

EFFECTS OF INSULIN RESISTANCE IN THE PATHOGENESIS OF HYPERTENSION

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SUMMARY : *It has been considered lately that, resistance to insulin stimulated glucose uptake and hyperinsulinemia causes hypertension, dislipidemia and atherosclerosis. Tissue insulin resistance frequently occurs in obesity, Type 2 Diabetes Mellitus (NIDDM) or impaired oral glucose tolerance test (OGTT), although, it may also be determined in non-diabetic, non-obese cases. Some techniques have been used in investigating the insulin resistance. A syndrome, Syndrome X, includes insulin resistance, hyperinsulinemia, high plasma triglyceride (TG) and low HDL. Tissue insulin sensitivity can be affected and be partially prevented by diet, medications and exercise. To prevent reduction of insulin sensitivity serves the purpose of preventing development of hypertension, dislipidemia and coronary artery disease (CAD).*

Key Words : *Hypertension, Insulin Resistance, Hyperinsulinemia.*

Arterial blood pressure is a result of cardiac output (CO) and systemic vascular resistance (SVR) (36). Elevated arterial blood pressure is a major risk factor for coronary, cerebral and renal arterial diseases. The risk for cardiovascular disease begins to increase when systolic blood pressure exceeds 140 and diastolic blood pressure 90 mm Hg (36). In hypertensive cases, first result to increased cardiac after-load is hypertrophy of myocardium. Although it is a compensatory mechanism, after a certain period it may end in cardiac disfunctions. In a hypertrophic heart, first, the myocardial mass increases together with the ejection fraction (EF) and fractional shortening (FS) augmentation and a adnormal period beigns (19). Then, we may see a disorder in the coordination of isovolumic relaxation in the left ventricular diastolic phase. Systolic dysfunction may be followed and

congestive heart failure (CHF) may occur (75).

Hypertension is a major risk factor for myocardial ischemia and infarction. Even in hypertensive patients with no obstructive coronary heart diseases, we may determine reduced coronary blood flow and thallium perfusion defects caused by diminished perfusion caused by left ventricular hypertrophy (31). In the Framingham Heart Study, it has been determined that, hypertensives are predisposed to silent infarctions, silent ischemias and sudden deaths (34). But, lowering blood pressure may be insufficient to prevent the atherosclerotic process (36). Antihypertensives, such as thiazide diuretics and β -blockers, even increase the prevalence of atherosclerosis (15). These determinations direct investigators to a better knowledge of relationship of hypertension and atherosclerosis.

Most of the hypertensive cases are in the category of primary (essential) hypertensives. In this group, cause of hypertension is not unique, but a lot of factors which increase CO and SVR have been determined (36) (Fig 1). During the last 20 years, in researches about the pathogenesis of hypertension, insulin have been mentioned frequently as one of the factors (Fig 2).

In the pancreatic β cells insulin is produced as the primary biosynthetic product, pre-pro insulin. This peptide is rapidly converted by proteolytic cleavage into insulin and C-peptide. Final product of β -cell is 95 % insulin and C-peptide and 5 % nonconverted insulin. The release mechanism of

insulin is being influenced by glucose, aminoacids, intestinal insulinogenic hormones, glucagon, neural effects and other factors, however, the most important factor is glucose. Insulin, which has a brief circulation time ($t_{1/2}=4-8$ min), reaches in a short time the target tissue's cell surface insulin receptors (63). The human insulin receptor is encoded by a gene located on chromosome 19 (73). (Fig 3). Exercise, diet, hormones (growth hormone and glucocorticoids) can change the number of receptors (61). The dose-dependent ability of insulin to reduce the number of receptors by accelerating the receptor degradation is called down-regulation.

Insulin is a hormone which has a major role in the systemic regulation of carbohydrate, protein and lipid metabolism, which can be summarized as follows:

a) Effects on carbohydrate metabolism are providing glucose uptake, storage and utilization in all tissues. This effect is most important in hepatic, adipose and muscular tissues.

b) Insulin has also an important function in lipid metabolism. After the glycogen concentration reaches 5 to 6 percent, this per/se inhibits glycogen synthesis. Insulin increases the utilization of glucose by most of the tissues, a process which automatically decreases the utilization of fat. Insulin thus functions as a "fat sparer". Insulin does also promotes fatty acid synthesis. Almost all of this synthesis occur in the liver cells. Most of the fatty acids then are converted into triglycerides, the usual

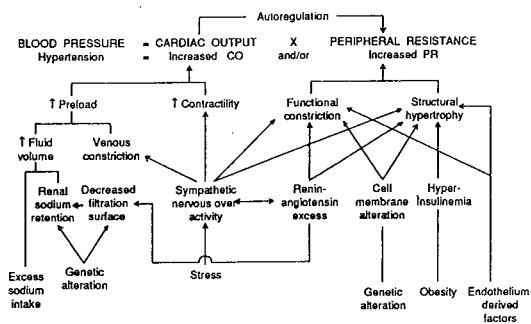


Fig - 1 : Some of the factors involved in the control of blood pressure.

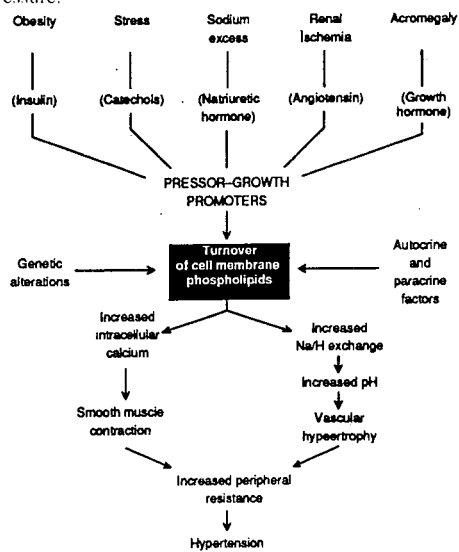


Fig - 2 : Scheme for the induction of hypertension by numerous pressor hormones that act as vascular growth promoters.

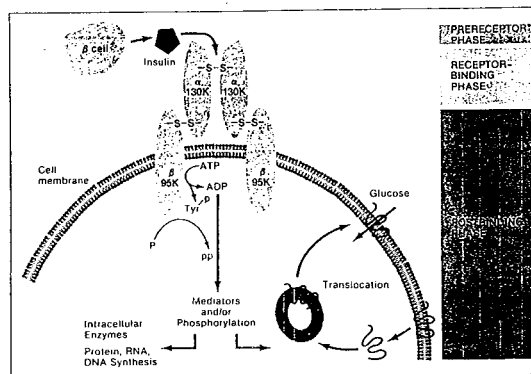


Fig - 3 : Model of insulin action and categories of insulin resistance.

form of storage fat. These are released from the liver cells to the blood in the form of lipoproteins. Insulin activates lipoprotein lipase in the capillary walls of the adipose tissue, which splits the triglycerides again into fatty acids, a requirement for them to be absorbed into the adipose cells, where they are again converted to triglycerides and stored. Insulin also prevents the hydrolysis of triglycerides by inhibiting the action of hormone sensitive lipase.

c) Insulin has an anabolising effect in protein metabolism and deficiency of insulin secretion results in growth retardation (54).

Certainly less well known actions of insulin are:

- 1) Stimulation of potassium transport in muscles,
- 2) Cellular differentiation in adipocytes,
- 3) Ovarian production of androgens,
- 4) Renal retention of sodium (54).

Many of the defects in the synthesis, release, receptor and postreceptor processing of insulin may lead to some functional defects of insulin. The most important case of these is DM, which can be divided into two different forms like insulin dependent diabetes mellitus (IDDM) and non insulin dependent (NIDDM) diabetes. In the IDDM, the islets are destroyed and dysfunctional pancreatic islet cells. But, whereas in NIDDM, there is also peripheral insulin resistance which is a major problem.

80 percent of NIDDM patients are obese. Fasting insulin levels may be normal or high, but there is a diminished first phase response to the oral glucose. And, there is a blunted response to aminoacids, sulfonyl urea, glucagon and β -agonists which are also stimulators of insulin secretion. Last condition can be characterized by insufficient recognition of glucose by islet cells. Insulin resistance is a second important reason.

Insulin resistance means, subnormal biologic response to a certain determined concentration of insulin. It has a broad spectrum. This spectrum contains either diabetic persons who need insulin treatment, but cannot be regulated; or normal blood glucose achieved with high doses of insulin (Table 1). It has been determined that insulin resistance occurs from pre-receptor, receptor and postreceptor defects (54), and may frequently appear in obese, lean, latent diabetic and diabetic

<p>Defects intrinsic to target cells</p> <ul style="list-style-type: none"> Mutations of the insulin-receptor gene Defects in other genes important for insulin action (putative) Glucose transporters Substrates for insulin - receptor kinase or signaling intermediates Cellular inhibitors of insulin- receptor kinase <p>Secondary factors affecting target cells</p> <ul style="list-style-type: none"> Abnormal physiologic states Stress (e.g. fever, sepsis) Fasting or starvation Uremia Cirrhosis Ketoacidosis Obesity Diabetes or hyperglycemia <p>Normal physiologic states</p> <ul style="list-style-type: none"> Puberty Advanced age Pregnancy <p>Specific hormonal or metabolic factors</p> <ul style="list-style-type: none"> Glucocorticoids (e.g. Cushing's syndrome) Growth hormone (acromegaly) Catecholamines (e.g. pheochromocytoma) Glucagon (e.g. glucagonoma) Thyroid hormone (thyrotoxicosis) Hyperinsulinemia (e.g. insulinoma) Hyperglycemia (diabetes) Free fatty acids (nonesterified fatty acids) Adenosine Perhaps islet amyloid polypeptide (amylin) <p>Autoantibodies to the insulin receptor</p>
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Table 1 : Causes of insulin resistance (53).

patients (2, 22). These conditions can be the cause for compensatory insulin hypersecretion (30, 81). In other words, insulin resistance correlates plasma insulin concentration in cases which have β -cell secretory capacity. Hypersecretion of insulin can prevent diabetes mellitus (DM), but it may end in costly results (32). In patients with these characteristics, we can observe :

- . Defects in glucose metabolism and certain enzymatic dysfunctions caused by lack of insulin effect.
- . Hypertension, dislipidemia and atherosclerosis, led by insulin hypersecretion.

The case of diabetics who require exogenous insulin doses of more than 100 to 200 units per day may be roughly viewed as evidence of unusually severe insulin resistance. When such increased requirement of insulin develops from the now rare occurrence of high titers of antibodies to insulin or

the degradation of injected insulin, the insulin dose does not reflect insulin resistance at the level of target cells (54).

It is now clear that the ability of insulin to stimulate glucose uptake can vary substantially in non-obese and non-diabetic persons (30). In addition, differences in either degree of obesity or level of habitual physical activity can also modulate in-vivo insulin action (62). Diet and exercise can increase insulin sensitivity either acutely or chronically (6). In one study, it was determined that insulin resistance can be achieved by the typical American diet with high fat-high sucrose.

In CARDIA study, it has been cited that fasting insulin levels do not directly measure insulin resistance. But there is evidence that the basal and stimulated insulin levels correlate highly with the reciprocal tissue insulin sensitivity (65). Hyperinsulinemia is the result of insulin resistance and gives an opinion that we should use more sophisticated measures of insulin sensitivity (54). Quantitative in-vivo measurements of insulin sensitivity are, euglycemic insulin clamp technique, or in-vitro studies with cultured cells and tissue samples. Insulin sensitivity can be researched also by insulin suppression tests (8, 9).

Insulin resistance may be selective for cell's glucose transport (one can be insulin resistant but having normal androgen production even if hyperandrogenic) (33). In studies with untreated hypertensives, researchers have determined that compensatory insulin levels achieved up to 60-70 $\mu\text{U/ml}$ increases and other functions of insulin were normal (20).

Welborn et al., have determined higher plasma insulin levels in hypertensives who have been treated or untreated (82).

In CARDIA study, Manolio et al. showed relations with insulin, blood pressure, lipidemia and other variables. It was determined that fasting insulin levels are correlated with systolic and diastolic blood pressure, and also with total and LDL cholesterol, apoprotein B. On the contrary, it was negatively correlated with HDL cholesterol, apoprotein A, and hard physical activity. Body mass index (BMI) was correlated with fasting insulin levels, but it was less important. Blacks had higher fasting insulin levels.

In San Antonio Heart Study, which is another important study in this field, it has been said that

hypertension is not isolated but a combined phenomena. 80 % of hypertensive cases goes with multiple metabolic anomalies. Hyperinsulinemia is regularly present in hypertension and age, gender, blood fat distribution, glucose intolerance, insulin sensitivity, blood pressure and lipoprotein anomalies are all interrelated phenomena (39). In CARDIA study, it was found that diastolic blood pressure was related with fasting and stimulated insulin levels (21).

In another study, in comparison with normal cases, it has been determined that even patients who are isolated hypertensives (not obese, not diabetic, not glucose intolerant, not having any high triglyceride and cholesterol levels) have had not over-limit but higher blood glucose, fasting and stimulated insulin, triglyceride levels and (HDL/Total cholesterol) ratios (51). Lehtonen et al. have established in hypertensives higher glucose and insulin levels in comparison with normotensives (20) and have said that it was related not only to systolic but diastolic blood pressure as well.

Ferrannini et al, have said that fasting and stimulated insulin levels were most frequently determined as metabolic anomalies in essential hypertension. According to them, it was not selective for hypertension but could be seen in obesity, glucose intolerance, mild NIDDM and mild hypertriglyceridemia (22). But, insulin resistance in essential hypertension has been determined as a primary factor, independent from obesity and diabetes.

Axelrod et al have demonstrated that hyperinsulinemia was a common characteristic of obesity, glucose intolerance and hypertension and may lead to increased SVR (52).

Reaven et al have shown that insulin's functional defects and hyperinsulinemia may be determined in obese and non obese patients even after antihypertensive therapy (76). In a different study, they have demonstrated in Sprague Dawley rats that insulin resistance, hyperinsulinemia and hypertriglyceridemia have occurred in 1 week, independent from obesity. At the same time, this diet may have led to increasing of blood pressure by 20 mm Hg, this augmentation has occurred in 10 days, and lasts for at least 3 months if the diet is continued (26), has decreased with exercise (82). In another study, they have researched the response of these metabolic anomalies and hypertension to somatostatin infusion which was stimulated by

fructose diet. They have concluded that somatostatin antagonized the insulin, decreased blood levels and as a result, reduced the hypertension and hypertriglyceridemia (49).

In another study, insulin's stimulated glucose uptake has been investigated in isolated adipose tissues of spontaneously hypertensive rats (SHR) and Wistar Kyoto rats (WKR). It has been demonstrated that glucose uptake was too much depressed in SHR's in comparison to WKR's. This reduction was not related with the number of insulin receptors, receptor autophosphorylation or insulin receptor kinase activity, so the insulin's functional defect was limited with glucose metabolism defect. (Catecholamin induced inhibition rate of lypolysis was same in SHR and WKY.)

Researches about the ways of the causative role insulin resistance plays in hypertension went on until 1969. The hypothesis are actually as follows: (Fig 4)

1) An increase of renal sodium absorption: Insulin can increase blood pressure by increasing renal sodium reabsorption (1, 7). This condition increases total body sodium and extracellular fluid volume. It has been proved that insulin increases renal tubular sodium reabsorption of toad and human kidneys (1, 17).

2) By increasing renal water absorption: Insulin increases renal water absorption through proximal tubuli (7,59).

3) Another mechanism by which insulin could

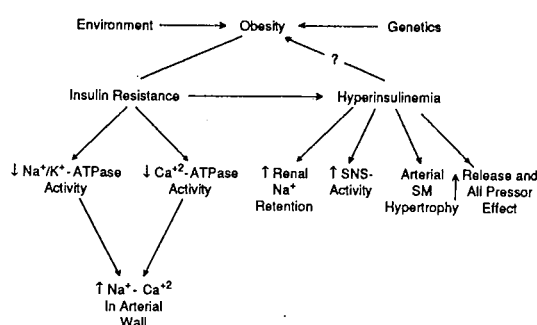


Fig - 4 : Mechanisms by which insulin resistance and compensatory hyperinsulinemia might affect blood pressure.

influence blood pressure relates to insulin's ability to enhance sympathetic nervous system (SNS) activity. It has been demonstrated that increased plasma insulin levels accompany enhanced plasma insulin levels and both are independent from blood glucose levels (59,70). Increased SNS activity causes renal vasoconstriction, renal tubular sodium reabsorption, renin release; all of which appear to further increase CO, SVR and blood pressure. (42, 70).

4) Over-activation of (Na⁺/H⁺) counter transport system: This is a mammalian cell membrane transport system. It stabilizes intracellular pH, regulates cell replication and hypertrophy, an active role in protein synthesis (69, 71). Thus in-vivo it might be expected that subjects with a high (Na⁺/H⁺) countertransport activity would show some degree of tissue hypertrophy. Studies have demonstrated that cardiac and renal volumes measured by an ultrasonic technique were greater in these cases (23, 44).

Some researchers measured tissue (Na⁺/H⁺) countertransport activity in their study with hypertensive diabetics and determined that insulin resistance is greater in patients with greater (Na⁺/H⁺) countertransport activity using insulin clamp study. Intensity of the insulin resistance is parallel to enhanced (Na⁺/H⁺) countertransport activity.

(Na⁺/H⁺) countertransport activity also relates to the sodium homeostasis. It has been thought that over activation of this system results in increased intracellular sodium levels and arterial smooth muscle contraction. Lately, authors have accepted that (Na⁺/H⁺) counter transport activity is higher in hypertension.

5) Effect on (Na⁺/K⁺/ATPase) and (Ca⁺/ATPase): This is an insulin sensitive pump. When insulin sensitivity decreases its activity lessens. Increased intracellular sodium helps increasing intracellular calcium. Cell becomes more contractile (55).

Insulin can activate plasma membrane's (Ca⁺⁺/ATPase) by different mechanisms:

. Increasing membrane calmodulin content (24);

- . Increasing membrane calmodulin phosphorylation (24);
- . Increasing affinity of calmodulin to calcium (46,79);
- . Increasing calcium ATPase gene expression (80).

Decreased membrane Ca^{++} efflux is partially responsible for the elevated Ca^{++} levels. Since the ($Ca^{++}/ATPase$) linked extrusion pump is in part responsible for maintenance of the optimal level of Ca^{++} (46), insulin resistance could lead to increases in intracellular Ca^{++} levels -which in turn would result in enhanced vascular responses to various agonists. Decreased activity of the erythrocyte membrane ($Ca^{++}/ATPase$) has been observed in insulin resistant NIDDM patients with hypertension (84). Reduced erythrocyte ($Ca^{++}/ATPase$) activity has also been observed in insulinopenic diabetics (74). Another study has also demonstrated decreased erythrocyte and kidney basolateral membrane ($Ca^{++}/ATPase$) in insulin resistant rats (74). Further, the regulatory effects of insulin on cell membrane ($Ca^{++}/ATPase$) activity were absent in an insulin resistant diabetic rat model (46, 47).

Data support that, the concept of regulation of intracellular Ca^{++} by insulin, (mediated partially by cell membrane $Na^{+}/K^{+}/ATPase$ and $Ca^{++}/ATPase$ pumps) is impaired in cases of insulin resistance and hypertension (Fig 5).

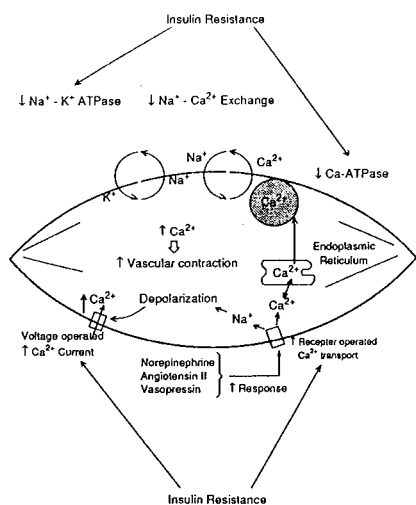


Fig - 5 : Altered mechanisms of cellular Ca^{2+} transport in insulin - resistant states.

6) Inhibition of PGI_2 and PGE_2 synthesis by hyperinsulinemia: PGI_2 and PGE_2 both are vasodilator substances which have additive effects (57,58). Their synthesis need catecholamine stimulation. PGI_2 is more potent (3). Insulin, in physiologic concentrations, can decrease the synthesis of prostaglandins (2,5). When insulin resistance and hyperinsulinemia are achieved, enhanced inhibitory effect can give rise to decreased antagonism of sympathetic effects, decreased PGI_2 and PGE_2 synthesis and high blood pressure (4) (Fig 6).

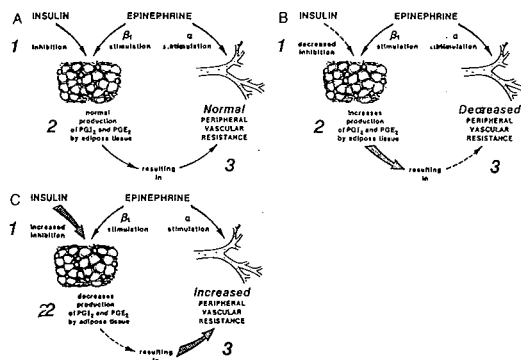


Fig - 6 : Role of insulin and prostaglandins in the regulation of blood pressure.

Obesity and sedentary life style can accompany hypertension and lipoprotein metabolism disturbances (53) (Fig 7). Our knowledge of the relation between obesity and hypertension is the most important evidence about the role of insulin resistance and hyperinsulinemia in blood pressure regulation. Hypertension frequently occurs in obese patients and hyperinsulinemia is a marker in obesity. It's most striking in upper body obesity (24). These patients have the highest prevalence of hypertension and most pronounced hyperinsulinemia (12). High insulin levels in upper body obesity (central or android obesity) arises both from increased secretion and decreased hepatic removal and degradation of insulin. Decreased hepatic removal of insulin appears to be related to the high rate of lipolysis of intra-abdominal fat. The excessive quantity of free fatty acids originating from this fat are believed to be

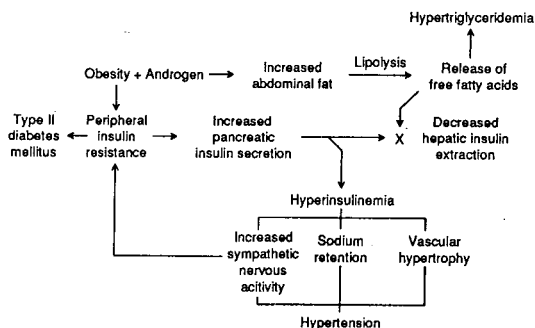


Fig - 7 : An overall scheme for the mechanism by which upper-body obesity could promote glucose intolerance, hypertriglyceridemia, and hypertension via hyperinsulinemia.

responsible for both hyperinsulinemia and hypertriglyceridemia and low HDL-cholesterol levels common in upper body obesity as hepatic removal of insulin decreases.

Studies in obese cases determines that losing weight increases insulin sensitivity (62). Furthermore, improved tissue insulin sensitivity has been demonstrated in obese subjects who accomplished a 7 % increase in maximal oxygen consumption during physical training even with only minor changes in body weight and fat composition (11). More important and evident result of one study is that obese patients who have improved blood pressure levels by exercise programs are hyperinsulinemics (38). Either insulin resistance or hyperinsulinemia have hereditary components (46,80). But studies have proved that, dietary restriction can also increase insulin sensitivity, decrease blood pressure and improves the lipoprotein profile. This condition points to the important relations of environment and genetics.

Obese patients have higher basal insulin levels than lean subjects (40). However, reduced insulin sensitivity, insulin resistance and high basal insulin levels can be determined in lean subjects (20). Studies have proved relations in insulin resistance-hyperinsulinemia and hypertension also in lean subjects (67). The fact that hyperinsulinemia is also common in nonobese patients with primary hypertension is less obvious but more important

(20). Their hyperinsulinemia is attributable to peripheral insulin resistance. It could reflect a simple inability of insulin to reach the skeletal muscle cells by microcirculation wherein its major action in the glucose metabolism occur (29). Another possible explanation for the peripheral insulin resistance and the resultant hyperinsulinemia in hypertension is a genetical or acquired increase in the proportion of type IIB muscle fibers, fibers that are fast twitch, glycolytic, and less sensitive to the action of insulin (48). Marked interindividual variations in the proportion of these fibers are seen in normal subjects. Hypertensives have been found to have a greater proportion of fast-twitch fibers (77). The proportion of type IIB fibers is reduced after extensive isotonic exercise, which is known to improve insulin sensitivity while it lowers the hypertension (43).

Zavaroni et al. in studies with lean factory workers with and without hyperinsulinemia determined that those with hyperinsulinemia had higher blood pressure and triglyceride levels and lower HDL cholesterol than those without hyperinsulinemia (83). In euglycemic hyperinsulinemic clamp studies of lean hypertensives, Ferranini et al observed a strong inverse correlation between the systolic blood pressure and total body glucose uptake, the latter being a measure of the tissue insulin sensitivity (20).

Insulin resistance and hyperinsulinemia are associated with multiple lipoprotein anomalies (53,80); which are decreased HDL and increased TG levels and a lesser degree rise of total and LDL cholesterol levels (53, 62, 80, 83).

Because of peripheral insulin resistance, there is a reduced activity of endothelial bound lipoprotein lipase in skeletal muscle and adipocytes. This enzyme is responsible for the metabolism of triglyceride-rich particles like VLDL and chylomicrons. Thus, triglyceride levels rise because of increased hepatic production of TG lipoproteins coupled with reduced peripheral metabolism of VLDL. Because of the inefficient triglyceride metabolism, HDL levels fall in a parallel manner.

Under normal circumstances, approximately 50 % of VLDL is metabolised to VLDL remnants, which are cleared from the circulation by hepatic apo B/E receptors, while the remaining 50 % is

converted into LDL. In the setting of peripheral insulin resistance, conversion of VLDL to VLDL remnants is reduced. This results in increased VLDL conversion to LDL explains the increased LDL levels in persons with insulin resistance and hyperinsulinemia (24). Loss of weight, which is known to increase insulin sensitivity can decrease plasma insulin concentration, lessen hepatic VLDL and TG synthesis and reduce plasma TG concentration.

In a number of studies on human and rat models of hypertension, investigators have determined the same metabolic anomalies: Insulin resistance, hyperinsulinemia and hypertension (68). It has been shown in multiple forms of hypertension and it suggests that the noted relationship is more than coincidental. Results of the studies with isolated hypertensives are in agreement with those of hyperinsulinemics and patients having important degrees of hypertriglyceridemia (82). Also in nondiabetic normotensive patients, there is a relationship between plasma insulin levels, TG and HDL concentrations and changes in blood pressure (83).

It has been accepted that carbohydrate metabolism is frequently disturbed in treated and untreated hypertensives (52, 76, 83). There are some studies which claim that insulin resistance is mild in untreated hypertensives (20, 66), but increases with antihypertensive therapy (76). Mondan et al. have searched the prevalence of glucose intolerance in hypertensive patients (52). Hypertension coincided with glucose intolerance in 52.9 % of patients. Glucose intolerance was more frequent in patients using antihypertensive therapy. In this study, 31 % of patients were using thiazides, 33 % β -blocker, 16 % thiazide plus β -blocker. It has been known in antihypertensive therapies on thiazide plus β -blocker, that metabolic abnormalities with hypertension are increased at a much more higher rate (56).

In another study with normal, untreated and treated hypertensive patients; insulin stimulated glucose uptake is measured by exogenous glucose and insulin infusion after suppression of endogenous insulin with somatostatin. Insulin infusion doses were same in all three groups. Glucose levels were higher in treated hypertensive patients than the untreated ones. Highest levels have been determined in treated hypertensives. It was concluded that hypertensives were insulin resistant

and antihypertensive therapy did not improve, but increased this resistance (76).

In comparison with normal cases, impaired OGTT cases have doubled the prevalence of hypertension (13). Some researches have determined that impaired OGTT leads to hyperinsulinemia and it may be a factor in the pathogenesis of hypertension (20,76).

CAD is a major cause of morbidity and mortality in NIDDM but it does not occur only in DM. High plasma insulin levels, increased blood pressure, high plasma TG concentrations can be determined in impaired OGTT patients. For this reason there is a high risk of CAD in impaired OGTT patients (28).

Even in hyperinsulinemic but normal OGTT patients, high blood pressure, high plasma TG concentrations and low HDL concentrations can be seen (83). Highest CAD risk have been shown in patients who have the highest insulin levels among the OGTT normal group (25).

Experimental and epidemiologic data have shown that hyperinsulinemia accelerates hypertension (78, 80). Insulin stimulates subintimal smooth muscle cells, fibroblast and increases their lipoprotein cholesterol uptake and esterification (78). Insulin is a potent mitogenic factor (64). In experimental rat models insulin decreases the protective effects of estrogen in atherosclerosis (Fig 8). It accelerates dietary induced atherosclerosis. Thus, hyperinsulinemia, which is parallel with carbohydrate metabolism disturbances in DM and hypertension, accelerates

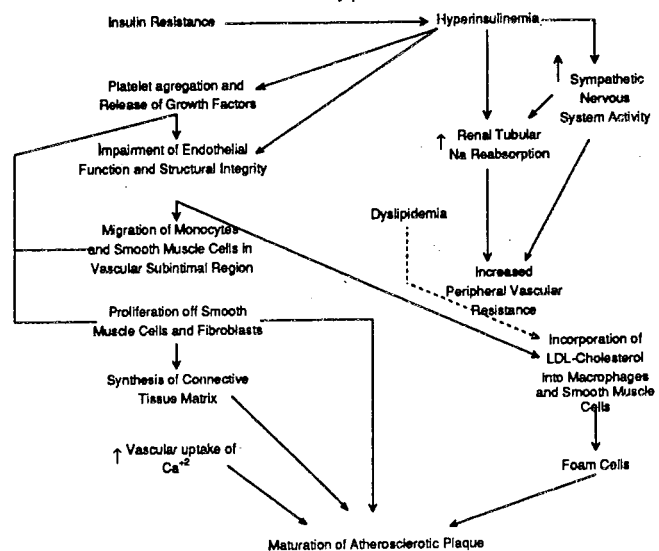


Fig - 8 : Putative role of hyperinsulinemia in the pathogenesis of accelerated atherosclerosis.

atherosclerosis not only primarily but secondarily by leading hypertension as well (80). It is widely known that insulin, fibrinogen and plasminogen activator inhibitor (PAI) are related with each other, so that insulin resistance leads to atherogenic lipoprotein and haemostatic profile (41). Insulin resistance, hyperinsulinemia, hypertension, hypertriglyceridemia and low HDL are given the name of Syndrome X (68). All of the components in this syndrome are interrelated. Insulin resistance is the key factor in Syndrome X and leads other problems (18). Stimulated insulin and C peptide levels are high in Syndrome X (16). Cumulating all these factors that can cause atherosclerosis, increases CAD risk (72).

Some researchers have mentioned that insulin resistance is an important component of the Syndrome X (35, 37, 68). High total and LDL cholesterol levels may not be fixed in hyperinsulinemia but hypertriglyceridemia is a fixed part of Syndrome X (8, 10, 68). Generally, it is believed that LDL has a major role in the CAD pathogenesis (27, 60). But, it is proved that CAD can occur independently from high LDL levels (45). Its demonstration is Syndrome X and it has a major role in CAD. Although the role of hypertension in CAD is widely accepted, treatment of hypertension may not cure the CAD risk, but may decrease it a little (14), or not (50).

Therefore, in treating hypertension, preferring medications that do not cause metabolic side-effects such as hyperinsulinemia can help in decreasing CAD risk.

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