International Journal of Biomedical Research

ISSN: 0976-9633 (Online)
Journal DOI:10.7439/ijbr
CODEN:IJBRFA

Research Article

Obesity and metabolic syndrome

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Abstract

Prevalence of Metabolic syndrome in the general population in India is about 40%, much higher than of 25% quoted for western population. Obesity leading to Metabolic Syndrome is the soil for Diabetes and Cardio vascular diseases like PVD, strokes, MI. If we control the incidence of Obesity, we can prevent the future cardiovascular problems. In my study it is found that persons with increased abdominal obesity, levels of FBS, PPBS, MA, BP, Triglycerides, and decreased levels of HDL. These values were normal in persons without abdominal obesity. So person can escape from the future complications if he controls obesity by adopting simple change in life style to loose weight like regular physical exercise and healthy diet habits.

Keywords: Micro albuminuria (MA), Albumin creatinine ratio, Metabolic syndrome (MS), abdominal obesity, Insulin Resistance Syndrome (IRS), Leptin, Adiponectin, Peripheral vascular diseases, Cerebrovascular accidents

1. Introduction

Metabolic Sydrome (M.S) is a collection of risk factors that together increase the cardiovascular mortality. In the current WHO description of metabolic syndrome, it is a dysmetabolic state induced by insulin resistance. IRS 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.[1,2,3]

1.2. New criteria for the diagnosis of IRS – By
1.2.1 Adult Treatment Panel III (ATP) / WHO
1. Central obesity by waist circumference.
   Men > 40 inches
   Women > 35 inches
2. Triglycerides ≥ 50 mg/dl
3. HDL cholesterol
   Men < 40 mg/dl

Women < 50 mg/dl
4. Blood pressure > 130 / 86 mm of 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.

1.2.2 Indian criteria[4,5]

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 of Hg
5. Fasting glucose – > 110 mg/dl
6. Two hours post glucose – >140 – 199 mg/dl

Metabolic Syndrome is a dysmetabolic state induced by Insulin resistance. Insulin Resistance is a change in physiologic regulation such that a fixed dose of insulin causes less of an effect on glucose metabolism than it occurs in normal individuals. Fasting hyper insulinemia in the presence of a normal or elevated plasma glucose level implies insulin resistance. Insulin resistance per se produces no symptoms. If the β Cell function is adequate to cope up with the insulin resistance, individual can compensate for hyperinsulinemia.[6,7]

1.3 IRS develops with contributions from genes, obesity and environment.[8]

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

1.3.2 Thrifty genotype verses thrifty phenotype: Neel (1962) proposed the above to explain the rise in the incidence of Type II Diabetes.[9,10,11]

1.3.3 Obesity: Visceral adipocytes are more metabolically active compared to subcutaneous fat. Visceral fat cells are relatively resistant to the actions of insulin.[11,12] 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 increases 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 translocation of (GLUT-4) Glucose transporters from the intracellular storage sites in to the plasma membrane, thus decreasing glucose transport into the cell.[13]

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.

1.4 TNF (Tumor Necrosis Factor- α): 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 Interleukin-6: Circulating IL-6 levels 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.

1.6 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.[14]

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.

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

1.8 Adiponectin: It is an adipose specific plasma protein, has decreased concentrations in obese individuals and patients with NIDDM. Hypoadiponectenemia is postulated to be atherogenic and to decrease insulin action.[15]

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.

2. Components of IRS

2.1 Dyslipidemia: Individuals with IRS have a characteristic patron of lipid disturbances like elevated VLDL, triglycerides, decreased plasma HDL. Plasma LDL are quantitatively within the same range as individuals with no insulin resistance, but qualitatively different in that the LDL particles are smaller and more dense.

Adipose tissue increases the release of and reduction in the uptake of FFA. The net result is the exces sive flux of FFA into the liver. Since the assembly and secretion of apoliprotein B 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 VLDL 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.[16,17]

2.2 Endothelial dysfunction: It is the first stage of atherosclerosis and result from exposure to cardiovascular risk factors such as IRS and NIDDM. Oxidized LDL is an important component of the atherogenic pathway. Macrophages take up oxidized LDL to from foam cells. Oxidized LDL stimulates monocyte tissue factor expression and inhibits endothelial Nitric oxide synthase (eNOS) thus impairing endothelium dependent vasodilatation.[18]

2.3 Hypertension: Hyperinsulinemia is postulated to cause hypertension by various mechanisms.[20,21,22]

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

2.3.2 Anti natriuretic effect: Antinatriuretic effect of hyperglycemia 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.

2.3.3 Sympathetic over activity: Insulin has been demonstrated to cause proliferation of smooth muscle leading to hypertrophy of vascular smooth muscles and causes hypertension.

2.3.4 Endothelial effects: It remains unclear whether blunting of insulin mediated endothelium dependent vaso dilatation to insulin resistance contributes to hypertension.

2.3.5 Pro coagulant state: 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.[23]

2.4 Microalbuminuria – MA: MA is defined as the presence of minute quantities of albumin in the urine not detected by the usual heat coagulation tests.[24,25,26]

2.4.1 Normal values:

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

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

Value above 300 mg/day is called Macroalbuminuria.

2.4.2 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 haemo dynamic effects cause change in the size of the pore, increased filtration fraction, hyper perfusion, 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 extracellular matrix due to increased production or glycation of matrix proteins. Increased production 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.

2.5 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.

3. Objectives

Obesity leads to Metabolic Syndrome. M.S. is a cluster of abnormalities of increased FBS, PPBS, Triglycerides, MA, BP and decreased HDL level.

The above values are compared in persons who are not obese and who were obese, to reinforce that if obesity is controlled, future complications can be avoided.

4. Materials and Methods

4.1 Study Design: This is a prospective study with randomly selected sample.

4.2 Inclusion Criteria For Selection: Persons were selected in the age group of 20 to 40 years. 60 cases with abdominal without obesity as controls and another 60 persons with obesity as per the criteria given below

4.3 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 of Hg.
9. Avoiding strenuous exercise
10. Rule out fever.
11. Rule out severe uncontrolled hypertension.

4.4 Methods

4.4.1 Waist circumference

a) Measuring technique[27,28]: 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 the circumference at the end of normal expiration. To diagnose IRS, the circumference should be,

Male > 35 inches
Female > 27 inches.

b) Measurement of Micro albuminuria: 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 specimen. A value above 30 mg per day or 0.03 mg/mg suggests that albumin excretion 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 result that correlate with the 24 hours urine values. With standard units comparable values are 2.25 to 3.4mg of albumin/mm mol of creatinine.

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

Fig 1 Comparison of control and cases in males with various parameters- BP, HDL, TG, FBS, PPBS AND ACR.

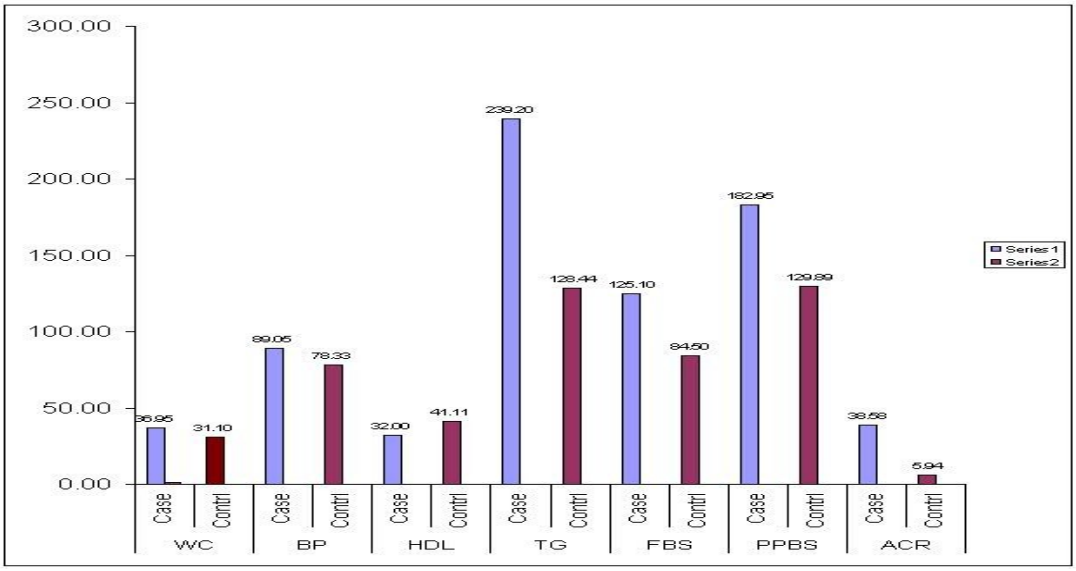
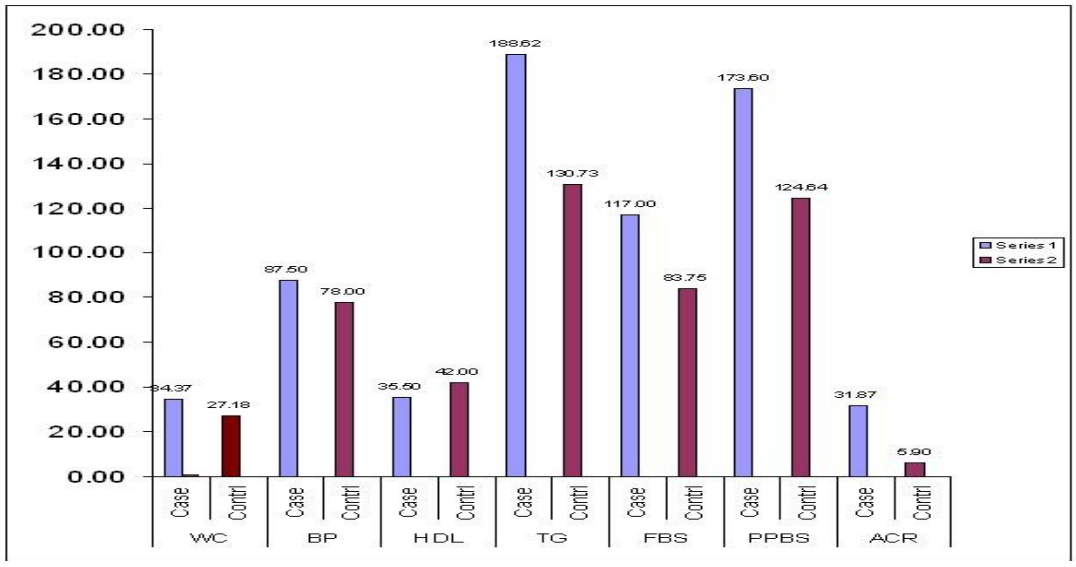


Fig 2 Comparison of controls and cases in females, with various parameters BP, HDL, TG, FBS, PPBS, ACR.



5. Discussion and conclusion

In my study it is observed that persons whose waist circumference is more than normal were having increased levels of FBS, PPBS, Triglycerides, MA, decreased HDL and Hypertension this named as Metabolic Syndrome

The above values were not significant in persons whose waist circumference is in normal limits.

Metabolic Syndrome is a metabolic stage leading to major cardiovascular diseases like PVD, ischaemic strokes and cardiovascular accidents etc.,

A person can be safeguarded from the above complications if he can reduce abdominal circumference by healthy diet and regular exercise.

5.1 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 stage if we decrease the incidence of obesity we can prevent the problem.

5.2 Life style changes aimed towards:

Emphasize the importance of avoiding further weight gain.

Reduce the intake and increase the physical activity in regular fashion[29,30,31].

Aim for slow weight reduction.

5.3 Dietary changes: Total caloric consumption should be reduced. Adjust total fat to <30% of calories, saturated fat to <10%, avoiding transfatty acids, preference to monounsaturated and poly unsaturated fats. Increasing intake of cereal fiber and food with low glycemic index

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

5.5 Other changes:

Yoga

Cessation of smoking

Achieving and maintaining ideal body weight.

Statins should be used for the correction of dyslipidemia.

Screening for Micro albuminuria should be at the intervals of 6 months.

Drugs like metformin and glitazones should be used to improve insulin sensitivity.

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