INTRODUCTION
Insulin resistance means different things to different people. Insulin resistance is considered as a molecular and genetic mystery involving defective insulin signalling and glucose transport into cells. Insulin resistance represents a major underlying abnormality driving cardiovascular disease, the major cause of morbidity and mortality globally. Previously physicians often treated co-existing diabetes, hypertension or dyslipidemia as separate diseases without considering the impact of treatment for one on the other. Gerald Reaven drew attention to a constellation of features associated with coronary heart disease. 1

INSULIN RESISTANCE: [IR]
IR is a condition of low insulin sensitivity. Insulin sensitivity is the ability of insulin to lower the circulating glucose concentrations by stimulating peripheral glucose utilisation at the level of muscle and fat and also by suppressing glucose production from the liver.

Insulin resistance can occur because of defects in insulin action at prereceptor, receptor, or postreceptor level. Besides rare cases of abnormal insulins or presence of receptor antibodies [prereceptor defects], reduction in the insulin receptor number is a relatively common factor contributing to insulin resistance.

Definition of IR
Currently, insulin resistance is defined clinically as the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual as such as it does in a normal population.2

Components of metabolic syndrome:
Resistance to insulin–stimulated glucose uptake
Glucose intolerance
Hyperinsulinemia
Increased VLDL triglyceride
Decreased HDL cholesterol
Hypertension
Central obesity
Microalbuminuria
High plasminogen activator inhibitor – 1
Hyperleptinemia
Hyperuricemia

Contribution of insulin resistance to the various components of the insulin resistance syndrome and to cardiovascular disease will be discussed in this article.

Inherited and Acquired Influences for IR
There are depicted in Fig. 1

IR Syndrome
The cluster of abnormalities found in insulin resistance syndrome and the impact of all the risk factors associated with this syndrome are depicted in Fig. 2.

Clinical Manifestations of IR Syndrome with the following
Central obesity
Acanthosis nigricans
Glucose intolerance
Hypertension
Atherosclerosis
Polycystic ovary syndrome

**Clinical Identification of The Metabolic Syndrome**
See Table 1: for NCEP – ATP III definition

**IR and Dyslipidemia**
See Fig. 3 for mechanisms relating insulin resistance to dyslipidemia.

A simplified model relating insulin resistance to dyslipidemia and cardiovascular disease. Insulin resistance at the adipocyte results in increased release of fatty acids into the circulation. A similar accumulation of fatty acids could arise from defects in fatty acid transporters or intracellular binding proteins. Increased FFA flux to the liver stimulates the assembly and secretion of VLDL resulting in hypertriglyceridemia. In addition, VLDL stimulates the exchange of cholesterol esters from both HDL and LDL for VLDL TG. Apo A-1 can dissociate from TG enriched HDL. This free apoA-1 is cleared rapidly from plasma, in part by excretion through the kidney, thus reducing the availability of HDL for reverse cholesterol transport. TG- enriched LDL can undergo lipolysis and become smaller and more dense. Low levels of HDL and the presence of small dense LDL are each independent risk factors for cardiovascular disease. IR – Insulin Resistance; CE – Cholesteryl Ester, SD –Small dense.

**IR & Development of Diabetes**
Genes and the environment play a role in the development of type 2 diabetes (Fig. 4). The early prediabetic phase begins in young adulthood and can be identified as insulin resistance in peripheral tissues. Initially, insulin levels are elevated in response to the resistance, but as glucose desensitisation develops, insulin secretion decreases. This eventually leads to clinical non-insulin–dependent diabetes. Both the insulin resistance and the decreased insulin secretion are genetically programmed. This program is modified by a variety of environmental factors, especially diet and activity.

Overt diabetes will develop when insulin cannot be increased to overcome insulin resistance. In comparison with thin patients, many obese patients without diabetes produce 5 to 8 times more insulin 500 U/day to overcome insulin resistance.

**IR and Obesity**
Some controversies exists not only on the association of obesity with CV disease but whether or not obesity should be included as a feature of the metabolic syndrome. Regional adiposity is closely associated with morbidity and mortality than general obesity.

Several large studies provide convincing evidence of the link between obesity per se and coronary heart disease. More recently, in the analysis of the Nurses’ study, a body mass index of 25
– 28.9 was associated with a twofold increase in CV disease; the risk rose to almost fourfold once the BMI exceeded 29. It is important to note, however, that the association with CV disease is not direct: there is a strong etiologic association between obesity and other CV risk factors. Strong evidence now links obesity with left ventricular hypertrophy, hypertension, alterations in hemostatic factors, and alteration in lipid profiles. Visceral adiposity plays a greater role in the development of diabetes, IGT, and atherosclerosis than generalized obesity.

**IR without Obesity**
An association between IR and hypertension is also seen in non-obese hypertensives [Reaven et al] These persons have been referred to as “Metabolically obese normal weight” individuals [Ruderman et al].

**Table 1 : Clinical diagnosis of metabolic syndrome**

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>DEFINING LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Abdominal obesity</td>
<td>[Waist circumference ]</td>
</tr>
<tr>
<td>Men</td>
<td>&gt; 102 cm [ &gt;40 in ]</td>
</tr>
<tr>
<td>Women</td>
<td>&gt; 88 cm [ &gt;35 in ]</td>
</tr>
<tr>
<td>2. Triglycerides</td>
<td>≥ 150 mg /dl</td>
</tr>
<tr>
<td>3. HDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt; 40 mg/dl</td>
</tr>
<tr>
<td>Women</td>
<td>&lt; 50 mg/dl</td>
</tr>
<tr>
<td>4. Blood pressure</td>
<td>≥ 130 / ≥ 85 mmHg</td>
</tr>
<tr>
<td>5. Fasting blood glucose</td>
<td>&gt; 110 mg/dl</td>
</tr>
</tbody>
</table>

• National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III) Guidelines
Clinical diagnosis is made when 3 of the 5 criteria stated above are met.

**IR and Hypertension**
Although several large epidemiologic studies have supported an association between insulin and hypertension, interethnic differences and contradictory in vitro and in vivo data have cast doubt over its validity. Experimentally, several theories have been proposed. Using euglycemic hyperinsulinemic clamps in young healthy subjects, DeFranzo and colleagues have demonstrated a decline in sodium excretion rate within 30 minutes and a nadir approx 50% lower than the basal excretion rate. Both proximal and distal tubules appear to be affected both directly by insulin and indirectly by activation of the sympathetic nervous system and augmentation of the angiotensin–induced aldosterone secretion. Activation and involvement of the sympathetic nervous system and its association with the syndrome are, in fact, far reaching. Such activation is closely linked to changes in plasma insulin concentration, and clamp studies have shown a link with increased noradrenaline levels and increases in blood pressure and pulse.

Critics of the association cite evidence suggesting that this effect is only acute. Certainly, insulin has a direct vasodilatory effect when given either systematically or locally, with no elevation in blood pressure despite the demonstration of elevated noradrenaline levels in clamp studies. Furthermore, therapeutic use of exogenous insulin, clinical diagnosis of insulinoma, or the presence of an insulin-resistant disease process such as the polycystic ovary syndrome or one of the rarer insulin resistance syndromes are all free of such a close association with hypertension.

![Fig. 3: Mechanisms Relating IR to Dyslipidemia](image)

**CE** = Cholesterol ester; **CETP** = Cholesterol ester transfer protein;

**SD LDL** = Small, dense LDL

Fig. 3: Mechanisms Relating IR to Dyslipidemia
Adipokines and the Metabolic Syndrome

Adipose tissue is now recognized as an endocrine organ. Leptin, PAI-1, Tumour necrosis factor-α \([\text{TNF}-\alpha]\) are the products from adipose tissue which provide further links with IR syndrome.

Leptin & IR

Leptin is the product of \(\text{OB}\) gene. It is produced by mature adipocytes and is secreted in the plasma. Plasma levels are strongly correlated with adipose mass. Leptin inhibits food intake, reduces body weight and stimulates energy expenditure. Leptin binds to the receptor in the hypothalamus, thus stimulating the release GLP-1 and decreasing the production of neuropeptide \(\gamma\), a stimulator of food intake (Fig. 5). Recent studies have shown that leptin inhibits insulin secretion and has antiinsulin effects on liver and adipose tissue. Serum leptin is increased in insulin resistance offspring of type 2 diabetic patients.

Plasminogen Activator Inhibitor – 1 \([\text{PAI-1}]\) & IR

Association of PAI-1 with components of the metabolic syndrome, in particular triglyceride and body mass index \([12,13]\) and insulin are now well established through epidemiologic, experimental, and interventional studies. \([13\text{-}17]\) This association exists not only with insulin and other features of the metabolic syndrome; several large-scale prospective studies have shown a more direct link between PAI-1 and future CHD both in apparently healthy individuals and in patients with known CHD. \([18]\) Human adipose tissue produces PAI-1 and that modulations in weight are matched by modulations in PAI-1 antigen levels. Visceral fat is an important site for PAI-1 production.

Tumour Necrosis Factor \(\alpha\) \([\text{TNF}-\alpha]\)

This protein forms part of cytokine family and is produced by number of cells. It has a variety of effects including IR, growth promotion, angiogenesis and growth inhibition, \([19]\) increases in TNF \(\alpha\) levels associated with obesity. Its production by adipose tissue and the insulin resistance stimulated interest in this molecule as a potential therapeutic target. The exact mechanism by which it induces IR is not known. Probably plays a part in adipose tissue distribution and thermogenesis with alterations in the lipolytic pathway.

IR and Clotting

Increased fibrinogen levels – cause is not clear, probably obesity plays a role, factor VII increase with PP hyperlipidemia. Factor X is also increased. Increased PAI-1 production is a marker for risk for premature CAD.

IR and Microalbuminuria

Microalbuminuria is not only a predictor of diabetic kidney disease but also a recognized independent CV risk factor. Has microalbuminuria a direct pathophysiological link to IR? Is it related to the syndrome by sheer associations? Largely unknown. Endothelial dysfunction occurs in IRS. Abnormal endothelial permeability is also present in the glomerulus which is in reality an arteriole, leading to microalbuminuria and proteinuria. The level of proteinuria has been shown to be inversely proportional to the insulin sensitivity.

Microalbuminuria and IR – Type 1 Diabetes

Two recent studies have shown the association between microalbuminuria and insulin resistance. The nondiabetic first degree relatives of diabetic patients with microalbuminuria were found to have a more atherogenic lipid profile and higher fasting insulin levels than relatives of normoalbuminuric diabetic patients. Recent study from Italy: Parents of diabetic patients with nephropathy were shown to be more insulin resistant than parents of those without renal disease. Insulin resistance and / or its accompanying metabolic / hemodynamic disturbances may be a risk factor for microalbuminuria.

Microalbuminuria and IR – Type 2 Diabetes

Recent studies indicated that Type 2 diabetic patients with hypertension and / or microalbuminuria were more insulin resistant than those with normal BP and albumin excretion rate. The insulin resistant microalbuminuric patients had more coronary events over a 6-yr follow up period compared to normoalbuminuric diabetics.

FINNISH REPORT: Baseline microalbuminuria predicted the development of type 2 diabetes independent of BP. These findings suggest that microalbuminuria and insulin resistance / hyperinsulinemia are closely intertwined.
Mortality from CHD is common to all main groups of migrants in other groups settled in the same countries. In England, high mortality from CHD is higher in South Asians overseas than in other groups settled in the same countries. This is consistent with association of CHD with glucose intolerance, elevated insulin and increased TGL in South Asians as per cross sectional and case control studies.

IR and Polycystic Ovary Syndrome (See Fig. 6)

**CLINICAL AND THERAPEUTIC IMPLICATIONS**

The concept of the metabolic syndrome has been useful in clinical practice for the treatment and prevention of CV disease. First, patients with any one of the components of the syndrome are at risk of having the other conditions, for which they should be screened. Second reduction in CV risk in such a patient will require treatment of all risk factors, and it is important to recognize that treatment of one may sometimes lead to detrimental changes in another. For example, some antihypertensive agents may have deleterious effects on glucose and lipid metabolism. Third, obesity aggravates the syndrome, and therefore adiposity, in particular visceral adiposity, should be included in patient assessment. Several different techniques, including methods of measuring height, weight, skinfold thickness, and waist circumference, have been employed in epidemiologic studies to assess obesity. Body mass index [weight [kg]/ height [m^2]] is currently the most frequently used parameter to assess and classify obesity. Abdominal adiposity, however, provides better prognostic information. Several studies have used the relationship between skinfold thickness and waist – hip ratio to assess abdominal obesity. Waist circumference alone provides a good measurement of visceral fat and that metabolic complications may first be observed with circumferences of >100 cm.

Two important studies have shown not only the clustering of CV risk factors in the young, but also a direct correlation of these risk factors with the extent of underlying atherosclerotic lesions. Thus it has been argued that intervention should begin in childhood. The benefits of alterations in lifestyle, such as cessation of smoking, physical exercise, and attention to weight, however, are important interventions in both the young and adult populations. Weight loss is associated with marked improvement in metabolic and physiologic profiles. The main obstacle is achieving and sustaining this weight loss, with pharmacologic intervention being required in most patients. Insulin sensitizers are the drugs of choice for PCOS apart from therapeutic lifestyle changes.

**PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-γ AGONISTS AND IR**

Rosiglitazone and pioglitazone are the two available thiazolidinediones [ glitazones ]. Glitazones are the first group of agents targeted to activate PPARγ. Many nonglitazone PPARγ agonists and agents that activate both PPARα and PPARγ are currently under development. PPARγ agonists reduce insulin resistance in the periphery [i.e. they sensitize fat and muscle to the actions of insulin]. Whether the effects on muscle are primary or are secondary to reductions of free fatty acids is unknown. Effects of PPARγ agonists on cardiovascular risk factors are listed in fig.6 Insulin must be present for these agents to work. Although...
concentrations of triglycerides and HDL-C often improve with these agents, LDL-cholesterol may actually increase, at least in the short term.

**Effects of PPARγ Agents on CV Risk Factors**
These are shown in Fig. 7.

**Metformin**
Metformin, another antidiabetic drug, has also been shown to decrease hepatic glucose production and to reduce plasma insulin levels.22. Intervention studies in the case of metformin have also shown that it can lead to a reduction in PAI-1 levels.22

**Newer Classes of Drugs**
Trials with newer classes of drugs in the form of pancreatic lipase inhibitors [orlistat] and centrally acting serotonin and noradrenaline reuptake inhibitors [sibutramine] have shown that both products produce modest [5-10%] weight loss.

**SUMMARY**
The concept of IR is now firmly established. It has important pathologic and therapeutic implications. It probably represents pathologic state secondary to a complex mixture of insulin resistance and hyperinsulinemia. Clinically, IR provides an important concept for screening and aggressively treating patients for multiple CV risk factors with an increasing battery of drugs, some of which now allow the treatment of insulin resistance itself.

**REFERENCES**