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Original article

Significance of Microalbuminuria in Metabolic syndrome

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ABSTRACT

Obesity and Metabolic Syndrome are current problems in the society. They lead to Cardio vascular problems and Diabetes. Metabolic Syndrome is a cluster of abnormalities seen in persons with increased waist circumference who were having increased levels of fasting blood glucose, postprandial blood glucose, Microalbuminuria, elevated blood pressure and decreased levels of HDL. In my study, it is observed that Microalbuminunia is significantly associated with other features of Metabolic Syndrome and it is the earliest sign in this condition. So it is like a warning sign to the physician about the problems of the vascular wall. MA at this stage is reversible if the person adopts simple changes in lifestyle like loosing weight by regular exercise and healthy diet habits.So there should be a screening for MA biannually in the obese persons.

1.Introduction:

M.S. is a collection of risk factors that together increase Cardiovascular mortality. In the current WHO description of metabolic syndrome, it is a dysmetabolic state induced by insulin resistance. M.S predisposes to both cardiovascular diseases and Type 2 Diabetes.

1.1. Magnitude of the problem :

Currently available data suggest the prevalence of Metabolic syndrome in the general population in India is about 40%, much higher than of 25% quoted for western population.

Metabolic Syndrome is a dysmetabolic state induced by Isuline resistance. Insulin Resistance is a change in physiologic regulation such that a fixed dose of insulin cause less of an effect on glucose metabolism than it occurs in normal individual. Fasting hyperinsulinemia in the presence of a normal or elevated plasma glucose level implies insulin resistance. Insulin resistance per se produces no symptoms. If the b Cell function is adequate to cope with the insulin resistance, individual could compensate for hyper insulinemia.

2.New criteria for the diagnosis of IRS by Atp III/WHO

1. Central obesity by waist circumference.

Men	>	40 inches
Women	>	35 inches
2. Triglycerides	>	150 mg/dl
3. HDL cholesterol		
Men	<	40 mg/dl
Women	<	50 mg/dl
4. Blood pressure	>	130 / > 86 mm Hg
5. Fasting blood sugar	>	110 mg/dl
6. Post prandial blood sugar	>	140-199 mg/dl

7. Post glucose blood sugar after 2 hrs of 75 gm oral glucose. > 140 – 199 mg/dl.

* ATP – Adult treatment panel III report

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1.3.Indian criteria

1. Waist Circumference

Men	>	35 inches
Women	>	27 inches

2. Triglycerides > 150 mg/dl

3. HDL – Cholesterol

Men	<	35 mg/dl
Women	<	38 mg/dl

4. Blood Pressure – 130 / > 86 mm Hg

5. Fasting glucose – 110 mg/dl

6. Two hours post glucose – 140 – 199 mg/dl

IRS develops with contributions from genes, obesity and environment.

1.4.Environment :

Refers to a variety of factors including hormones (steroid and stress hormones) increased nutrient availability, decreased physical activity and age.

1.5.Thrifty genotype verses Thrifty phenotype

As it was proposed by Neel (1962) to explain the rise in the incidence of Type II Diabetes.

1.5.1.Obesity :

Visceral adipocytes are more metabolically active compared to subcutaneous fat. Visceral fat cells are relatively resistant to the actions of insulin. They also show more sensitivity to lipolytic effects of catecholamines. This deadly combination increases lipolysis, allowing more fatty acids to enter the liver. Increased flux of free fatty acids into the liver increase VLDL particle synthesis and hepatic triglyceride concentration. Free fatty acids cause insulin resistance in human skeletal muscle by interfering with the effect of insulin in increasing Glut-4 medicated glucose transport across plasma membrane. FFA block the effect of insulin on the trans location of (GLUT-4) Glucose transporters from the intracellular storage sites in to the plasma membrane there by decreasing glucose transport into the cell.

Adipose tissue influences insulin action both through release of free fatty acids and also by release of adipose derived proteins, these are known as adipocytokines which include hormones like leptin, resistin, adiponectin and also proinfloammatory peptides like TNF, IL-6 etc which are now known to exert immense effect in insulin action as a whole.

1.5.2.TNF (Tumor Necrosis Factor-a). :

TNF reduces the availability of GLUT-4 in the adipocytes by reducing the expression of GLUT-4 gene.

In addition TNF significantly increases the expression of IL-6, reduces expression of resistin and adiponectin and correlates with increased expression of leptin.

1.5.3.Interleukin-6 :

Circulating IL-6 were significantly higher in obese individuals, that too with greater expression in visceral compared with subcutaneous adipose tissue. There is a 30-70% elevated levels in obese than compared to lean.

Ability of IL-6 to induce insulin resistance may be indirect via modulation of the production and secretions of other adipokines. IL-6 increases the expression of resistin from human peripheral blood mononuclear cells

1.5.4.Leptin :

Expression of leptin is directly related to the lipid content of the cells with greater levels being expressed in the subcutaneous compared with the visceral adipose tissue.

Leptin is a mediator of energy status and metabolism. It interacts with other hormones such as insulin, glucagons, Insulin like growth factor, growth hormone and glucocorticoids, to regulate hepatic insulin action, peripheral glucose utilization, food intake and thermogenesis.

Insulin in vitro and in vivo has been shown to increase systemic and adipocyte leptin release.

1.5.5.Resistin :

In the first study to describe resistin, rodents treated with this molecule developed glucose intolerance and impaired insulin function.

1.5.6.Adiponectin

It is an adipose specific plasma protein, has decreased concentration in obese individuals and patients with NIDDM. Hypoadiponectenemia is postulated to be atherogenic and to decrease insulin action.

Clearly much more information is needed to define the role if any that agents such as these have in the development of human Insulin Resistance.

1.6.Components of IRS

1.6.1.Dyslipidemia :

Individuals with IRS have a characteristic lipid disturbance elevated VLDL triglycerides, decreased plasma HDL Cholesterol. Plasma low density lipo protein are quantitatively within the same range as individuals with no insulin resistance, but qualitatively different in that the LDL particles are smaller and more dence.

Adipose tissue increases the release of and reduction in the uptake of FFA. The net result is the excessive flux of FFA into the liver. Since the assembly and secretion of apoliproteinB is regulated at the post translational stage by the availability to lipids. In synthesis of VLDL particle core much ApoB is incorporated in the production of VIDL and less is degraded.

Excessive VLDL particle in the circulation exchange their triglycerides for cholesterol esters with HDL and LDL particles through the actions of cholesterol ester transfer protein. The resulting triglyceride rich HDL particle is a substrate for hepatic lipase, which reduces it in size and causes the release of some APOA, which is lost through the kidney. The HDL particle clearance is increased. The triglyceride rich LDL particle is hydrolysed by endothelial bound lipoprotein lipase and hepatic lipase generates small dense LDL particles.

1.6.2.Endothelial dysfunction :

It is the first stage of atherosclerosis and result from exposure to cardiovascular risk factors such as IRS and NIDDM. Oxydized LDL is an important component of the atherogenic pathway. Macrophages take up oxidized LDL to from foam cells. Oxydized LDL stimulates monocyte tissue factor expression and inhibits endothelial Nitric oxide synthase (eNOS) thus impairing endothelium dependent vasodilatation.

1.6.3.Inflammatory Markers :

C reactive protein (CRP) is an acute phase protein made in the liver. CRP levels were highly correlated with the magnitude of insulin resistance, as measured by frequently sampled glucose tolerance test, with other components of IRS.

1.6.4.Hypertension :

Hyperinsulinemia is postulated to cause hypertension by various mechanisms.

1.6.5.Sodium and Water retention :

Raised insulin levels cause sodium reabsorption and water retention through a direct effect on the distal renal tubule.

1.7.Anti natriuretic effect :

This anti natriuretic effect of hyperglycemia which is due to the core absorption of sodium ions and glucose in the proximal convoluted tubule and is related to the hypokalaemia induced by hyper insulinemia.

1.8.Sympathetic over activity :

Insulin has been demonstrated to cause proliferation of smooth muscle leading to hypertrophy of vascular smooth muscles and causes hypertension.

1.9.Endothelial effects :

It remains unclear whether blunting of insulin mediated endothelium dependent vasodilatation to insulin resistance contributes to hypertension.

Detailed analysis of the coagulation and fibrinolytic systems in individuals with insulin resistance and or hyperinsulinemia have shown that several factors which influences thrombus development or dissolution altered and appear to be part of the IRS. The factors which have significant correlation with either insulin resistance or hyperinsulinemia are plasminogen activator inhibitor 1 (PAI-1), Von Willibrand factor (VWf), fibrinogen and factor VII.

1.10.Microalbuminuria:

MA is defined as the presence of minute quantities of albumin in the urine not detected by the usual heat coagulation tests.

Normal values : Normal rate of albumin excretion is less than 15 mg/day

Persistent values between 30-300 mg/day in a patient is called MA.

Value above 300 mg/day is called Macroalbuminuria.

Pathogenesis :

Increased transmembrane (glomerular basement membrane) permeability for albumin causing microalbuminuria is due to increased intraglomerular pressure causing transvascular leakage of albumin. Intraglomerular pressure rise is due to increased systolic or diastolic pressure. Intraglomerular hypertension is caused by hyperinsulinemia which increases vascular smooth muscle proliferation, and increased sodium reabsorotion and water retention through direct effect of insulin on the DCT. Other haemodynamic effects cause change in the size of the pore, increased filtration fraction, hyperperfusion, increased GFR.

Increased transmembrane permeability is also due to increase in the pore size and decrease in the number of negative charges in the membrane because of the thickening of membrane. Thickening is due to increased exyracellular matrix due to increased production or glycation of matrix proteins. Increased prduction is due increased sensitivity of mesangial cells to Insulin like growth factor due to hyperglycemia. As the membrane thickens there is increase in the pore size due to loss of attachment to the podocytes due to widening of membrane. Decrease in the number of negative charges is due to reduction in the quantity of Heparan sulfate proteoglycan caused by diluting of the available proteoglycan by excessive matrix material or reduced production by the epithelial cells is unclear. MA is the earliest change and it is reversible if the causative factors are controlled.

1.11.Managements of MS :

IRS is a prediabetic and prevascular disease. It is a silent disorder. This problem starts 20 years before the actual clinical picture. By creating increased awareness about IRS the person can be saved from the macro and microvascular disease in future.

In the early stages, IRS is a reversible condition, if we decrease the incidence of obesity we can prevent the problem.

1.11.1.Life style changes aimed towards:

Emphasize the importance of avoiding further weight gain.Reduce the intake and increase the physical activity in regular fashion. Aim for slow weight reduction.

1.11.2.Dietary Changes:

Reduction in total caloric consumption, reduction in total fat to <30% calories, saturated fat <10% , avoiding transfatty acids, preference to monounsaturated and poly unsaturated fats. Increasing intake of cereal fibre and low glycemic index foods.

1.12.Physical activity :

At least 30-45 minutes per day of physical activity.

1.13.Other changes : Yoga,

Cessation of smking. Achieving and maintaining ideal body weight. Statins for the correction of dyslipidemia. Sreening for Microalbuminuria at the intervals of 6 months. Use of drugs like metformin and glitazones to improve insulin sensitivity.

2.Objectives of the study:

Microalbuminuria is a marker of earliest renal changes which is related to vessel changes. Presence of Microalbuminuria is a kidney's notice to the physician about the problems of vascular wall, so that safety measures can be taken early, to prevent the dreadened complications in future.

The objectives of the present study is to see the association of Microalbuminuria with other associated risk factors of IRS.

3.Materials And Methods:

3.1.Study design :

This is a prospective study with randomly selected sample.

3.1.2.Inclusion Criteria for selection :

In the age group of 20 to 40 years.

3.1.3.Exclusion Criteria :

1. Urine sample negative by heat coagulation test (Macroalbuminuria)
2. Blood urea and creatinine in the normal range.
3. Urinary tract infection ruled out by urine analysis.
4. Rule out congestive cardiac failure.
5. Rule out Diabetic ketoacidosis.
6. Rule out pregnancy
7. Rule out other kidney diseases.
8. Exclude persons with Bp>160/106 mm/Hg.
9. Avoiding strenuous exercise
10. Rule out fever.
11. Rule out severe uncontrolled Hypertension.

3.2.Methods:

Waist Circumference :

3.2.1.Measuring technique :

Place measuring tape, holding it parallel to the floor around the abdomen at the level of iliac crest. Hold tape but do not compress the skin. Measure circumference at the end of normal expiration. To diagnose IRS, the circumference should be,

Male > 35 icches

Female > 27 inches.

3.2.2.Measurement of Microalbuminuria :

Establishing the diagnosis of MA requires the demonstration of a persistent elevation in albumin excretion. Transient microalbuminuria is caused by fever, exercise, heart failure, urinary tract infection etc.

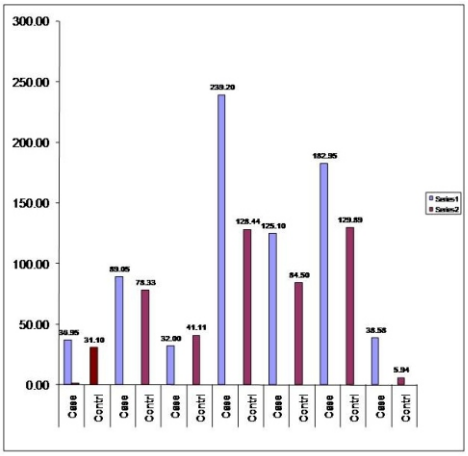
One problem with measuring the albumin concentration is that false negative and false positive results can occur since albumin concentration is also influenced by the urine volume.

This can be avoided entirely by the calculation of albumin to creatinine ratio in an untimed urine specimine. A value above 30 mg per day or 0.03 mg/mg suggests that albumin execretion is above 30 mg/day.

A random sample albumin-creatinine ratio had a sensitivity of 100% for the detection of MA. It gives a quantitative results that correlate with the 24 hours urine values. With standard units comparable values are 2.25 to 3.4mg of albumin/mmol of creatinine.

National kidney foundation recommended spot morning urine measurement of albumin to creatinine ratio (ACR) as the standard test for measuring proteinuria.

Comparision of control and cases in Males with various parameters BP, HDL, TG, FBS, PPBS, ACR.



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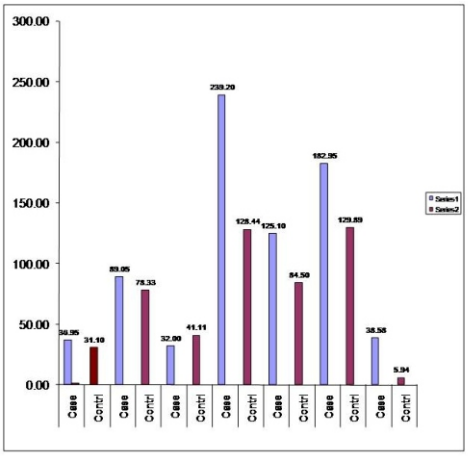
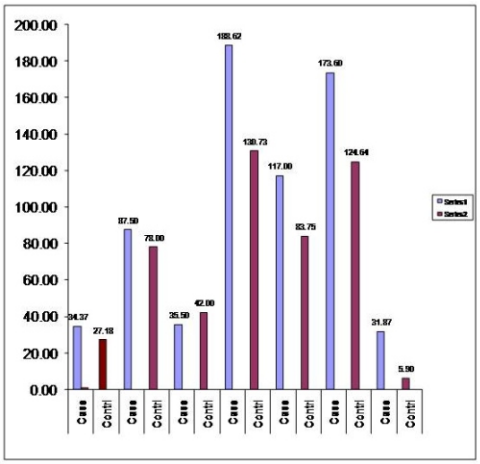


Comparision of control and cases in females with various parameters BP, HDL, TG, FBS, PPBS, ACR.



4.Discussion and Conclusion

In the present study individuals in the age of 20 to 40 years, who were diagnosed to have IRS were taken. Control groups were age and sex matched normal individuals. The parameters studied were wiast circumference, ACR, FBS, PPBS, HDL, TG, BP. Because the causative factor is Insulin Resistance caused by Obesity. Waist circumference is compared with other parameters. And comparison was done will all parameter + waist circumference and MA, there is a significant association of obesity with other factors MA is also significantly associated with other parameters.

MA is the earliest clinical change is Nephropathy. The basic mechanism for the excretion of MA, is that both systolic and Diastolic hypertension causes both systemic and intraglomerular pressure causing transvascular leakage of albumin. Heamodynamic effects cause change in the size of the pore, increased filtration fraction, hyper perfusion, increased GFR, causing albumin leakage. So it is reversible if the above factors are controlled.

From this we can conclude that MA which is an earliest renal change detected clinically, is associated with other risk factors for cardiovascular diseases.

MA is a cardinal sign and a warning to the physian about the problems of vascular wall. It is a reversible condition so that the person by adopting control measures to reverse MA like loosing weight by increased physical activity and diet changes can be safeguarded from the dreadened complications of cardiovascular and renal diseases in future life.

So all the persons have to be screened for MA biannually.

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