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Clinical sub typing of newly detected type 2 diabetics on the basis of pancreatic beta cell function and degree of insulin resistance and their clinical characterization

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ABSTRACT

Background: Insulin resistance is a major cause for developing type 2 diabetes but is not synonymous with the type 2 diabetes. Pancreatic beta cell dysfunction probably needs to be sets in for clinical occurrence of type 2 diabetes. So knowledge regarding residual beta cell function and degree of insulin resistance is essential. **Aims and Objectives:** The objectives are as follows: (1) To estimate degree of insulin resistance (HOMA-IR) and pancreatic beta cell functional capacity (HOMA-B %) among newly detected Type 2 diabetics and (2) to identify different clinical phenotypic presentations of type 2 diabetes on the basis of these parameters. **Materials and Methods:** This present study was conducted in newly diagnosed type 2 diabeticpatients. After obtaining informed consent, anthropometric and clinical examination was carried out in all patients.Venous blood samples were drawn for fasting plasma glucose,c-peptide,fasting insulin level,HbA1c,lipid profile, etc.HOMA-IR and HOMA-B% were calculated with HOMA 2 calculator. **Results:** A total 100 newly diagnosed type 2 diabetic patients were studied. About 71% pt of study population had HOMA-B% value below 50% and half of study population had significant amount of insulin resistance. Three distinct clinical phenotypes had identified. Insulin resistance predominant group (30%), beta cell dysfunction predominant group (45%), and both abnormalities coexist group (25%). **Conclusion:** By the time of diagnosis of Type 2 diabetes, more than two-third study population had <50% residual beta cell function left and more than half had significant degree of insulin resistance. Hence,this functional assessment needs to be done for appropriate antidiabetic drug selection and for identification of different clinical phenotypes.

Key words: HOMA-B%; HOMA-IR; Type2 diabetes mellitus

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INTRODUCTION

We know that type 2 diabetes is not a homogeneous disease. A lot of heterogeneousity does exist in its etiopathogenesis and clinical presentations.[1] Type 2 diabetes can be hepatogenic or pancreatogenic or obesogenic, etc. Contrary to our traditional belief it has now become prevalent among children, adolescent. Now we have learned eight to 12different pathophysiological defects that are contributory to hyperglycemia in type 2 diabetes.[2] Now we realized that kidney, brain, gut hormones and gut microbiota all have contribution in the development of type 2 diabetes.[3,4] At the same time same of the recent studies proposed that incretin defect may be the result of chronic hyperglycemia and can be improved once euglycemia is achieved.[5]Hence,we proposed that pancreatic beta cell secretary defect and insulin resistance continue to be the major determinant of type 2 diabetes. Basically, whatever forms of diabetes it is, at the end of the day it is a simple imbalance between insulin secretion and insulin resistance. While EASD/ADA considered various co-morbidities while selecting various anti-diabetic medications, they did not mention the consideration of these basis endocrinal defects of type 2 diabetes.

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What is the rationality behind giving a diabetic patient insulin secretagogues without knowing his or her beta cell reserve? Pancreatic beta cell reserve and degree of insulin resistance are not the same between a diabetic patient who is older in age, overweight, having long standing diabetes with multiple co-morbidities and a diabetic patient who is younger, not overweight, recently been diagnosed and without any co-morbidities. So this kind of functional assessment is helpful for sub typing type 2 diabetic patients into different subgroups and each subgroup might have different diseases progression rate, different complications rate, and different drug response to different oral antidiabetic agents. As all we know the gold standard method for detection of insulin resistance is hyperinsulinemic euglycemic clamp method, but it is cumbersome to apply this method in day to day clinical practice.[6] We can measure these by indirect method as well. Homeostatic Model Assessment (HOMA) 2 calculator is one of this method. HOMA test was first introduced in 1985 by Matthews et al.[7]Then, in 1998, Levy et al., published an updated HOMA model (HOMA-2)[8] Where after putting fasting plasma glucose and fasting plasma insulin levels, we can get individual's beta-cell function (HOMA-B%) and degree of insulin resistance (HOMA-IR). In China,Li et al. found a modified model using c-peptide to replace insulin in HOMA assessment.[9] Some studies reported c-peptide modified HOMA might be more appropriate in this regard.[9] Hence,this present study was carried out to estimate degree of insulin resistance and pancreatic beta cell functional capacity in the form of HOMA-IR and HOMA-B%, respectively, with the help of HOMA-2 calculator, among newly detected treatment naïve Type 2 diabetes patients. We also tried to subclassify them on the basis of these functional assessments and looked into their clinical and laboratory parameters.

Aims and objectives

1. To estimate degree of insulin resistance (HOMA-IR) & pancreatic beta cell functional capacity (HOMA-B %) among newly detected Type 2 diabetic patients.
2. To identify different clinical phenotypic presentations of type 2 diabetes on the basis of this functional assessment.

MATERIALS AND METHODS

This was an observational cross sectional single center based study done in Eastern India with the out patients of diabetes of clinic of our institution from March 2020 to December 2021. This study included patients who had recently been diagnosed with type 2 diabetes (as per ADA criteria) and came to our clinic for initiation of drug therapy. Those patients having other types of diabetes such as type 1, GDM, secondary diabetes, and those presented with concurrent infection, other illnesses or were in metabolic decomposition state, were excluded from the study. After detail explanation of study procedure, informed consent was taken from each participant and Institutional ethical clearance was obtained for the study. Details history, anthropometric measurements, and clinical examination werecarried out in every enrolled patient. Then, blood samples were taken for estimation of fasting plasma glucose, fasting plasma insulin, C-peptide, lipid profile, 2 h post prandial glucose, HbA1c, etc. HOMA-2 calculator was used where after putting fasting plasma glucose, insulin valves we got HOMA-B% and HOMA-IR values for each participant.HOMA-IR value more than equal to 2.5 was considered as presence of insulin resistant and HOMA-B% value less then equal to 50% was considered as poor pancreatic beta-cell reserve.[10] Then we subdivided the whole study population on the basis of these values and characterize each subgroups in terms their anthropometric glucose, lipid parameters.

Sample size

Sample size was calculated using this formula with 5% absolute precision and 95% confidence level as per the study by Daniel.[11] The required sample size as per the above-mentioned calculation was 95. To account for a non-participation rate/loss to follow-up rate of a about 5%, another 5, subjects will be added to the sample size. Hence, the final required sample size would be 100.

$$n' = \frac{NZ^2P(1-P)}{d^2(N-1) + Z^2P(1-P)}$$

Statistical methods

Assessment of Pancreatic beta cell function and degree of insulin resistance was considered as primary outcome of interest. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. For normally distributed quantitative parameters, the mean values were compared between study groups using ANOVA (>2 groups).Categorical outcomes were compared between study groups using Chi-square test. $P<0.05$ was considered statistically significant.Data will be analyzed by using coGuide software, V.1.0.[12]

RESULTS

A total 100 newly diagnosed treatment naive type 2 diabetic patients were studied. The mean age of the study population was 45.55±11.64 years. Among the study

population, 58% were comprised of male. The mean BMI calculated was 25.93+4.39 kg/met. The positive family history of diabetes was present in 33% of study population. The mean values of HOMA-B% and HOMA-IR were 40.67±23.55 and 2.22±1.75, respectively. Figure 1 shows bar chart of HOMA A-B% values in the study population which represents 39 % of study population had HOMA-B % values below 30% and 32% had values between 30% and 50%.

Figure 2 shows bar chart of HOMA-IR values in the study population which represents 49% of study population had HOMA-IR values below 2.5and remaining 51% pts had significant amount of insulin resistance that means their HOMA-IR values were more than equal to 2.5.

Then we subdivided the study population into three subgroups.These were insulin resistance predominant group in whom significant degree of insulin resistance was present (HOMA-IR>2.5) but they had good pancreatic beta cell functional reserve (HOMA-B%>50%), Beta cell dysfunction predominant group in whom insulin resistance was not significant but they had poor beta-cell reserve (HOMA-B%<50%), third group where insulin resistance and beta cell dysfunction both co-exist (HOMA-IR>2.5 and HOMA-B%<50%). Our study population comprised of 30% insulin resistance predominant group, 45% beta cell dysfunction predominant group, and 25% both abnormalities exist

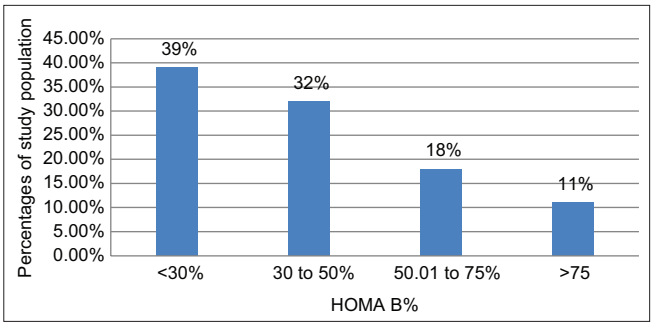

Figure 1: Bar chart of HOMA B% in the study population (n=100)

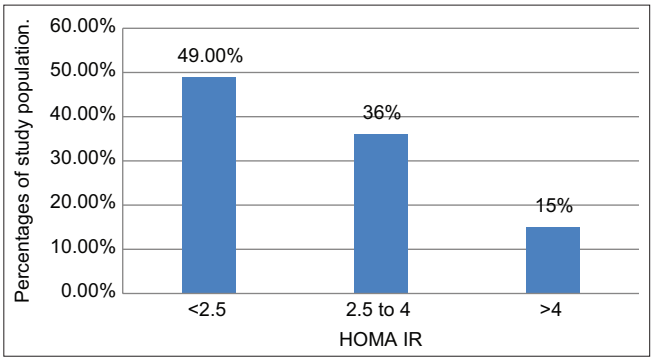

Figure 2: Bar chart of HOMA IR in the study population (n=100)

group. We characterized these sub groups in terms of age, BMI, waist circumference, B.P, fasting,and post-prandial glucose value, HbA1c, lipid parameters, fasting insulin, and fasting C-peptide levels (Table 1).

Surprisingly despite all having the same disease that is type 2 diabetes they are different from each other in respect to these variables. There was no statistically significant difference in mean ages of disease detection among these groups. When BMI and abdominal circumference werecompared among them statistically significant differences were found and Beta cell dysfunction predominant group had both lowest BMI of 23.76±2.98 kg/m^2 and lowest abdominal circumference of 87.29±7.24cm.Insulin resistance predominant group had significantly higher blood pressure values as compared to other groups(P=0.002).In terms of entry level HbA1c there had been significant difference among them with both abnormalities coexist group had highest value of 8.65±1.38%.Lipid parameters were not significantly different among these groups. As far as fasting insulin and fasting c-peptide levels were concerned, significant difference was exist among these groups with insulin resistance predominant group had highest of these values(P<0.001). Insulin resistance predominant group had highest HOMA-IR value of 3.95±1.47.Whereas beta cell dysfunction predominant group had lowest HOMA-B value of 29.06±11.77%.

DISCUSSION

India is facing an epidemic of diabetes. India is currently home to 77 millions of diabetic people and 90% of them are of type 2 kind of diabetes mellitus. Most of the type 2 diabetic patients are being treated with oral antidiabetic agents. We have different classes of oral drugs which address different pathophysiological aspects of the disease. Hence,it is very important to select anti diabetic drugs appropriately. We have been taught by our teachers in our medical school days that type-2 DM occurs due to defect in beta cell insulin secretion, insulin resistance,and increased hepatic gluconeogenesis which was known as Triumvirate Hypothesis.[2] For the last few decades, we came to know eight to 12different mechanisms contributing to blood hyperglycemia.[3,4]Hence, type 2 diabetes is very heterogeneous in etiopathogenesis and clinical presentations. But contribution of each pathophysiological defects to blood glucose rise is not well understood till now. Recently few studies have come up with the proposition of many of these defects are secondary to chronic hyperglycemia like incretin defect.[5]Hence,probably pancreatic beta cell secretary defect and insulin resistance continue to be the most significant determinant of type 2 diabetes. We have high level of abdominal fats and

Table 1: Comparison of various parameters across subgroups in the study population (n=100)

Parameters	Subgroups			P value
	Insulin Resistance Predominant (n=30) Mean±SD	Beta Cell Dysfunction Predominant (n=45) Mean±SD	Both Abnormalities Exist (n=25) Mean±SD	
Age (yrs)	42.26±9.58	48.33±12.18	44.96±11.47	0.112
Body mass index (kg/m^2)	28.95±4.74	23.76±2.98	26.5±3.79	<0.001
Abdominal circumference in male (cm)	97.53±14.11	87.29±7.24	89.9±14.73	0.015
Blood pressure (mm of Hg)	135.2±10.4/86.4±3.3	125.4±8.1/81.1±4.7	127.1±6.3/83±4.4	0.002
FPG (mg/dl)	153.11±52.47	206.04±91.29	222.8±67.95	0.003
2 h PP glucose (mg/dl)	246.89±80.58	315.84±123.92	323.32±113.25	0.030
HbA1c(%)	7.83±1.58	8.66±2.3	8.65±1.38	0.227
Total cholesterol (mg/dl)	176.15±38.32	174.2±36.04	184.72±50.68	0.754
LDLc (mg/dl)	107.56±32.08	111.36±27.6	107.48±34.7	0.907
HDLc (mg/dl)	39.22±7.24	39.96±6.31	38.12±7.22	0.753
Triglyceride (mg/dl)	199±123.24	190.89±67.65	240.88±144.34	0.296
Insulin fasting(µIU/ml)	12.43±5.63	3.61±2.02	7.44±5.21	<0.001
C PEPTIDE fasting (ng/ml)	3.04±1.15	1.95±0.78	2.48±0.83	<0.001
HOMA-IR	3.95±1.47	1.17±0.61	3.56±1.67	<0.001
HOMA-B%	69.94±17.64	29.06±11.77	26.79±12.86	<0.001

increased insulin resistance.[13] However, recent studies suggest that Beta cell dysfunction and secretary defect occurs quite early and rapidly in Asian Indians, as we have relatively less amount of Beta cell reserve due to low BMI.[14] Hence,we progressed faster and need Insulin early in the disease course. Same way development of diabetes related complications are also not uniformly distributed in diabetics and present in unpredicted way. One subset gets complications at an early phase in the disease course while others remain devoid of any complications for a long time. Hence, we need to identify different phenotypes of type 2 diabetes in respect to disease progression rate, different drug responsiveness and different disease related complications rate.

In this present study, we sub classified 100 newly detected type 2 diabetes patients from eastern India on the basis of these two basic endocrinal defects.We identified three novel clinical phenotypes of type 2 diabetic patients with different clinical and laboratory characteristics.In our study, insulin resistance predominant sub group comprised of 30% of the study population and they had highest BMI, abdominal circumference, blood pressure fasting insulin, fasting C-peptide levels as compared to other groups and these attained statistical significance. Whereas beta cell dysfunction predominant sub group that comprised of 45% of study population, had lowest B.M.I, abdominal circumference, blood pressure fasting insulin, fasting C-peptide levels as compared to other groups and found to be statistically significant. Both abnormalities co-exist sub group had 25% occurrence and had highest fasting plasma glucose; 2 h post prandial glucose, HbA1c values and their other parameters were intermediate between the values of other two groups. This group probably represents most aggressive phenotype; it is likely that the presences of dual pathophysiology render these individuals at high risk of developing diabetes at younger ages and predispose them to faster disease progression and early need of insulin therapy. More aggressive therapy with a combination of agents targeting multiple pathophysiology's of type 2 diabetes may be indicated in this group of patients to help them to prevent long-term complications. They also need to be screened more aggressively for complications. Recently, distinct "clusters" or subgroups of individuals with type 2 diabetes have been identified in a Scandinavian population of 8980 individuals, based on five parameters representing the clinical presentation as well as the presence of insulin resistance and beta-cell dysfunction.[15] These five subgroups have been termed severe autoimmune diabetes, severe insulin deficient diabetes, severe insulin resistant diabetes, mild obesity-related diabetes, and mild age-related diabetes. Further analyses of these subgroups have shown that such clustering might have implications with respect to the risk of diabetes complications as well as selection of the most appropriate treatment. However, as the above study has been performed on a white Caucasian population, there is still no clarity on whether this classification is applicable to individuals with diabetes belonging to other ethnic groups. For the first time in India, clustering was done on 19,084 individuals with T2DM in INSPIRED study published in 2020 done by Anjana et al.,[16] using eight clinically relevant variables-age at diagnosis, body mass index, waist circumference, glycated hemoglobin, triglycerides, high-density lipoprotein cholesterol, and C peptide fasting and stimulated. Four replicable clusters were identified, differing in phenotypic characteristics as well as disease outcomes: Severe Insulin Deficient Diabetes group (SIDD) in 26.2% of study population, Insulin Resistant Obese Diabetes group in 25.9% of study population, Combined Insulin Resistant and Deficient Diabetes (CIRDD) group in 12.1% of study

population, and Mild Age-Related Diabetes group in 35.8% of study population.[16] Cox proportional hazards showed that SIDD had the highest hazards for developing retinopathy, followed by CIRDD, while CIRDD had the highest hazards for kidney disease. This kind of classification of type 2 diabetes will provide insights into the pathophysiological processes driving diabetes in this ethnic group, which could also help in predicting the risk of complications and individuals with the highest risk of morbidity and mortality.

Our study also demonstrated, in more than two-third study population pancreatic beta cell function has reduced to < 50% by the time of diagnosis and more than half of the study population had significant degree of insulin resistance. Hence,we should select appropriate antidiabetic drugs that have beta cell preservation effect and will break insulin resistance. Every diabetic pts may not have same amount of pancreatic beta cell functional reserve and similar degree of insulin resistance, so if we calculate these parameters before going to select antidiabetic drugs for a particular pt,it would have been a more logical approach. The study findings have to be tested prospectively through well-planned randomized clinical trials.

Limitations of the study

Our study has certain limitations like it was done in a single tertiary care center, so generalizability of study findings to other parts of India were not ascertained.Similarly,we have done this assessment by indirect method and have not followed up these patients with serial measurement of these parameters over the course of disease progression. HOMA-2 calculator has its own limitations like it is unreliable in presence of very high blood glucose value and in the presence of poor beta cell function.[17]

CONCLUSION

Our study demonstrated, every diabetic pt is different from each other in terms of their residual pancreatic beta cell functional capacity and degree of insulin resistance. Our study found more reduced beta cell function compared to reduced insulin sensitivity in new T2DM patients. So this kind of functional assessment needs to be done for selection of appropriate antidiabetic drugs for a particular patient. This is also helpful for identification of different clinical phenotypes of type 2 diabetes and to evaluate the effect of newer therapy on pancreatic beta cell reserve and insulin resistance.

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