INSULIN RESISTANCE, BETA CELL FUNCTION AND LIPID PROFILE IN METABOLIC SYNDROME AND TYPE 2 DIABETES MELLITUS

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ABSTRACT

BACKGROUND

Type 2 Diabetes mellitus is the commonest form of diabetes constituting 90% of the diabetic population. The global prevalence of diabetes is estimated to increase from 4% in 1995 to 5.4% by the year 2025. The highest prevalence of diabetes (16.6%) is seen in the city of Hyderabad in south India, as per the survey conducted by the 'National Urban Diabetes Survey' in 2001 by Ramachandran and Sneha Latha[7] et al.

The aim of our present study is to compare insulin resistance, beta cell function and the lipid profile of controls, individuals with metabolic syndrome and diabetic individuals in an urban setting like Hyderabad.

MATERIALS AND METHODS

This study is a descriptive comparative study. We enrolled 54 subjects in our study. Of the 54 subjects 15 are controls, 10 are insulin resistant/ individuals with metabolic syndrome and 29 are newly detected diabetic patients. Individuals with fasting plasma glucose < 110 mg/dL and without the minimum of three features of the metabolic syndrome set by the NCEP (Adult Treatment Panel- III)[1] were selected as controls for the study. The insulin-resistant group was selected on the basis of the guideline set by the NCEP Adult Treatment Panel- III. Subjects with a minimum of three features were enrolled into the study as the insulin resistant group/ metabolic syndrome group. None of them had a fasting plasma glucose concentration of > 110 mg/dL. Hence, we referred to this group as the metabolic syndrome group/ insulin resistant euglycaemic group. Fasting plasma glucose of ≥ 126 mg/dL on 2 occasions was taken as the primary requisite for enrolling subjects into the diabetic group as per the guidelines of ADA. Fasting blood sample of 5 mL was collected by venepuncture into 3 different vacutainers (NaF, EDTA and plain). Fasting plasma glucose was estimated by GOD/POD (glucose oxidase-peroxidase) method. HbA1c is assayed for glycated haemoglobin by low-pressure cation-exchange chromatography in conjunction with gradient dilution. (Courtesy- Yashoda Hospitals, Malakpet). Fasting insulin, triglycerides and HDL-C were measured in the serum. Fasting insulin was assayed by ELISA method (BioTek instruments, Yashoda Hospitals, Malakpet). Triglycerides and HDL-C was assayed by Bayer's kit on RA-50 semi auto analyzer. Reagents were purchased from Siemens and performed at Gandhi Hospital, Secunderabad.

RESULTS

Despite the small group of our present study, our findings correlated very well with the work done by previous researchers with regard to insulin resistance, pancreatic ß-cell function and lipid status in diabetes and the metabolic syndrome. HOMA-R was high in both 'metabolic syndrome' and 'type 2 diabetes mellitus' indicating insulin resistance in both the groups. Metabolic syndrome patients are able to maintain euglycaemia at the cost of hypersecretion by the pancreas. This is evident by the high HOMA-B in the metabolic syndrome group. Dyslipidaemia is a common feature found in metabolic syndrome and type 2 diabetes mellitus.

CONCLUSION

HOMA-R[2] index is a simple, non-invasive useful marker for measuring 'insulin resistance.' Insulin sensitising drugs like Metformin can be used for metabolic syndrome individuals to prevent early onset of the disease and its sequel like retinopathy, nephropathy, neuropathy and cardiovascular disease. HOMA-B gives us an idea about the insulin produced by the beta cells of pancreas.

KEYWORDS

Insulin Resistance, Beta Cell Dysfunction, Lipid Profile, HOMA-R, HOMA-B.

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BACKGROUND

Type 2 Diabetes mellitus is the commonest form of diabetes constituting 90% of the diabetic population. The global prevalence of diabetes is estimated to increase from 4% in 1995 to 5.4% by the year 2025 (King H, Aubert RE et al, 1998).[3]

Epidemiological studies in India in the last decade have highlighted the increasing prevalence of type 2 diabetes in our country, especially in the urban population (12%). This increase in the incidence of diabetes is due to increased longevity and adoption of western lifestyle. The prevalence of type 2 diabetes is high even in the rural population (7.8%), which indicates a genetic basis for type 2 diabetes (Ramachandran, Snehalatha et al, 1999).[4] Prospective and cross-sectional studies at the Diabetes Research Centre, Chennai, indicate that 'insulin resistance' is a forerunner of type 2 diabetes and cardiovascular events (Snehalatha,

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Ramachandran et al, 1998).[5] The highest prevalence of diabetes (16.6%) is seen in the city of Hyderabad in south India, as per the survey conducted by the 'National Urban Diabetes Survey' in 2001. Keeping in view the increasing prevalence of type 2 diabetes and insulin resistance in the urban Indian population, the present study was taken up in Hyderabad.

The aim of the present study is to compare insulin resistance, beta cell function and the lipid profile of controls, individuals with metabolic syndrome and diabetic individuals in an urban setting like Hyderabad.

MATERIALS AND METHODS

This study is a descriptive comparative study. We enrolled 54 subjects in our study. Of the 54 subjects 15 were controls, 10 were insulin resistant and 29 were newly detected diabetic patients. Sample size was taken conveniently.

The Inclusion Criteria for each of these groups is given below-

a. Individuals with fasting plasma glucose < 110 mg/dL and without the minimum of three features of the metabolic syndrome set by the Inclusion criteria were enrolled as the control group.
b. Newly diagnosed type II diabetics, Fasting Plasma Glucose ≥ 126 mg/dL on at least 2 occasions as per the ADA guidelines.
c. Metabolic syndrome group or the insulin resistant group will be selected on the basis of the guidelines set up by the NCEP Adult Treatment panel- III.[1]

Risk Factor	Defining Value
1. Abdominal Obesity	
Men	> 40 inches
Women	> 35 inches
2. Triglycerides	≥ 150 mg/dL
3. HDL-C	
Men	< 40 mg/dL
Women	< 50 mg/dL
4. Blood Pressure	≥ 130/85 mmHg
5. Fasting Plasma Glucose	≥ 110 mg/dL

*Three or more features are required to make the diagnosis of Metabolic syndrome.

Exclusion Criteria

Longstanding diabetics, newly diagnosed type II diabetics who were on medication, chronic hypertensives, congenital hyperlipoproteinaemia heart failure and renal failure patients were excluded from the study.

Fasting blood sample of 5 mL was collected by venepuncture into 3 different vacutainers (NaF, EDTA and plain). Fasting plasma glucose was estimated by GOD/POD (glucose oxidase-peroxidase) method. HbA1c is assayed for glycated haemoglobin by low-pressure cation-exchange chromatography in conjunction with gradient dilution. (Courtesy- Yashoda Hospitals, Malakpet).

Fasting insulin, triglycerides and HDL-C were measured in the serum. Fasting insulin was assayed by ELISA method (BioTek instruments, Yashoda Hospitals, Malakpet). Triglycerides and HDL-C was assayed by Bayer's kit on RA-50 semi auto analyzer. Reagents were purchased from Siemens and performed at Gandhi Hospital, Secunderabad.

Statistical analysis was performed using the SPSS 17 version. Test used is One Way ANOVA with post-hoc test.

RESULTS

Analyte	Group	Mean	Standard Deviation
Insulin	Controls	9.2 µIU/mL	2.6
	Metabolic syndrome	23.0	4.6
	Diabetes mellitus	12.0	7.3
Fasting Plasma Glucose	Controls	87.5 mg/dL	9.3
	Metabolic syndrome	87.5	9.8
	Diabetes mellitus	215.5	103.2
HbA1c	Controls	4.5 %	0.38
	Metabolic syndrome	4.5 %	0.33
	Diabetes mellitus	8.2 %	2.5
HOMA-R	Controls	1.9	0.4
	Metabolic syndrome	5.0	1.3
	Diabetes mellitus	6.3	5.1
HOMA-B	Controls	169%	100.7
	Metabolic syndrome	459%	386.4
	Diabetes mellitus	41%	41
	Group		
HDL-C	Controls	44.4 mg/dL	2.7
	Metabolic syndrome	42.5 mg/dL	4.4
	Diabetes mellitus	40.5 mg/dL	4.2
Tri-glycerides	Controls	154.1 mg/dL	21.6
	Metabolic syndrome	265.9 mg/dL	71.9
	Diabetes mellitus	290.2 mg/dL	222.7

Table 1. The Mean Fasting Insulin, Mean Fasting Plasma Glucose, Mean Glycated Haemoglobin, Mean HOMA-R, Mean HOMA-B, Mean HDL-C and Mean Triglycerides in Controls, Metabolic Syndrome and Type 2 Diabetes Mellitus

Analyte	Groups	P value
Fasting Insulin	Controls vs Metabolic syndrome	< 0.001
	Controls vs diabetes	0.15
	Diabetes vs metabolic syndrome	< 0.001
Fasting Plasma Glucose	Controls vs Metabolic syndrome	0.997
	Controls vs diabetes	< 0.001
	Diabetes vs metabolic syndrome	< 0.001
HbA1c	Controls vs Metabolic syndrome	0.7
	Controls vs diabetes	< 0.001
	Diabetes vs metabolic syndrome	< 0.001
HOMA-R	Controls vs Metabolic syndrome	0.05
	Controls vs diabetes	0.001
	Diabetes vs metabolic syndrome	0.41
HOMA-B	Controls vs Metabolic syndrome	< 0.001
	Controls vs diabetes	0.003
	Diabetes vs metabolic syndrome	< 0.001
HDL-C	Controls vs Metabolic syndrome	0.1
	Controls vs diabetes	0.003
	Diabetes vs metabolic syndrome	0.2
Triglycerides	Controls vs Metabolic syndrome	< 0.001
	Controls vs diabetes	0.01
	Diabetes vs metabolic syndrome	0.4

Table 2. Multiple Comparison of Variants

DISCUSSION

In our study, the mean fasting insulin is 9.2 µIU/mL in controls, 23.0 µIU/mL in the metabolic syndrome group and 12.0 µIU/mL in the diabetic group. The markedly elevated fasting insulin in the insulin resistant group in our study confirms the previous studies by Godsland IF and Stern MO[6] et al that insulin concentration is directly related to the severity of insulin resistance and can be used as a surrogate marker for tissue insulin resistance.

The mean fasting plasma glucose is 87.5 mg/dL in controls, 87.6 mg/dL in the metabolic syndrome group and 215.5 mg/dL in the diabetic group. From these statistics, it is evident that there is not much variation in the fasting plasma glucose concentration in the control and metabolic syndrome groups. Insulin resistant individuals maintain euglycaemic status at the expense of pancreatic oversecretion as indicated by the high insulin values. A state of decompensation indicated by an insignificant elevation in insulin concentration in the diabetic group leads to elevated fasting plasma glucose concentrations of 215.5 mg/dL in the diabetic group.

The mean glycated haemoglobin is 4.5% in controls, 4.6% in the insulin-resistant group and 8.2% in the diabetic group. The mean glycated haemoglobin values confirm the glycaemic status of the 3 subgroups.

In our study, the mean insulin resistance index (HOMA-R) is 1.97 in controls, 5.01 in the metabolic syndrome group and 6.3 in the diabetic group. The above data clearly shows that the control group has the lowest HOMA-R of the three groups and insulin resistance is a common feature to the metabolic syndrome (insulin resistant, euglycaemic) group and the diabetic group. But HOMA-R index is the highest in the diabetic group. This can be explained by the formula we use to calculate the HOMA-R index, (Mathews[2] 1985).

$$\text{HOMA- R: } \frac{\text{Fasting Insulin} \times \text{Fasting Plasma glucose mmol/L}}{22.5}$$

One noteworthy point from the above formula is 'fasting plasma glucose concentration is a reflection of the sensitivity of the hepatic tissue to insulin action.' Greater the insulin sensitivity greater is the inhibition on gluconeogenesis in the fasting state by the lone hypoglycaemic hormone, insulin and a resultant decrease in the fasting plasma glucose. In Metabolic syndrome and Diabetes, there is a variable degree of insulin resistance and a reversal of these pathophysiological mechanisms resulting in elevated fasting plasma glucose. Determining the cut-off point for HOMA-R was based on an article entitled 'Identification of individuals with insulin resistance using routine clinical measurements' by Steven E Stern in the Journal of Diabetes. The article clearly stated that HOMA-R ≥ 3.6 must be considered as insulin resistant. The lowest HOMA-R in our study was 3.8, which reiterates the findings by Steven E Stern.[7]

The mean HOMA-B is 169.3% in controls, 459% in insulin resistant and 46% in diabetes. The pancreatic beta cells secrete adequate amount of insulin in the basal state as indicated by a mean value of 169% in controls, which maintains an euglycaemic status. In the metabolic syndrome group, a compensatory hyperinsulinaemia[8] in the presence of insulin resistance achieves normal or near normal euglycaemic levels. In the diabetic group, a decompensation in the pancreatic beta cell function indicated by the lowest mean HOMA-B of 41%, in the presence of variable degrees of insulin resistance leads to hyperglycaemia. These findings in our study reiterate the role of pancreatic hyposecretion and insulin resistance in the development of Diabetes Mellitus.

$$\text{HOMA- B: } \frac{20 \times \text{Fasting Insulin}}{\text{Fasting Plasma glucose mmol/L-3.5}}$$

Lipid abnormalities are common in type 2 diabetes mellitus and hence HDL-C and triglycerides were measured in all the sub-groups and subjected to statistical analysis. The mean HDL-C concentration is 44.4 mg/dL in controls, 42.5 mg/dL in metabolic syndrome group and 40.5 mg/dL in the diabetic group. On sub-group comparison, the 'p' value is 0.1 between the control and the metabolic syndrome group. This can probably be explained by the presence of 7 young females in a group of 10 in the metabolic syndrome group. Oestrogen which is abundant in women inhibits the activity of hepatic lipase- an enzyme that catalyses the degradation of HDL-C and hence a higher HDL-C in women in the reproductive age group. The p value is 0.2 between the metabolic syndrome group and the diabetic group, which is insignificant, which indicates HDL is comparable in both the groups.

The mean triglyceride concentration is 154.13 mg/dL in controls, 265 mg/dL in insulin resistance and 290 mg/dL in diabetics. The p value with respect to triglycerides between controls and the metabolic syndrome is < 0.01. The p value between the metabolic syndrome group and the diabetic group is > 0.1, which means to say that hypertriglyceridaemia is a common feature to both the conditions. The p value is < 0.01 between controls and diabetics. This is significant. From these data, it is evident that diabetes and insulin resistance are associated with variable dyslipidaemia. This characteristic picture termed diabetic dyslipidaemia characterised by high triglyceride and a low HDL-C concentration has been attributed to inactivation of 'lipoprotein lipase' and activation of hormone sensitive lipase. In insulin resistance, 'lipoprotein lipase' is inactivated resulting in impaired hydrolysis of triglyceride rich lipoproteins and increased degradation.

One noteworthy point in our study is that both metabolic syndrome and type 2 diabetes mellitus are characterised by variable degrees of dyslipidaemia with respect to the control group. But it is too premature to comment on whether insulin resistance precedes dyslipidaemia or dyslipidaemia precedes insulin resistance, as our study is not a prospective study. Two prospective studies by Haffner and Mykkanen[9] demonstrated that hyperinsulinaemia precedes dyslipidaemia. But, Yki-Jarvinen[10] (1988) proposed that subjects with endogenous hypertriglyceridaemia are resistant to the glucoregulatory effects of insulin, i.e. 'dyslipidaemia precedes insulin resistance.'

CONCLUSION

Insulin resistance is a forerunner of Diabetes. And, hence measuring insulin resistance can help us in assessing the tendency to develop Diabetes Mellitus. HOMA-R index is a simple, non-invasive, useful marker for measuring 'insulin resistance.' Insulin sensitising drugs like Metformin can be used for metabolic syndrome individuals to prevent early onset of the disease and its sequelae like retinopathy,

nephropathy, neuropathy and cardiovascular disease. HOMA-B gives us an idea about the insulin produced by the beta cells of pancreas

Our study is a descriptive comparative study. Prospective studies must be carried out to know whether dyslipidaemia causes insulin resistance or insulin resistance causes dyslipidaemia.

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