 nmol/L. They have shown that overall frequency of detectable non fasting C-peptide was 29% which was decreasing with increasing duration of the disease regardless of age at diagnosis. Also, 19% of those with undetectable non fasting C-peptide were found to have detectable C-peptide upon stimulation by mixed meal. Our study also showed similar results (14% of those with undetectable fasting C-peptide had detectable C-peptide after stimulation with glucose).

We have also subdivided detectable C-Peptide values into three tertiles, not done in previous studies. We found that differences of mean duration of diabetes between different tertiles of fasting and stimulated C-peptide level were statistically significant ($p = 0.003$ and $p < 0.001$ respectively). We have shown that duration of diabetes in the patients having highest C-peptide levels were longer than the patients having medium C-peptide level and shorter than the lowest C-peptide level. It means with increasing

duration C-peptide value increases initially but in long run it ultimately decreases. This result can be explained by initial increase in C-peptide level suggestive of endogenous insulin secretion which is probably due to remission of glucotoxicity after treatment with insulin. After that there is progressive destruction of beta cell occurs leading to decline in C-peptide level.

In our study, out of total 100 Type 1 Diabetes patients, 77% of them were antibody positive & rest 23% were both antibody negative. Among antibody positive group, 47% of patients were only GAD-65 antibody positive, 14% were only IA-2 antibody positive & rest 16% were both IA-2 antibody & GAD-65 antibody positive. It indicates a significant proportion (23%) of young type 1 diabetes patients were antibody negative, though we could not test serum IAA & Zinc Transporter 8 antibodies. In other studies in India⁽²⁵⁾ it was found that, a high frequency of patients (45%) with presumed diagnosis of T1D lack GAD-65 & IA2 autoantibodies and therefore establishing the autoimmune basis becomes difficult in those cases. In a study by Prasannakumar et al⁽²⁶⁾, it has been mentioned that inclusion of ZnT8A presumably reduces the proportion of patients with negative autoantibodies. Jiang wang et al⁽²⁷⁾ showed that, 19% of children with newly diagnosed diabetes were all antibody negative and antibody negativity was significantly increased with age ($p < 0.01$). In the literature it was mentioned that, Antiislet cell autoantibodies may be present years before the onset of type 1A diabetes and usually continue to be present even during the pre-diabetic period⁽²⁸⁾, although the titres may decline gradually with eventual loss in nearly half of the patients after several years of the disease⁽²⁹⁾. It might also be possible that a small proportion of cases could lose autoantibodies before diabetes onset.

Mean fasting C-peptide (0.30 ± 0.10) values in both antibody negative groups were significantly higher than the other antibody groups ($p < 0.001$). Mean stimulated C-peptide (0.62 ± 0.13) values in both antibody negative group were significantly

higher than the other antibody groups ($p < 0.001$). Mean stimulated C-peptide (0.14 ± 0.10) value in isolated GAD 65 positive group was significantly lower than the other antibody groups ($p < 0.05$). The difference of mean stimulated C-peptide level between the groups was found to be statistically significant ($p < 0.05$). Mirella et al study⁽¹²⁾ have shown GAD-65 antibody was present in 43.7% of type 1 diabetes, but GAD-65 positivity did not correlate with C-peptide level. Limei et al⁽¹³⁾ have shown ZnT8 antibody positivity was the only factor, which correlate with C-peptide level. Emad et al⁽³⁰⁾ have studied 747 type 1 diabetes population & have shown that patients with positive IA-2 antibody had reduced C-peptide concentration ($p = 0.003$) and patient with no detectable antibodies had higher C-peptide level ($p = 0.007$) than others. But no significant correlation was found between C-peptide level GAD-65 positivity. Avery old review⁽³¹⁾ have shown that median C-peptide values among the persistently islet cell antibody positive patients decreased from 0.11 pmol/ml at 18 months, to 0.09 pmol/ml at 24 months, to 0.06 pmol/ml at 30 months compared to 0.18 ($p = 0.04$), 0.15 ($p = 0.05$) and 0.16 ($p < 0.003$) pmol/ml, respectively, in the islet cell antibody negative patients & they concluded that islet cell antibodies may be a useful marker for predicting an increased rate by which endogenous B cell function is lost in Type 1 diabetes. In contrast, our study have shown significantly lower C-Peptide level in GAD -65 antibody positive patients than IA-2 positive & both antibody positive group. However, the exact cause was not clear at this point of time.

No previous studies have evaluated the correlation of antibody titres with C-peptide level except one study⁽³²⁾ which concluded that urinary C-peptide level correlates negatively with the GAD antibody titre. But our study have shown a statistically significant negative correlation between stimulated C-peptide level & GAD-65 antibody titre in both IA-2 & GAD-65 antibody positive group ($r = -0.587$; $p = 0.017$). So, increasing GAD- 65 antibody titre is associated with

decreasing Stimulated C-peptide level. No significant correlation found between C-peptide level & IA-2 antibody titre.

In our study fasting & stimulated C-peptide levels were not significantly correlated with total daily insulin dose and baseline HbA1C. In contrast, Mirella et al⁽¹²⁾ have shown patients with detectable C-peptide level required lower insulin doses ($p < 0.009$) though there was no significant correlation with HbA1c ($p = 0.182$). It may be due to some additional factors that play a role in predicting insulin dose and HbA1c level like insulin resistance and patient's compliance to treatment which were there in some of our study population.

Limitation of our study was small sample size, homogeneity of population and narrow age range of type 1 diabetes patients. Also, we were unable to do genetic tests in our patients to look for maturity onset diabetes of young and other monogenic diabetes that can present in young age because of financial constrain and less accessibility. ZnT8 autoantibody level was also not measured in this study because of similar reason.

Conclusion

It can be concluded that there may be significant amount of residual beta cell mass in majority of type 1 diabetes patients even after diagnosis and stimulated C-peptide can be a better predictor for residual beta cell function than fasting C-peptide. There is progressive decline of C-peptide level occurs with increasing duration of diabetes. A significant proportion of patients of type 1 diabetes may be antibody negative and these patients may have higher residual beta cell mass than antibody positive group.

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