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A STUDY OF THE PATTERN OF INSULIN RESISTANCE IN EUGLYCEMIC OFFSPRINGS OF DIABETIC PARENTS AND COMPARISION WITH AGE, SEX MATCHED CONTROLS AMONG SOUTH INDIAN POPULATION.

N.ANURADHA*[1] AND J.CARLTON JOHNNY[2]

[1]Assistant professor of general medicine , Sree Balaji medical college and hospital , Bharath University , India .
[2] Undergraduate, SreeBalaji Medical Collage & Hospital, India.

ABSTRACT

To study the pattern of insulin resistance among euglycemic offspring of diabetic parents by appropriately matching for sex, and age in controls. Using inclusion & exclusion criteria 52 euglycemic offspring as subjects and 25 controls were taken. FBS, PPBS, Fasting insulin levels and Insulin resistance were calculated by HOMA-IR method. The results were tabulated and studied. siblings of diabetic parents had higher levels of fasting insulin level, insulin resistance when compared to the controls with a P value of 0·001 and 0·00 respectively. The sub group analysis among the male, female offspring also showed similar results and an additional finding was that female offspring of diabetic fathers had a higher IR when compared to the other groups.There is significant association between parental diabetic status and onset of insulin resistance in offspring when compared to the controls.

KEY WORDS: **diabetes, offspring, insulin resistance, HOMA-IR.**

N.ANURADHA
Assistant professor of general medicine , Sree Balaji medical college and hospital , Bharath University , India .

***Corresponding author**

INTRODUCTION

Insulin resistance(IR) has become the subject of research of late because of its association with various diseases like type 2 diabetes mellitus, polycystic ovarian disease, etc and its role in abdominal obesity has been proved beyond doubt. Recently, deeper understanding of the pathogenesis of diabetes has shown that "*Insulin Resistance"* is a period which precedes the fatal onset of pancreatic burn out, and has been designated as a state of inflammation[1]. The inflammatory mediators that are involved in the development of insulin resistance tend to alter the lipid balance [2] in the metabolic pathway ultimately leading to fatal cardiovascular co morbidities. The mechanistic pathway of insulin resistance is not fully understood, whether it is a risk factor for other diseases that are associated with it or just a part of a bigger picture which is yet to be teased out. The finding that Insulin Resistance could be hereditary when it is associated with polycystic ovarian disease has changed the management approach for this syndrome. Some studies say that insulin resistance may be seen in siblings of those with Poly Cystic Ovarian Syndrome [3]. Studies which focus individually on insulin resistance also have shown the prevalence of it among siblings of type 2 DM parents is 26·67%[4]. Other Studies have proved that IR is associated with mutation in certain genes like ADIPOQ, ADIPOR1, ADIPOR2[5]. "IR is cloudedwith hypertension in the oriental countries[6]. Variation of inheritance was seen among maternal and paternal involvement[7]. Normal glucose tolerant siblings of Diabetic parents had increased insulin secretion and insulin resistance [8]since Insulin resistance is a product of insulin secretion times fasting glucose level divided by 22·5. These heterogeneity in the phenotype of IR gave us the impetus to study the pattern of IR among Indian population, since India is heading towards becoming the diabetic capital of the world. We selected diabetic parents with their offspring who are euglycemic and looked at few glycemic parameters and the pattern of insulin resistance in them.

MATERIALS AND METHODS

The study was conducted in 52 off springs of diabetic parents and 25 controls matched appropriately for age and sex.

INCLUSION CRITERIA

1. Age group – 20 – 40 yrs
2. Either of the parent being a diabetic
3. FPG< 100 mg%
4. 2 HR PPBS - <140 mg%

EXCLUSION CRITERIA

1. Age group <20 yrs and >40 yrs
2. Both parents diabetic
3. FPG > 100 mg%
4. PPBS> 140mg%
5. Subjects on anti Diabetics

Approval was obtained from the institutional ethical committee the blood was collected after an overnight fasting of at least 8 hours and analyzed by Glucose Oxidase – Peroxidase Method. The cutoff values were kept according to ADA guidelines where impaired fasting glucose (IFG) (FPG levels 100–125mg/dL [5.6–6.9 mmol/L]), or impaired glucose tolerance (IGT) (2-h PG OGTT values of 140–199 mg/dL [7.8–11.0 mmol/L])[9]. Serum insulin assay was estimated by the ACS:180 Insulin assay is a two site sandwich immunoassay using direct chemiluminiscent technology which uses constant amounts of two antibodies .The first antibody in the lite Reagent is a monoclonal mouse anti- insulin antibody labeled with acridium ester . The second antibody in the solid phase is a monoclonal mouse anti insulin antibody which is covalently coupled to paramagnetic particles. Insulin resistance was calculated based on the HOMA-IR model[10]. The HOMA-IR was calculated using the formula the average fasting insulin range is 0 – 11 uIU/ml with an Median value of 5uIU/ml. HOMA-IR = S.FASTING INSULIN * S.FASTING GLUCOSE / 22·5, where serum fasting insulin is in mU/l and serum fasting glucose is in mmol/l. The results obtained were tabulated and studied.

RESULTS

Afterthe study the results were analyzed between three groups
Group 1: Where the father was a diabetic
Group 2: Mother was a diabetic
Group 3: Consisted of Controls

Sub grouping (Table 2):
Male offsprings of 3 groups
Female offsprings of 3 groups

The study population consisted of 52 subjects (M 25/ F 27) and 25 controls (M 12/ F13).
The mean values of different parameters are given below as a table

Table 1
DESCRIPTIVE STATISTICS

Characteristics	Diabetic father	Diabetic mother	Controls	SD	P value
Fasting blood glucose (mg/dl)	85·33	78·44	79·40	7·9412	0·002
Post prandial blood glucose (mg/dl)	101·48	93·88	98·16	97·93	0·193
Fasting insulin level (uIU/ml)	11·33	8·10	5·34	5·8705	0·001
Insulin resistance	2·4126	1·5722	1·0469	1·6963	0·00

Table 2
Results among sub groups

Characteristics	Father diabetic	Mother diabetic	Controls	P value
	Male offspring			
FBS (mg/dl)	83·33	75·46	77·41	0·033
PPBS (mg/dl)	98·66	92·15	97·75	0·501
Fasting Insulin level (uIU/ml)	8·5267	9·3662	4·7400	0·026
Insulin resistance	1·7609	1·7694	0·8921	0·026
	Female offspring			
FBS (mg/dl)	86·93	81·66	81·23	0·065
PPBS (mg/dl)	103·73	95·75	98·53	0·359
Fasting Insulin level (uIU/ml)	13·5773	6·7292	5·9031	0·002
Insulin resistance	2·9339	1·3586	1·1899	0·002

Insulin resistance of the different study groups

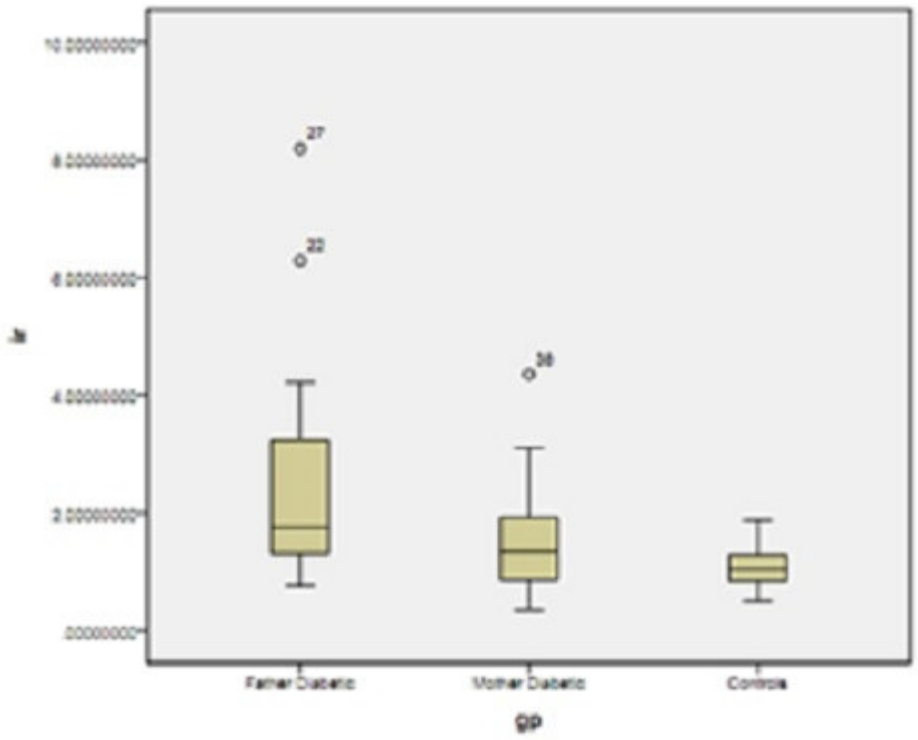

Figure 1

There is a significant difference among the IR levels among the study groups and there are also some extreme values seen among the siblings of diabetic parents which is outside the interquartal range when compared to the controls.

DISCUSSION

Our study is done among euglycemic sibling of diabetic parents. The results show a unique pattern. When we compare the FBS levels among the siblings of different groups the mean FBS levels are 85·33 mg/dl, 78·44 mg/dl, 79·40mg/dl respectively. Thus, there is no significant difference among them even though there are under the cutoff of < 100mg/dl according to ADA guidelines. The same fact can also be applied to the PPBS levels where the mean PPBS values among the siblings of diabetic father is 101·44 mg/dl, siblings of diabetic mothers is 93·88 mg/dl, and the control group is 98·16 mg/dl. These values are also under the cutoff value of <140 mg/dl. But a gross variation of this pattern is seen in the fasting insulin levels where the insulin level in the sibling of diabetic father's is 11·33 uIU/ml, diabetic mother is 8·10 uIU/ml, and the control group is 5·34 uIU/ml. this pattern is seen to affect the total insulin resistance when it is substituted and calculated using the formula HOMA-IR. The IR, thus calculated is 2·41, 1·57 and 1·04 for the siblings of diabetic father, diabetic mother and controls respectively. It can be inferred that even though the siblings of diabetic parents are at present in euglycemic levels based on their FBS, PPBS values their fasting insulin levels show a vast difference among them. This can be representative of the pathogenesis of type 2 diabetes mellitus itself, the fact is that these siblings are in the process of developing insulin resistance and the disease process has not yet fully developed to reflect on the other parameters. There has also been significant statistical values when the data were analyzed. The P value for the fasting insulin among the diabetic parents and the controls were 0·001, a similar value of 0·00 was obtained among the values of IR among the

studied groups. When we consider the male offspring individually the P value of fasting insulin level, IR among the subgroups is 0·026 which is significant. Study of female offsprings also showed a P value of 0·002 for fasting insulin level, IR among the sub groups. Other studies also have published similar results Migdalis IN et al[11]where high levels of fasting insulin,normal blood glucose levels were seen in the non diabetic offspring's with one NIDDM parent. The Bogalusa heart study showed results that hyperinsulinemia was seen among subjects of age group 4 to 17 years of type 2 diabetic parents[12]. Studies, which were conducted in adult offspring's of parents with type 2 DM also showed increased insulin resistance[13]which also proved the hypothesis in adults. prevalence of insulin resistance among siblings of type 2 DM in this study was 26·67%, according to DyahPurnamasarist al[4] . Similar results of familial clustering was observed in a study conducted by PONTIROLI et al where insulin resistance, and high pro-insulin levels are frequent findings in siblings of type 2 diabetic patients[14]. Studies, which were conducted with OGTT, low dose insulin ,glucose infusion test also showed that pro bands with type 2 DM has increased incidence of IGT, type 2 DM, while NGT had insulin resistance[8]. In this study C peptide was estimated to determine the insulin resistance while in our study, we used insulin assay and the HOMA-IR method. The reason for relatively high insulin levels but normal glucose levels, reduced C peptide levels in the decreased hepatic insulin clearance[15]. Genetic studies also show that alteration in genes such as ADIPOQ, ADIPOR1, and ADIPOR2 may also modify insulin resistance in siblings[5]. Studies on human glycoprotein PC1 gene which is associated with insulin resistance when mutated did not increase the susceptibility to type 2 DM[16]. Thus, genetic analysis in type 2 DM still remains to be a topic where excessive work has to be done. Other studies also show evidence of mitochondrial dysfunction in offsprings of type 2 DM[17]. Over weight siblings of type 2 DM parents have a 4 times increased risk of abnormal glucose tolerance when compared to other obese children[18]. This study is more in view of metabolic syndrome, which starts at an early age. A unique observation which was seen in the study by Baillargeon et at where brothers of women with PCOD were seen to have reduced insulin sensitivity and glucose tolerance which was independent of obesity[3]. Thus, scope of research is not only limited to siblings, but also to siblings, relatives, etc. When we study sub group individually i.e. the male and female offspring it gives us interesting results. In the male offspring the FBS,PPBS values is approximately similar but the fasting insulin level varies. It is observed that in the male offspring who's mother is a diabetic have a significantly higher fasting insulin value of 9·3662 uIU/ml when compared to the male offsprings of diabetic father 8·5267 uIU/ml and controls 4·7400 uIU/ml. But the insulin resistance values in the siblings of diabetic father and mother, which are 1·7609 , 1·7694 respectively do not show much of a difference between them, but there is a significant difference with the control values of 0·8921 this can be explained based on the fact that when IR is calculated using the formula of HOMA-IR it is also affected by the FBS levels. While we study the female offspring individually, we can see a similar pattern among the FBS,PPBS variables, but the change is seen in the Fasting insulin levels. The female offsprings of diabetic fathers had a insulin level of 13·5773 uIU/ml while the siblings of diabetic mother and controls had levels of 6·7292 uIU/ml , 5·9031uIU/ml respectively. This pattern is also seen in the IR where it can be stated that females offsprings of diabetic fathers have a higher level of IR when compared to the siblings of diabetic mother , controls. Similar results were also obtained from the Framingham Offspring Study where it suggests that the offsprings of diabetic fathers have a more rapid course from euglycemic level to abnormal glucose tolerance in a more rapid pace when compared to the siblings of diabetic mother[7]. Other studies show that daughters resembling their parents in relation to metabolic parameters more than sons[19]. The study has few limitations: It would have been more representative if other glycemic parameters like HbA1C, C peptide, Pro insulin levels, OGTT were included as it would have given us more

insights to discuss on. Incorporation of genetic analysis would have been an additional tool. The study design was a cross sectional one, but better would have been a prospective case control study.

CONCLUSION

Thus, in conclusion our study aims at proving the association and transmission of insulin resistance (Statistical significance observed in the FBS, Fasting Insulin level, and Insulin resistance) Even though Current FBS, PPBS values are not indicative of impaired glucose status, the levels of fasting insulin, IR show the trend towards altered glycemic status. The trend is indicative of the pathogenesis of type 2 diabetes mellitus where the insulin resistance has just started and on the path towards altered glycemic balance. Sub group analysis between male, female population shows an equal distribution among both sexes, but we assume that female siblings of diabetic fathers have a rapid disease course because of exponentially high level of IR in them compared to other groups. Thus we propose a significant association between insulin resistance in siblings and the diabetic status of parents. If we are able to tease out this group in an early stage we can offer them interventions to prolong the progression towards full blown diabetes and associated co-morbidities.

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