PREVALENCE OF HYPERTENSION IN DIABETES MELLITUS

Although the relationship between diabetes mellitus and hypertension has been noted for many years, only recently have researchers begun to study any consistent risk factors and causal relationships. Several recent studies have highlighted a strong association between diabetes and hypertension, as well as the increased risk of cardiovascular disease in people with diabetes. The mechanisms underlying this association are not fully understood, but there is growing evidence to support the notion that diabetes and hypertension share common risk factors, including insulin resistance, high blood pressure, and increased levels of blood triglycerides. These factors may contribute to the development of both conditions and worsen their long-term outcomes.

REVIEW OF LITERATURE
Diabetes-mellitus, insulin resistance and hypertension: A Pandora's Box

Prevalence of hypertension in diabetes-mellitus

Although the association between diabetes mellitus and hypertension had been noted for many years, there were no controlled studies to derive any conclusion with certainty. Pell and D'Alzo (1967) were the first to conduct a study using carefully matched non-diabetic control population and reported that the prevalence of hypertension was 54% greater in diabetic patients than in the control population. Studies from 50 years ago (Major 1929) documented a higher frequency of increased blood pressure in NIDDM subjects. Later, the Framingham Study (Dawber 1980) reported that mean systolic pressures were slightly higher in the diabetic population, especially in female subjects. In 1981, a study of patients between the ages of 50 and 80 years showed a high prevalence of hypertension in NIDDM population even when adjusted for obesity (Barret-Connor et al 1981). Christlieb et al (1981) showed a significant excess of hypertension in a diabetic population that had an onset of diabetes before age 21. The Whitehall Whitehall (Fuller et al 1983) and Bedford (Jarrett et al 1982) studies also showed that existence of hypertension in diabetic subjects was frequent.

Epidemiological data also present prevalence of NIDDM in patients with essential hypertension (Skarfors et al 1989). Acute loading studies have suggested that even non-diabetic hypertensives have significantly increased glucose and insulin levels compared with matched normotensive subjects (Ferrannini et al 1987). Fuh et al (1987) reported that hypertensive non-diabetic males when compared with normotensive non-diabetic males of comparable age and body weight show an increase in both plasma glucose and insulin response to a glucose challenge. The plasma glucose and insulin responses showed a significant correlation with the levels of both systolic and diastolic blood pressure (Fuh et al 1987). The association between impaired insulin action and hypertension was first suggested by Welborn et al (1966). Since then there have been several epidemiological and clinical studies supporting this hypothesis (Berglund et al 1976, Modan et al 1985, Lucas et al 1985, Manicardi et al 1986, Swislocki et al 1989, Singer et al 1985). However, there are also several studies refuting the link between insulin and hypertension (Asch et al 1991, Collins et al 1990, Saad et al 1990, Mbanya et
al 1988). In many studies, the correlation between plasma insulin levels and hypertension became weak after accounting for obesity (Meechan et al. 1993). Other studies that contradict this hypothesis are those by Anderson and Mark (1993) and Sawicki et al. (1992). First, insulin when administered acutely is a vasodilator and does not cause an increase in blood pressure (Anderson and Mark 1993) and second, patients with insulinoma who are hyperinsulinemic are generally not hypertensive (Sawicki et al. 1992). Although it is important to remember that insulin resistance is not always associated with hypertension and vice versa, these evidences can be argued upon. The inability of insulin to increase blood pressure acutely suggests that if insulin is a vasoactive hormone, then resistance to its vasodilatory effects may manifest as an increase in peripheral vascular resistance and thereby raise blood pressure. What further strengthens the contention that chronic hyperinsulinemia may exert presser effects in insulin resistant humans are two separate studies one of which have demonstrated that blood pressure falls when the dose of insulin is decreased in obese, hypertensive patients with NIDDM (Tedde et al. 1989) and the other one which reports that when insulin treatment is started there is an increase in blood pressure in NIDDM patients (Randeree et al. 1992). This view is further supported by the study of Ohigara et al. (1995) who have shown that troglitazone, a drug that improves insulin sensitivity, lowers blood pressure in diabetic-hypertensive patients. However, it is not clear as to why patients with insulinoma are generally not hypertensive (Sawicki et al. 1992). In such patients there are marked hormonal counter-regulatory responses, besides, these patients do not have primary insulin resistance. These patients also lack the substrate for insulin (i.e. glucose), the availability of which is essential for insulin for its metabolic and vascular smooth muscle responses (Yanagisawa-Miwa et al. 1990).

Further, in an effort to resolve the issue of link between hyperinsulinemia and hypertension, Denker and Pollock (1992) performed a meta-analysis on the various studies reported between the years 1983-1991. The results of the meta-analysis indicated that fasting serum insulin concentration was strongly correlated with both systolic and diastolic blood pressure when data from all the studies were pooled together to yield a statistically meaningful result (Denker and Pollock 1992). In another study, Maheux et al. (1994) quantified insulin resistance in 5 different groups of subjects: normotensive-obese, normotensive-nonobese, hypertensive-obese, hypertensive-nonobese and hypertensive-obese with NIDDM. That the effects of obesity, hypertension and NIDDM
on insulin resistance are additive and that each one of these diseases contributes independently towards the glucoregulatory effects of insulin was proved by this study.

As far as the correlation between hyperinsulinemia and insulin resistance is concerned, it looked certain. However, it was not obvious if hyperinsulinemia was a consequence or cause of elevated blood pressure. In an attempt to resolve this problem a study was conducted by Ferrari et al (1991) in which insulin sensitivity and plasma insulin levels in normotensive offsprings of essential hypertensive patients were compared with those obtained from age and weight matched normotensive subjects with no parental history of hypertension (Ferrari et al 1991b). Young, lean, normotensive (predominantly male) adults who had a positive family history of hypertension were insulin-resistant and hyperinsulinemic when compared to normotensive controls without a hypertensive parent. It was found that insulin sensitivity was decreased by about 28% and insulin levels were increased by about 15% in subjects with parental history of hypertension, which indicated that these defects antedate the increase in blood pressure and are not secondary to hypertension. A similar study, that reported identical results, was conducted by Facchini et al (1992) where majority of subjects included in the study were females. Another study demonstrated that hyperinsulinemia was present even in young children (around 14 years of age) who were normotensive, normolipidemic but had a positive family history of hypertension (Grunfeld et al 1994). All these results indicate that the link between insulin and hypertension has a genetic basis that is independent of age, gender or body weight and also that defects in insulin action antedate most of the metabolic and hemodynamic abnormalities seen in hypertensive subjects. However, insulin resistance can be modified by environmental influences such as body weight or physical exercise (De Fronzo and Ferrannini 1991) and this suggests that the final phenotypic expression of these defects is probably a combination of both genetic and acquired influences. Nevertheless, it now appears to be clear that insulin resistance is genetically inherited and is not simply a consequence of increased blood pressure.

The view that insulin resistance is not secondary to an increase in blood pressure is further supported by studies indicating that insulin-mediated glucose utilisation and glucose-stimulated insulin secretion is normal in patients with secondary hypertension such as renovascular hypertension and primary hyperaldosteronism (Shamiss et al 1992). More direct evidence for such a link has come from studies where it was observed that
physical exercise lowered blood pressure in obese patients (without any change in body weight), but only in those patients who were hyperinsulinemic before the start of the training program (Kroktiewshi et al 1979). There are several other studies that confirm the link between insulin resistance and hypertension. Ferrannini et al (1987) provided evidence that there is about 40% reduction in insulin sensitivity in young, lean, untreated hypertensive subjects.

The association between insulin and hypertension has also been documented in several models of rodent hypertension including the Dahl rat (Kotchen et al 1991), the Spontaneously hypertensive rat (Mondon and Reaven 1988, Reaven 1991a,b), the Milan hypertensive rat (Dall-Aglio et al 1991) and the fructose-hypertensive rat (Hwang et al 1987). All these hypertensive rat models, although unrelated to each other, exhibit common defects in glucose metabolism. In Dahl rats, insulin resistance and hyperinsulinemia occur in salt resistant animals and are independent of the salt content of the diet (Reaven et al 1991). In Spontaneously hypertensive rats, hyperinsulinemia precedes the development of hypertension (Reaven and Chang 1991), however, the presence of insulin resistance in this rat strain remains controversial (Buchanan et al 1992a, Buchanan et al 1992b, Frontoni et al 1992, Hulman et al 1993). Insulin resistance and hyperinsulinemia have been reported to be induced in normotensive Sprague Dawley rats when fed with a fructose-enriched diet (Hwang et al 1987). Induction of these metabolic defects was associated with a concomitant increase in blood pressure in these rats.

Furthermore, exercise training (which resulted in improved insulin sensitivity) and somatostatin administration (which decreased hyperinsulinemia) to the fructose-fed rats attenuated the fructose-induced increase in blood pressure in the animals (Reaven et al 1988; Reaven et al 1989b). These results again support the link between hyperinsulinemia and hypertension. However, results obtained from studies conducted in dogs are in contrast to those reported in rats. Acute insulin infusion in dogs did not raise blood pressure (Liang et al 1982), whereas it led to a dose-dependent increases in blood pressure in rats (Edwards and Tipton 1989). Furthermore, a six-fold increase in plasma insulin levels in dogs given chronic insulin infusion for 4 weeks was not found to produce hypertension (Hall et al 1990a). Insulin did not cause an increase in blood pressure even when dogs were made susceptible to hypertension by partial nephrectomy coupled with a
high salt intake (Hall et al 1990b). On the other hand, chronic physiological increases in plasma insulin concentration increased blood pressure in rats (Brands et al 1991). It is however interesting to note that dogs fed with a fat or high fructose diet became insulin resistant, hyperinsulinemic and hypertensive (Martinez et al 1994). Thus there are species differences with regard to the effects of insulin on the blood pressure, which may be a result of differential effects of insulin on the sympathetic, renal or cardiovascular systems. Although there is sufficient evidence to suggest the link between insulin and hypertension, considering the contradictory results from animal studies we have to look into the possible mechanisms that link insulin to an increase in blood pressure. From the human and animal studies we may conclude that hyperinsulinemia/insulin resistance in hypertension is a reflection of resistance to the peripheral uptake and utilisation of glucose, with high levels of insulin needed to maintain and sustain euglycemia and that compensatory increase in plasma insulin concentration is not a benign phenomenon but that hyperinsulinemia may contribute towards the development of hypertension by a variety of different mechanisms.

In summary, current evidence indicates that insulin resistance in hypertension is a primary defect (independent of obesity, diabetes or drug treatment). It is tissue specific i.e. resides primarily in skeletal muscle and pathway specific (involves glycogen synthesis). The defect in insulin-mediated glucose uptake may play a role in the development of hypertension or may chronically predispose a certain proportion of subjects with a specific neurohumoral phenotype towards an increase in blood pressure. However, the contribution of insulin resistance toward an increase in blood pressure is probably smaller and more complex than is often emphasised and to assume that insulin is directly linked to a rise in blood pressure in all hypertensive subjects is oversimplistic and incorrect.

In addition, there was a correlation between hyperinsulinemia and elevation of low density lipoprotein (LDL) cholesterol to high density lipoprotein (HDL) cholesterol ratio. In 1988 Reaven proposed that insulin resistance in diabetic (or non-diabetic) subjects would lead to compensatory hyperinsulinemia which is associated with increased LDL and reduced HDL concentrations. Hyperinsulinemia which is frequently encountered in NIDDM subjects is postulated to be causal in hypertension (Falkner et al 1990). Further, hyperinsulinemia is also reported to antedate essential hypertension in non-diabetic patients (Ohno et al 1993).
Mechanisms of hypertension in diabetes mellitus

**Plasma renin activity (PRA):** Measurements of PRA (as an indicator of the renin-angiotensin-aldosterone system) have shown normal, high and low levels in diabetic subjects depending on such factors as metabolic control, age and renal function (Beretta-Piccoli and Weidmann 1989). In general, when corrected for sodium intake, age and other variables, aldosterone levels (Feldt-Rasmussen et al. 1987) and PRA are lower in both IDDM and NIDDM compared to non-diabetic subjects (Trujillo et al. 1989, Christlieb 1978). However, it appears that changes in PRA in diabetes are secondary to increased extracellular volume, renal damage, and low sympathetic nervous system activity and probably do not contribute in a major way to hypertension in diabetes mellitus.

There are a number of factors in diabetes mellitus that impair renin release and are related to the microvascular complications of diabetes. In fact, nephropathy and retinopathy in diabetes are often associated with reduced PRA levels (Frenandez et al. 1981, Tuck et al. 1979, Nadler et al. 1986, Luetscher et al. 1985). Impaired beta-adrenergic renal action (Frenandez et al. 1981, Tuck et al. 1979) and decreased prostacyclins (Ditzel and Brochner-Mortesen 1983) contribute to lower PRA in some patients with diabetes. In addition, increased inactive renin may block renin formation by means of altered posttranslational renin processing and elevated prorenin may serve as a marker of complications in diabetes (Luetscher et al. 1985).

Although the suppressed circulating PRA in diabetes has been interpreted to indicate that the renin-angiotensin system (RAS) is not a factor in the etiology of hypertension in diabetes mellitus, recent findings of tissue RAS systems open the door for the tissue RAS in the development of hypertension and microvascular complications. In diabetic rats, circulating PRA is suppressed but aortic renin and renal renin mRNA is increased (Ubeda et al. 1988, Coriila-Rotter et al. 1992). Anderson et al. (1989) have reported tissue levels of renin protein and ACE immunostaining in kidneys from diabetic rats. They have postulated a role of tissue RAS in diabetic complications. Plasma ACE levels are high in human IDDM with nephropathy (Marre et al. 1994) and retinopathy (Feman et al. 1993); and ACE genotypes conferring either protection from or enhanced susceptibility to nephropathy have been described in diabetes (Hseuh 1992). ACE is
increased in the serum and mesenteric arteries of experimentally induced diabetes (Doria et al. 1994, Ermon et al. 1993, Jandeleit et al. 1992). Thus although PRA may not be the indicator of RAS-induced increase in blood pressure, the involvement of tissue RAS cannot be ruled out at this stage.

Effect of insulin on renin-angiotensin-aldosterone system (RAAS): Yet another recent approach to understanding the link between insulin resistance, hyperinsulinemia, hypertension and diabetes is the association of insulin, the renin-angiotensin-aldosterone system (RAAS) and the potassium (K) and sodium (Na) levels.

Insulin is a potent regulator of K metabolism. In healthy subjects insulin infusion with maintenance of euglycaemia (by glucose clamp technique) causes dose-dependent fall in plasma K concentrations (Ferrannini et al. 1994). Trovati et al. (1989) showed that during euglycaemic hyperinsulinemia, hypokalemia is accompanied by a significant increase in plasma renin activity (PRA) and serum angiotensin II concentrations, and a pronounced fall in serum aldosterone levels. Because aldosterone promotes urinary K excretion, the fall in aldosterone potentiates the effect of insulin-induced hypokalemia, which reduces K delivery to the kidney. The overall result is an efficient restraint on K loss through the urine.

There are several reports suggesting that hypokalemia impairs insulin release. Patients with primary and secondary hyperaldosteronism showed impaired carbohydrate metabolism (Conn 1965) and this has been attributed to aldosterone-induced hypokalemia, which interferes with the insulin secretory response to glucose, thereby worsening glucose tolerance (Gordon 1973). There is also abundant evidence that thiazide diuretics impair carbohydrate metabolism through the K depletion associated with their prolonged use (Rowe et al. 1980). When K supplementation is given, thiazide-induced glucose intolerance and insulin hyposecretion are fully prevented (Helderman et al. 1983). Further, preventing insulin-induced hypokalemia significantly increases the insulin secretory response to oral glucose (Ferrannini et al. 1994). Thus there exits a physiological glucose-K cycle. The main feedback loop in the cycle is that glucose, via insulin release lowers plasma K, which in turn downregulates the insulin response to glucose. The cycle appears to be operative under both long- and short-term circumstances.
Hyperglycaemia opposes the hypokalemic action of insulin (De Fronzo et al 1980). However, this does not appear to be the consequence of resistance to the hypokalemic action of insulin in diabetics (Bevilacqua et al 1990). On the other hand, hyperglycaemia appears to be associated with K depletion (Landin et al 1989). A blunting of the insulin-mediated hypokalemia exposes more plasma K to renal excretion, thereby leading to total-body potassium depletion in the long term, the latter is in turn associated with lower plasma K concentrations. Further, there exists an inverse relationship between plasma K concentrations and arterial blood pressure (Beretta-Piccoli et al 1982, Khaw et al 1990).

Insulin has antinatriuretic action under physiological circumstances (De Fronzo et al 1975) and chronic hyperinsulinemia probably induces a volume-dependent form of hypertension by virtue of its constant sodium retaining pressure. It is only in diabetic patients, however, that a consistent expansion of the total body sodium pool is found (DeChatelet et al 1977), thus giving hyperglycemia a decisive role in reinforcing sodium retention.

**Vascular reactivity:** Blood pressure responses to vasoconstrictor agents such as angiotensin-II and norepinephrine, are markedly exaggerated in diabetes mellitus (Weidman 1988, Tuck et al 1990). This effect is seen early in the disease and is evident in both normotensive and hypertensive IDDM and NIDDM subjects. There is an early exaggeration in blood pressure response to vasoconstrictors in experimental diabetes also (Weidmann 1988, Tuck 1990, Epstein and Sowers 1992). Diuretics correct the abnormality in vascular reactivity in diabetic patients indicating that sodium is responsible for exaggerated vascular properties (Weidmann 1988). This enhanced blood pressure reactivity in diabetes mellitus might also be attributable to alterations in the physical properties of the resistance arteries or to abnormal paracrine regulation of vascular tone. Passive distensibility of the vascular bed is diminished early in the course of diabetes mellitus (Faris et al 1982). Production of prostacyclin is decreased, thromboxane synthesis is increased (Halushka et al 1985), and nitric oxide (NO)-mediated dilation is impaired in blood vessels from experimental diabetes mellitus (Durante et al 1980, Saenez et al 1989, Calver et al 1992, Rees et al 1988).
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Hyperglycemia: Kelleher et al (1988) demonstrated that there is a moderately positive correlation between blood pressure and plasma glucose. Tight glucose control decreases blood pressure in diabetes mellitus and this occurs despite increase in plasma volume and exchangeable sodium (Ferris et al 1985). Blood pressure also increases with worsening of metabolic control (Randeree et al 1992). Further, drug interventions that directly reverse insulin resistance and improve metabolic control have produced a decline in blood pressure (Anderson and Mark 1993). Therefore, it appears that the combined abnormalities in both glucose and insulin have major importance in the abnormal blood pressure regulations in diabetes mellitus.

Glucose has been shown to produce several direct cellular effects on blood vessels. Elevated glucose levels impair endothelium-dependent relaxation, decrease NO formation (Tesfamarian et al 1991), and increased endothelin-I production (Yamauchi et al 1990). Na⁺ K⁺-ATPase in the aorta is inhibited by hyperglycemia (Gupta et al 1992) and this effect may be related to reduced endothelin-derived NO formation (McVeigh et al 1993). Glucose also causes a delay in cell replication and acceleration of cell death (Lorenzi et al 1985). Glucose affects the lipid metabolism at vascular level by enhancing LDL oxidation in vitro (Kawamura et al 1994).

Glucose is responsible for the formation of advanced glycosylation end products (AGEs), which elicit multiple effects that may promote vascular changes and hypertension. AGEs inhibit the antiproliferative effects of NO (Hogan et al 1992) and induce growth-promoting cytokines, such as interleukin-I and IGF-I (Vlassara et al 1988, Kirstein et al 1992), and transendothelial migration of monocytes to subendothelial spaces. All these factors may in turn lead to elevation of blood pressure.

Sodium and volume: In the early stages of diabetes mellitus, proximal tubular sodium reabsorption is increased by 20-40% (Ditzel et al 1989). Numerous studies have shown that exchangeable sodium, a positive indicator of body sodium, rises by approximately 10% in diabetes mellitus (both IDDM and NIDDM) associated with or without hypertension (Stern and Tuck 1995, Feldt-Rasmussen et al 1987, Tuck et al 1990).

Atrial natriuretic peptide (ANP), another factor in volume control, is increased in experimental (Ortola et al 1987) and in clinical diabetes mellitus (DeCanta et al 1986).
Because ANP directly increases the glomerular filtration rate (GFR), high circulating ANP levels may promote glomerular hyperfiltration in diabetes. However, Nosadini et al (1991) reported that ANP action has also been shown to be blunted in diabetic subjects.

Circulating digitalis-like substance(s), factors often associated with hypervolemic states, are elevated in experimental diabetes and are positively related to arterial pressure (Chen et al 1994). In humans, this factor increases with increased body mass index (BMI) and impaired glucose tolerance (Takahashi et al 1993). In addition, abnormalities in membrane Na transport systems exist in diabetes. For example, the erythrocyte sodium-lithium countertransport system, an index of sodium reabsorption in the proximal tubule (Weder 1986), is increased in IDDM with nephropathy (Canessa et al 1980). In NIDDM subjects, erythrocyte countertransport is high in patients regardless of renal function (Gall et al 1991).

**Sympathetic nervous system (SNS):** SNS activity as determined by measurements of the catecholamines epinephrine and norepinephrine is usually normal in uncomplicated diabetes-mellitus (Kribben and Phillip 1989, Ferris et al 1985, Beretta-Piccoli et al 1979). Patients with frank neuropathy can have subnormal norepinephrine levels despite hypertension, a finding that weakens the role of SNS activity in the etiology of diabetic hypertension (Tuck et al 1991).

**Effects of insulin on sympathetic nervous system:** An increase in plasma insulin causes a rise in plasma catecholamine levels. Elevations in plasma insulin levels at pharmacological concentrations were found to produce dose-dependent increase in plasma catecholamine levels accompanied by increase in pulse and blood pressure (Rowe et al 1981). Several other studies have demonstrated that fasting decreases catecholamine levels whereas, feeding leads to an increase in plasma norepinephrine levels (DeHaven et al 1980, Landsberg and Krieger 1989; O'Dea et al 1982). Although an increase in sympathetic activity would be expected to cause an increase in cardiac output, peripheral vasoconstriction and consequent elevation in blood pressure, there is an increase in muscle sympathetic activity and nerve firing rate with a decrease in vascular resistance and either no change or a decrease in blood pressure (Anderson et al 1991). It is possible that insulin causes preferential vasodilation in the skeletal muscle vasculature and thereby leads to a redistribution of cardiac output to skeletal muscle (Baron 1993).
Baron et al (1994) reported that obese subjects are more susceptible to the pressor effects of insulin.

**Antinatriuretic action of insulin:** Insulin has a direct sodium retaining effect in healthy humans (De Fronzo et al 1975, Gans et al 1991a), dogs (De Fronzo et al 1976) and rats (Kirchner 1988). It is reported that insulin increases sodium reabsorption in the proximal and distal tubules (Endre et al 1994, Kageyama et al 1994). In addition, Shimamoto et al (1994) have reported that although insulin-mediated glucose uptake is markedly lower in hypertensives, insulin-induced sodium retention is comparable to normotensive controls. These results suggest that hyperinsulinemia leads to renal sodium and fluid retention which in turn causes hypertension. It appears that the kidneys of hyperinsulinemic subjects maintain normal sensitivity to the antinatriuretic effect of insulin; however, the peripheral tissues remain resistant to insulin's glucoregulatory effect. This hypothesis is supported by a recent study which demonstrated that the sodium retaining effect of insulin was maintained in hypertensive patients. These patients were however, resistant to the natriuretic effects of atrial natriuretic peptide suggesting that such a resistance may be one of the mechanisms underlying the insulin-induced increase in blood pressure (Abouchacra et al 1994). However, young subjects with essential hypertension were reported to have increased body sodium or an increased plasma volume or a reduced renin concentration, indicating that these acute effects may not be sustained or may be compensatory for over a longer period of time (Beretta-Piccoli et al 1982).

**Trophic effects of insulin:** Insulin causes an increase in vascular smooth muscle cell growth in vitro through its action on insulin-like growth factor (IGF) receptors (Banskota et al 1989, King et al 1985). Insulin-stimulated DNA-synthesis in fibroblasts and vascular smooth cells has also been demonstrated (Capron et al 1986, Rechner et al 1974). It appears possible that chronic hyperinsulinemia may cause vascular hypertrophy leading to narrowing of the lumen of the resistance vessels and consequently to elevated blood pressure. This hypothesis is supported by the report that chronic insulin infusion into one femoral artery in dog caused vascular hypertrophy only on the ipsilateral side (Cruz et al 1961). One important thing to remember here is that these hypertrophic effects of insulin
Figure 1: Mechanisms of insulin resistance leading to hypertension

Ang II: Angiotensin II
ECF: Extracellular fluid
NE: Norepinephrine
pump decreases in hypertensive patients as well as in experimental models of hypertension (Boon et al 1985, Canessa et al 1984, Postnov and Orlav 1985) it was hypothesised that such a reduction could lead to increased intracellular sodium levels, which in turn could sensitise the arteriolar smooth muscle cells to the presser effects of catecholamines and angiotensin II. However, it has been demonstrated that insulin-dependent Na⁺-K⁺ ATPase activity is unrelated to the stimulatory effect of insulin on glucose metabolism (Ferrannini et al 1988) and therefore it seems less likely that resistance to insulin’s glucoregulatory effects also extends to its effects on the Na⁺-K⁺ ATPase enzyme.

Further, overactivity of the Na⁺-H⁺-antiporter could result in increased sodium levels inside the cell, which would sensitise vascular smooth muscle cells to the effects of various presser amine (Adragne et al 1982, Canessa et al 1987, Weder 1986). In addition, increased sodium levels could result in an indirect increase in intracellular calcium concentration which would also cause an increase in vascular tone. Finally, an increase in the activity of this proton pump would lead to intracellular alkalinization which is a stimulus for vascular smooth muscle growth (Lever 1986).

Insulin has a marked effect on intracellular calcium concentration (Sowers et al 1994). It has been demonstrated that insulin attenuates vascular calcium influx through receptor and voltage-operated calcium channels. In addition, insulin also modulates the activity of Ca²⁺-ATPase, which extrudes calcium from cells (Standley et al 1993). Resistance to these effects would cause an increase in intracellular calcium levels and a consequent vascular tone and blood pressure.

Other effects of insulin: insulin regulates the lipid metabolism via its effect on lipoprotein lipase enzyme (LPL) (Garfinkel et al 1976, Murase et al 1981). LPL plays crucial roles in both triglyceride and HDL cholesterol production. Diabetes mellitus (IDDM and NIDDM) is characterised by hypertriglyceridemia and reduced HDL (Reaven 1988, Haward 1987). Recently there has been increasing association between triglycerides and increased risk of cardiovascular disease (CVD) (Austin 1991), a risk that is especially high in subjects with low HDL cholesterol (Castelli 1986, National Institute of Health 1993). Because diabetes is a risk factor for CVD (American Diabetes Association 1989), an association of hypertriglyceridemia with low HDL cholesterol in diabetic subjects should increase the risk
for CVD, and thus, the combined lipid abnormalities must be considered. Moreover, hyperlipidemia also has a potential pathogenic role in progressive glomerular injury (Moorhead et al 1982). An increase in dietary cholesterol was found to favour development of glomerulosclerosis in experimental animals (Virchow 1860, French et al 1967). Reduction in lipid levels was found to reduce glomerular injury in experimental models of uraemia and nephrotic syndrome (Kasiske et al 1988, Harris et al 1990).

NIDDM patients are resistant to the actions of insulin and are often hyperinsulinemic. In such subjects another factor contributing to hyperlipidemia is the increased output of hepatic VLDL (Bourgeois et al 1995). Insulin administration in humans was found to suppress hepatic VLDL secretion (Lewis et al 1993). It has been proposed that the high output of VLDL in the presence of chronic hyperinsulinemia results from a diminished hepatic sensitivity to the normal inhibitory effect of insulin on VLDL release (Bartlett and Gibbons 1988, Gibbons 1989).

**Body Fat:** Obese subjects demonstrate adaptive changes in sodium metabolism and vascular hemodynamics comparable to those in diabetes. A causal relationship between salt and blood pressure in obesity has been proposed. Diets low in sodium but with normal calorie counts can decrease blood pressure in obese hypertensives (Dahl et al 1958), and sodium-sensitive blood pressure responses are found in obese adolescents (Rocchini et al 1989). Salt-sensitive blood pressure in obesity may be secondary to increased cardiac output and plasma volume, and the degree to which blood pressure responds to salt is directly correlated with insulin levels (Rocchini et al 1989). However, studies examining the mechanisms of the hypotensive effect of weight loss show that blood pressure can fall substantially, independent of sodium intake and excretion (Tuck et al 1981, Reisin et al 1987). Thus sodium may play different role during weight maintenance and weight loss. The reductions in PRA (Tuck et al 1981) and plasma catecholamines (Tuck et al 1983) with weight loss in obese subjects could also contribute to the hypotensive effect of sodium.

**Diagnosis of insulin resistance**

Insulin-stimulated glucose disposal (ISGD) is the key to the effectiveness of insulin in controlling blood glucose levels. Even among healthy subjects, there are remarkable
variations in the ability of insulin to promote glucose disposal, that is, there is considerable variation in insulin sensitivity among individuals (Akinmokun et al. 1992). Healthy subjects tend to adjust their insulin secretion (IS) to their ISGD, so that ISGD:IS remains constant (Bergman 1989). A large number of euglycemic subjects have been reported to have a reduced ISGD (in other words they are insulin resistant), which is compensated for by insulin hypersecretion. This results in hyperinsulinemia. Hyperinsulinemia can lead to a constellation of metabolic alterations causing an increase in cardiovascular risk (hypertension, obesity, dyslipidemia, atherogenesis). On the other hand in cases where the increase in insulin secretion is not enough to compensate for insulin resistance, glucose intolerance or NIDDM follow (Bergman 1989).

As the importance of insulin sensitivity assessment has now been recognised, many methods for in vivo assessment of insulin resistance have been developed. These methods may be classified as follows:

1. Closed-loop methods
2. Open-loop methods.
3. Model methods

1. Closed-loop methods: Himsworth (1936), Yalow and Berson (1960) and Alexander et al. (1969) have assessed insulin sensitivity by closed-loop approach. In these methods the changes in plasma insulin levels induce changes in the plasma glucose level. The change in plasma glucose level in turn alters the secretion of insulin and counter-regulatory hormones. The interrelationship between beta islet cells and peripheral insulin sensitive tissues prevents the separate evaluation of beta islet cell or peripheral tissue dysfunction.

2. Open-loop methods: In these methods insulin and/or glucose levels are fixed and the physiological feedback loop between peripheral tissues and beta islet cells is interrupted. By interruption of this loop it is possible to control both plasma glucose and plasma insulin levels; at the same time separate evaluation of the function of beta islet cells and peripheral tissue is possible. The two main techniques that use an open-loop approach are (a) glucose clamps, and (b) insulin suppression tests.
(a) **Glucose clamp method:** The euglycemic - hyperinsulinemic glucose clamp is the most usual variant of the glucose clamp method. In this method, glucose is administered exogenously so that the plasma glucose levels are maintained at approximately 5 mmol/L. Insulin, in a high dose of 40 mlU/m²/min or 1 mlU/Kg/min is infused systemically. The insulin infusion causes a reduction in the plasma glucose levels as insulin tends to increase peripheral glucose uptake and to reduce exogenous glucose output. The rate of glucose infusion is calculated to match the total reduction in the plasma glucose level induced by the insulin infusion. Blood sampling is performed every 5 minutes and when the plasma glucose levels attain a steady-state, the rate of exogenous glucose infusion provides a quantitative measure of the net effect of the insulin infusion on the endogenous production and utilization of glucose. Once the steady-state glucose levels have been achieved the rate of glucose infusion approximates the rate of glucose disposal by extrahepatic tissues. This is because liver usually takes up minimal amounts of glucose in the euglycemic state, and produces minimal glucose in the presence of hyperinsulinemia.

Although the rate of glucose infusion has been the most widely used measure of insulin sensitivity in glucose clamp techniques, the Michaelis-Menten parameters of insulin action in vivo ($K_m$ and $V_{max}$) can also be calculated in dose-response studies. In addition an insulin sensitivity index ($S_I$), defined as glucose disposal rate / (insulin concentration glucose concentration), has also been proposed.

The glucose clamp method can be combined with the infusion of radiolabelled glucose; by an isotopic dilution calculation, the effects of insulin on hepatic and extrahepatic tissues can be directly assessed. Indirect calorimetry may be used in combination with the glucose clamp, so that the effects of insulin resistance on the pattern of intracellular metabolism can be estimated. This is achieved by measuring oxygen consumption, carbon dioxide production and urinary protein excretion.

Organ perfusion techniques are an approach related to glucose clamp method. This method is invasive and technically difficult. In this method the tissue glucose uptake is measured by multiplying the arteriovenous difference in plasma glucose level by the rate of blood flow across an organ (Zierler 1961). Insulin resistance can be estimated from the ratio of plasma insulin level to tissue glucose uptake. Simultaneous measurement of glucose uptake and release can be achieved when this method is applied to the liver and...
combined with isotopic glucose infusion. One of the drawbacks of this method is that blood flow measurements are often not reproducible and glucose uptake across a particular tissue bed may not extrapolate to whole body glucose uptake.

(b) Insulin-suppression test (IST): This method measures the combined effects of hyperglycemia and hyperinsulinemia on glucose disposal. Shen et al (1970) introduced this method in which a constant intravenous infusion of glucose and insulin is given. Endogenous insulin secretion is pharmacologically suppressed with somatostatin or octreotide. Once a steady state is achieved, a similar plasma insulin concentration in the upper physiological range, is usually attained in all subjects tested. Glucose disposal at steady state equals glucose infusion plus endogenous glucose output. In situations of hyperinsulinemia (where hyperinsulinemia prevents significant output of glucose from the liver), the steady state plasma glucose level can be used as an index of insulin resistance. When insulin action is reduced, plasma glucose levels increase until the decrease in insulin-stimulated glucose disposal is compensated for by the physiological effects of hyperglycemia. In this method the preferred index for insulin sensitivity is the quotient: glucose infusion rate/steady state plasma glucose level.

3. Model methods: Insulin sensitivity for a tissue is assessed by using a physiological model and by analysing the rate of decline in plasma glucose levels and the pattern of insulin response after a glucose load.

Bergman et al (1979) have described a procedure (Minimal model) in which plasma and insulin levels are frequently sampled after an intravenous bolus of glucose. Intravenous bolus of insulin or tolbutamide is administered after 20 minutes in a modified form of this method. The data are obtained simply but the analysis and interpretation of data are complex. Furthermore this method has a few limitations which are as follows:

1. the analysis and interpretation of data depends on the adequacy of the model's assumptions and simplifications, and also on the ability of the model to accurately identify the data.
the Modified Minimal Model depends on the assumption that exogenous insulin or tolbutamide have the same effect on glucose metabolism as physiological secretion of insulin.

(3) it is difficult to distinguish between the effects of insulin on hepatic and peripheral tissues. The limitations of the model are particularly important when insulin secretion is impaired or when plasma glucose levels are changing rapidly (Alzaid and Rizza 1993). However, despite these limitations Bergman et al (Bergman et al. 1979) have reported that the insulin sensitivity index obtained by this method correlates with that obtained by the glucose clamp technique.

The Continuous Infusion of Glucose with Model Assessment (CIGMA) and the Homeostasis Model Assessment (HOMA) use an approach similar to Minimal Model. Results obtained from CIGMA reportedly have excellent correlation with those obtained by the glucose clamp method, but the adequacy of model assumptions is a limitation here. Moreover, the validity of CIGMA is confounded by the presence of glucosuria (Hosker et al. 1985). HOMA is simple and inexpensive, however it is poorly reproducible and its correlation with insulin sensitivity determined by the glucose clamp method is poor.

In conclusion we can say that the euglycemic-hyperinsulinemic glucose clamp method is the gold standard for measurement of insulin action. Interpretation of results by this method is simple when compared with other methods as the physiologic glucose level is maintained constant in all patients. However IST is adequate in most circumstances and is much simpler to perform.

Choice of antihypertensives in patients with insulin resistance

Hypertension is associated with increased incidences of cardiovascular diseases such as stroke, myocardial infarction (MI), congestive heart failure (CHF), peripheral artery disease, and renal insufficiency (Collins et al. 1990). Several interventional studies have demonstrated that this risk is reversible and the increased cardiovascular morbidity and mortality associated with hypertension can be reduced by antihypertensive therapy. Reduction of blood pressure prolongs survival by avoiding stroke, renal insufficiency, MI and the vascular lesions and organ damage typical of sudden, marked and prolonged
increase in blood pressure (Mancia 1991). While selecting the antihypertensive/s the overall risk profile of the patient must be evaluated. Effect of a given antihypertensive agent on glycemic control, lipid profile, left ventricular hypertrophy, albuminuria, insulin levels, age, presence or type of end organ damage must be carefully considered.

The issue that hyperinsulinemia antedates essential hypertension has been addressed in the previous sections. Hyperinsulinemia appears to be a compensatory phenomenon due to resistance that develops to the effects of insulin on several tissues, particularly the skeletal muscle. High insulin levels affect the sympathetic nervous system, sodium handling by the kidney, glucose homeostasis, the lipid metabolism and vascular functions. Insulin resistance also aggravates the risk of CAD. In the light of these it is essential to evaluate the efficacy of antihypertensives with respect to metabolic effects, reduction in vascular complications and risks of hypertension and diabetes, if the patient has both diabetes and hypertension.

**Diuretics:** Diuretics are effective and inexpensive drugs that still retain their place as first choice agents, particularly in the elderly patients. Diuretics are effective not only as monotherapy but also play a key role as part of a combined regimen in particular subsets of the population, including patients with refractory hypertension, the elderly, the obese, black patients and those with renal insufficiency (Petrie et al 1975). Diuretics effectively check abnormal sodium retention and exaggerated cardiovascular pressure reactivity, the most common pathophysiological features that occur when diabetes and hypertension coexist (DeChatelet et al 1977, Weidmann et al 1979). Further, the SHEP study (1991) has demonstrated that thiazide diuretics prevent CAD and stroke.

The disadvantages of diuretics principally relate to their adverse metabolic and clinical effects. Many of these adverse reactions are mainly dose dependent and may be avoided or minimised in some patients by using the appropriate hypotensive dose schedule (Aranda et al 1990) and not proceeding to an unnecessarily high dose. These adverse reactions include hyperurecemia (which may lead to gout), hypokalaemia, dyslipidemia and impaired glucose tolerance. Hypokalaemia and hypomagnesemia are of great concern as they can produce cardiac arrhythmias (Mc Lenachan et al 1987). Warram et al (1991) have reported that despite effective blood pressure control, diuretic therapy may actually increase the risk of CAD in hypertensive diabetic patients receiving diuretics.
as the only antihypertensive drug. Diuretics may thus hamper the beneficial effect of improved hypertension on CAD and other vascular complications (Ames 1983).

Glucose intolerance may be precipitated or the onset of diabetes triggered, especially in susceptible and obese patients or those with a family history of diabetes. At higher doses, diuretics impair glucose homeostasis in NIDDM patients (Wilson et al 1986). Pollare et al (1988) have shown that a 4-month treatment with hydrochlorothiazide (40 ± 12 mg/day) decreased insulin-mediated glucose disposal by approximately 11 % (from 5.7 to 6.3 mg/Kg/min) in 50 patients with essential hypertension. Beine et al (1991) also confirmed that a treatment with hydrochlorothiazide for more than 2 years decreased insulin-mediated glucose disposal from 6.3 to 5.2 mg/Kg/min in 10 patients with essential hypertension. The mechanism underlying this appears to be related to hypokalemia which causes suppression of pancreatic release of insulin (Helderman et al 1983). It may also depend on a failure of patients with diabetes mellitus to increase the number of their insulin receptors, as occurs with non-diabetic patients during thiazide treatment (Gill et al 1984). These effects may be prevented by maintaining suitable levels of potassium (Helderman et al 1983). However, supplementation of potassium may not be possible in presence of poor renal function, hyporenemic hypoaldosteronism.

Modest increase in total cholesterol, LDL, VLDL and triglycerides, all of which are atherogenic, are reported with the use of high doses of thiazide diuretics (Thompson 1990). However, this effect may be attenuated after several months of diuretic therapy (Weidmann et al 1985).

Thiazide diuretics are recommended by some, as a first-line drug for NIDDM patients based on the fact that these patients have increased levels of total body sodium and water (Feldt-Rasmussen et al 1987, DeChatel et al 1986, O'Hare et al 1985). However, the deleterious effects of thiazide diuretics on electrolyte levels and on VLDL and LDL levels can have damaging coronary effects. Furthermore, thiazide diuretics may decrease insulin sensitivity (Kendall et al 1988), making diabetic control more difficult. Thiazide diuretics also have, at least, in non-diabetic essential hypertensive patients, a comparatively weak regressive effect on left ventricular hypertrophy (LVH) (Bohlen et al 1994).
Indapamide, a non-thiazide diuretic, does not appear to have deleterious side effects on diabetic control and serum lipids (Kendall et al 1988). However, unless diuretics are needed for reasons other than hypertension, treatment of diabetic patients with thiazides or loop diuretics in conventional dosage should probably be avoided until the influence of these agents on prognosis is clarified.

**Vasodilators**: Hydralazine is commonly used now as third line drug for the treatment of hypertension. Hydralazine exerts a direct relaxant effect on vascular smooth muscle (Spokas et al 1963) and this causes a marked reduction in systemic vascular resistance with an increase in cardiac output (Conradson et al 1984). The ability of hydralazine to lower blood lipids has been reported by several workers (Deming et al 1956, Perry and Mills 1962) and this could be advantageous to diabetic patients. It has been reported that hydralazine does not alter glucose tolerance in humans and is beneficial in preventing coronary and other atherosclerotic diseases that accompany diabetes mellitus (Rodrigues et al 1986).

Alpha₁-adrenoceptor antagonists (alpha-blockers) are vasodilators that act upon arterioles and veins. Prazosin and the newer, longer-acting doxazocin and terazocin are among the vasodilators being used clinically. In recent reports published by the American Heart Association, the WHO and the International Society of Hypertension, alpha-blockers have been included as first-line therapy for hypertension. The specificity of these drugs for alpha₁ adrenoceptors induces relaxation of vascular smooth muscle with little reflex stimulation of cardiac output since catecholamine release is modulated via non-blocked alpha₂ receptors. The favourable haemodynamic effects translate into a lesser fall in systolic blood pressure but a better preservation of performance ability than with beta-blockers. Alpha-blockers may be used in patients with peripheral vascular disease. Vasodilators increase renal blood flow and may have a beneficial effect on renal function (Brazy et al 1989, Spitalewitz et al 1986).

Information about treatment with alpha-blockers in diabetics is scarce, but glucose tolerance seems to be unaffected by therapy with prazosin or doxazosin (Trost et al 1987, Weidmann et al 1985). In one study prazosin has been shown to increase plasma glucose levels in diabetic patients (Barbieri et al 1980). In contrast, another study demonstrated that chronic therapy with prazosin (3 mg/day) for a week significantly
improved glucose tolerance with slight increase in insulin levels in diabetic patients (Barbieri et al 1981). Goyal et al (1996) have reported that chronic treatment with prazosin does not alter hyperglycemia, hyperlipidemia and hypoinsulinemia in STZ-diabetic Wistar rats. Long term treatment with prazosin (mean dose 5.3 ± 1.6 mg/day) has been shown to increase insulin sensitivity assessed by the glucose clamp technique (Pollare et al 1988). Similar studies with longer acting alpha-blockers are lacking. Another advantage with alpha-blockers is that they lower the potentially atherogenic total and low density lipoprotein cholesterol and triglyceride levels and increase the antiatherogenic HDL cholesterol concentrations (Lardinois and Neuman 1988).

Orthostatic hypotension and retrograde ejaculation in particular may aggravate already existing problems in diabetics with even minor neuropathy. Postural hypotension is probably one of the reasons the alpha-blockers (particularly prazosin) have been used less frequently. However, postural hypotension may not be a significant problem with the longer acting alpha-blockers.

**Beta-adrenoceptor antagonists (beta-blockers):** These agents, along with diuretics, have been a cornerstone of antihypertensive therapy for the last 20 years. The principal non-selective beta blocker group includes propranolol, pindolol, sotalol, timolol and alprenolol. The principal cardioselective agents are atenolol, metoprolol and acebutalol. There are quite a few other beta-blockers with a vasodilatory component or with a partial agonist/intrinsic sympathomimetic activity (oxprenolol, celiprolol, pindolol, acebutolol), with additional alpha-adrenoceptor blocking activity (labetolol, carvedilol) or with additional non-specific vasodilatory quality (bucindolol, celiprolol).

In addition to their proven efficacy at lowering blood pressure, either alone or in combination, beta-blockers have a number of ancillary actions which may be useful in the management of individual patients with hypertension. These additional effects may be useful for the relief of anxiety and related symptoms (especially with lipid soluble drugs such as propranolol), as anti-anginal therapy and for their antiarrhythmic actions.

**Beta-blockers should be avoided in diabetics on insulin as they mask the adrenergically mediated symptoms of hypoglycemia via their non-selective beta-adrenoceptor blocking effect.** Beta-blockers not only prolong hypoglycemic episodes by
blocking glycogenolysis in muscles and lipolysis in adipose tissue, thereby reducing substrates for both gluconeogenesis and ketogenesis (Christlieb and Maki 1980) but also delay the counterregulatory response to hypoglycemia since glucagon secretion is also stimulated through beta_2-receptors which increases the risk of serious consequences of severe hypoglycemia (Newman 1976, Popp et al 1985).

Non-selective beta-blockers, in particular, promote insulin-induced hypoglycemia and peripheral ischaemia (as beta_2-mediated dilation no longer exists) leading to aggravation of microvascular disease in diabetics and insulin-induced hypoglycemia. Furthermore, blockade of beta_2 receptors by non-selective beta-blockers can provoke hypertensive crisis during hypoglycemia, as overstimulated alpha receptor-dominated arteriolar constriction is no longer counterbalanced by beta_2-mediated dilation (Ryan et al 1985). This effect can be avoided by the use of cardioselective beta-blockers.

Antihypertensive treatment with non-selective beta-blockers has been shown to worsen glucose tolerance (Stein and Black 1991). This probably may be due to impaired insulin secretion as a result of beta_2-blockade since insulin secretion is stimulated through beta_2 receptors, eventually leading to impaired glucose homeostasis. Studies conducted in by Pollare et al (1989b,c) have revealed that treatment with metaprolol and atenolol decreases insulin sensitivity in diabetic patients. These observations suggest that cardioselective beta-adrenoceptor blocking drugs can also impair glucose homeostasis. Pollare et al (1989b) showed that treatment with atenolol for 6 months decreased insulin sensitivity by 21%. This was accompanied by significant fasting hyperinsulinemia and increase in blood glucose and glycosylated hemoglobin. In another study, four months treatment either with metaprolol, 100 mg twice daily and atenolol, 25 mg twice daily decreased insulin sensitivity by 20 and 13 % respectively (Pollare et al 1989c). This was accompanied with a concomitant increase in fasting plasma insulin, blood glucose and glycosylated haemoglobin concentrations. Satia et al. (1995) reported that atenolol does not produce significant changes in blood glucose levels in hypertensive and diabetic-hypertensive patients.

Beta-blockers also have effects on plasma lipoprotein levels that may increase the cardiovascular risk. Beta-blockers increase the potentially atherogenic serum VLDL levels and decrease the antiatherogenic HDL levels (Ames 1983). This effect is less pronounced
with cardioselective beta-blockers. Several studies have shown that atenolol, 50 or 100 mg once daily, increases plasma triglycerides by 20 to 34% (Day et al 1982, Leren et al 1982, Lithel et al 1986) and VLDL levels by 28 to 46% (Day et al 1982, Lithel et al 1986). The concentration of antiatherogenic HDL cholesterol either decreased by 7% (Day et al 1982) or remained unchanged (Leren et al 1982). Total cholesterol was increased by 5% (Day et al 1982, Leren et al 1982) with such treatment. Similar changes were observed in patients with hypertension treated with atenolol, 50 to 100 mg daily from 5 months to 3 years (Fogari et al 1989, Frich et al 1987, Karlson et al 1988). Changes in triglycerides and total cholesterol levels were accompanied by an increase in VLDL cholesterol, VLDL triglycerides and apoprotein A1 levels and a decrease in levels of apoprotein AII (Chanu et al 1991, Lithell et al 1986, Vyssoulis et al 1991). Similar changes in lipid metabolism have been observed in non-insulin dependent diabetic hypertensive patients (Feher et al 1990). The increase in plasma concentrations of triglycerides associated with atenolol (24%) were less pronounced than those occurring with propranolol (51%) after 3 months treatment (Day et al 1982). However, changes in lipid concentrations tend to decrease few months after discontinuation of treatment (Fogari et al 1990, Feher et al 1988). Satia (1995) has reported that long term treatment with atenolol increases serum triglyceride levels and significantly decreases HDL cholesterol in hypertensive and diabetic-hypertensive patients.

Reduction of the blood pressure can slow the progression of diabetic nephropathy irrespective of the pharmacologic agents chosen. The use of beta-blockers as first-line agents for prevention of deterioration of kidney function is discouraged in microalbuminuric patients, therapy with metoprolol is associated with a decrease in urinary albumin excretion rate by 30-50%. However, in diabetic hypertensives with established nephropathy, the beta-blockers produce a significant reduction in the rate of decline of renal function (Parving and Hommel 1989). On the other hand, Epstein and Oster (1982) have reported that long term treatment with propranolol produced a 10-20% reduction in glomerular filtration rate (GFR) and renal blood flow (RBF). Some investigators reported that atenolol treatment to cause a marked decrease in GFR (Cook et al 1986), creatinine clearance or renal vascular resistance (Furman et al 1986), while others failed to show any significant effect on these parameters (Brater et al 1983, Satia 1995, Dreslinski et al 1982). Among other disadvantages of use of beta-blockers are that they cannot be recommended in patients with poor left ventricular function since their negative
Inotropic effect can precipitate cardiac failure in such individuals. In addition, reduced peripheral blood flow can result in cold hands and feet and precipitation of Raynaud's phenomenon. Lipid-soluble beta-blockers may cause sleep disturbances, vivid dreams and fatigue - a decrease in physical performance can result in non-compliance of the regimen particularly in younger patients.

**Centrally acting agents**: The sympathetic system has a definite role in the pathogenesis of hypertension. Excess catecholamine levels in circulation may eventually lead to cardiovascular risk factors like cardiac hypertrophy, cardiac arrhythmia, and atherosclerosis. Use of sympatholytic central alpha_2_agonists like clonidine, guanfacine, guanabenz and alpha-methyldopa, in hypertensives can directly minimize the consequences of elevated catecholamine levels.

Centrally acting agents act at the central alpha_2_adrenoceptors, decrease sympathetic outflow and thereby exert their antihypertensive effect (Baum and Shropshire 1976). Guanabenz decreases peripheral resistance which adds to its central antihypertensive effect. With centrally acting antihypertensives there are minimal changes in heart rate, myocardial contractility or cardiac output (Shah et al 1976).

Centrally acting agents do not usually alter glucose homeostasis or serum lipoproteins in non-diabetic hypertensives, but there is little substantial information about this in hypertensive diabetics. Hauger-Klevene and Scornavacchi (1985) have reported that 1-year treatment with guanfacine improves glucose tolerance in hypertensive diabetic patients. Benfield and Hunter (1982) reported that methyldopa does not alter fasting blood glucose or plasma total cholesterol concentrations in IDDM hypertensive patients. Guanabenz treatment in diabetic hypertensive patients did not alter plasma glucose levels, decreased total cholesterol concentrations and had no effect on diabetic therapy requirements (Weber et al 1984). Guthrie et al (1983) have reported that treatment with clonidine in NIDDM patients with mild hypertension, decreases glucose tolerance without any significant effect on glycemic control. Animal studies have demonstrated that subcutaneous infusion of clonidine for 10 days produces elevation of serum glucose concentration with a concomitant decrease in insulin levels (Lewis et al 1989).
In patients with renal insufficiency, clonidine and guanabenz are effective and do not produce a decline in renal function (Bauer 1983, Hoober and Sagastume 1971). There is no change in renal blood flow or GFR on long term therapy with clonidine (Schmitt and Schmitt 1969). Clonidine inhibits the renin-aldosterone axis to a moderate extent (Weber et al. 1976). Guanabenz promotes sodium and water excretion and also increases GFR in dogs (Stranadhoy et al. 1982).

Centrally acting agents are usually combined with diuretics to counteract sodium retention and this may complicate the regimen. Central adverse effects like sedation and dry mouth are undesirable. Moreover, orthostatic hypotension and sexual dysfunction may aggravate the already existing problems in diabetics even with minor neuropathy. On the whole, these agents can no longer be considered as first-line medication in hypertensive diabetics.

**Calcium antagonists:** There are three classes of calcium antagonists namely the dihydropyrimidine derivatives (nifedipine, amlodipine, nicardipine, felodipine and lacidipine), the papavarine derivatives (verapamil) and the bezothiazine derivatives (diltiazem). The newer dihydropyridines (amlodipine, felodipine, nicardipine) have a relatively greater affinity for vascular smooth muscle than for cardiac smooth muscle (Kloowski et al. 1989). This translates into more coronary and peripheral vasodilation but less depression of myocardial contractility than that seen with other calcium antagonists including nifedipine. This difference may be of clinical relevance, primarily with hypertensive patients who are in overt or incipient cardiac failure.

Calcium antagonists have comparable efficacy in their hypotensive effect with the traditionally first line beta-blockers and diuretics, such as atenolol and bendrofluazide. In patients with diabetes mellitus, calcium antagonists have several advantages. Once daily formulations exist, and as monotherapy they lower pressure efficiently (by vasodilation and without salt retention). In these patients, the antanginal, antiarrhythmic and/or cardioprotective properties of these agents are often desirable, in addition to their peripheral vasodilating properties. In contrast to diuretics, calcium antagonists usually preserve cerebral and renal blood flow. Physical exercise performance is not impaired (Kindermann et al. 1986). However, since calcium is involved in insulin secretion (Malaisse and Mathias 1991), the use of calcium antagonists in diabetic hypertensives appears to
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be objectionable. In early experiments with these agents, albeit, in isolated perfused pancreas and islet cell plasma membranes have shown a dose related decrease in insulin output with nicardipine, a dihydropyridine calcium antagonist (Marre and Fressinaud 1990). In this context, calcium antagonists may theoretically alter insulin release and consequently affect glucose tolerance in NIDDM patients and individuals with borderline glucose intolerance. Impairment of insulin secretion by nifedipine, a calcium antagonist of the same class, has been reported in non-diabetic individuals (Charles et al 1981) and in patients with impaired glucose tolerance (Giugliano et al 1980). Morris et al (1993) demonstrated that a 2-week treatment with lacidipine had no influence on insulin sensitivity evaluated by the glucose clamp technique in healthy, male volunteers. Pollare et al (1989b) demonstrated, in their randomized, double blind, parallel comparison study, that diltiazem (mean dose of 329 mg/Kg) does not produce any change in insulin mediated glucose uptake. Several other clinical trials do not show any clinically important effect on glucose tolerance when calcium antagonists are used in therapeutic doses (Collins et al 1987, Faguer de Moustier and Paoli 1990, Hedner et al 1987, Kihara 1991, Marre and Fressinaud 1960, Teborio et al 1989, Pasanisi et al 1989). This was confirmed by a continuous long term study in elderly NIDDM patients on antihypertensive monotherapy with nitrendipine that antidiabetic regimen and body weight remaining constant. No change in carbohydrate homeostasis was found for up to 5 years (Trost and Weidmann 1985a). Shah et al (1995) reported that despite decreasing serum insulin levels, chronic treatment with nifedipine did not impair glucose homeostasis in Wistar rats. Satia (1995) reported that a reduction in the dose of oral hypoglycemic agent was necessary in diabetic hypertensives treated with nifedipine.

Calcium antagonists decrease long term mortality by CAD probably because of their neutral effect on the lipid and glycemic profile (Kendall et al 1988). In the study by Trost and Weidmann (1988b), which included 30 long term lipid trials, it was concluded that calcium antagonists give no indication of an adverse effect on the serum lipid pattern in non-diabetic or NIDDM patients. Satia (1995) reported similar findings with nifedipine. Houston et al (1990) recorded significant increase in HDL, HDL-2 and apolipoprotein A-I and A-II levels after nifedipine treatment. Experiments in animal models, especially cholesterol-fed rabbits, have indicated that nifedipine may reduce accumulation of atherosclerotic components and therefore slow the progression of atherosclerotic lesions.
Calculated antagonists are better choices as antihypertensive agents in diabetic hypertensives with overt nephropathy since they effectively lower blood pressure (which leads to a reduction in decline of renal function) and have neutral effect on plasma potassium and uric acid levels (Trost and Weidmann 1988b). Other advantages of calcium antagonists (particularly the non-dihydropyridine class) are that they improve glomerular permeoselectivity, reduce glomerular sclerosis, and prevent glomerular hypertrophy, all of which lead to nephropathy.

Further investigations into the long term protection of hypertensive diabetic patients treated with calcium antagonists are essential. However, from the above studies it appears that initiation of antihypertensive treatment in diabetics with a low to moderate dose of a calcium antagonist (e.g. 10 to 20 mg nitrendipine, 120 to 240 mg slow release verapamil, 90 to 180 mg slow release diltiazem or preferably 2.5 to 5 mg amlodipine) would be far better than using a diuretic or beta-blocker. Atrioventricular conduction should be watched under verapamil and diltiazem, and carbohydrate and lipid homeostasis should be monitored with all high-dose calcium antagonists.

Angiotensin Converting Enzyme (ACE) inhibitors: The ACE inhibitors may be differentiated according to chemical class, the presence or absence of sulphhydryl grouping, pro-drug or active agent, or by their affinity for converting enzyme in vascular and other tissue (Cushman and Onoletti 1980). There are few differences in their hypotensive efficacy. Any differences are manifested in differences in onset of effect, peak effect and duration of action. The mechanism of action of ACE inhibitors relates to the renin-angiotensin system which plays a central role in cardiovascular homeostasis and in the aetiology of hypertension (Kostis 1988). ACE inhibitors inhibit the production of the powerful vasoconstrictor angiotensin II (Ang II) both in circulation and in vascular tissues and inhibit the degradation of the vasodilator peptide, bradykinin. The antihypertensive effect of ACE inhibitors is primarily due to inhibition of local Ang II production (Unger et al 1984, Unger et al 1985). Use of ACE inhibitors in diabetics is particularly advantageous since they are either neutral or may actually improve glycemic control and lipid profile (Kendall et al 1988). Several studies have demonstrated that ACE
inhibitors may reduce insulin resistance and thereby increase insulin sensitivity whilst at the same time having apparently beneficial effects on lipid and glycemic profiles (Pollare et al 1989c, Paolisso et al 1992). ACE inhibitors improve regional blood flow and this could probably lead to increased insulin sensitivity. Kodama et al (1990) have reported that captopril enhances blood flow to skeletal muscle. Other investigators have hypothesized that the potassium sparing effect of ACE inhibitors may contribute to improving insulin sensitivity (Conn 1965, Helderan et al 1983, Rowe et al 1980). Pollare et al (1999a) measured the insulin-mediated glucose uptake of patients during euglycemic clamp therapy in hypertensive individuals and found an increase with captopril of approximately 15%. Jauch et al (1987) have reported that captopril increases forearm glucose uptake during insulin infusion. These investigators suggested that increase in bradykinin levels induced by ACE blockade enhances the insulin-mediated glucose metabolism in the muscle. Other workers have reported improvement in insulin sensitivity after chronic treatment with lisinopril (Sevak and Goyal 1996) and spirapril (Parulekar et al 1997). ACE inhibitors may, in NIDDM patients, slightly ameliorate insulin resistance (Weidmann et al 1993, Weidmann et al 1988) and may tend to lower plasma glucose levels (Bergmann et al 1992). Hypoglycemic episodes in NIDDM patients when ACE inhibitors are added to standard hypoglycemic therapy, a practical demonstration of the increase in insulin sensitivity, have been reported (Arauz-Pacheco et al 1990, Ferriere et al 1985). Satia (1995) has reported that a reduction in dose of hypoglycemic agent was essential in hypertensive diabetics on enalapril. Rett et al (1988b) and Prince et al (1988) have reported beneficial changes in glycemic control in NIDDM patients on ACE inhibitor therapy. Interestingly, Prince et al (1988) did not observe significant changes in insulin sensitivity or basal hepatic glucose output during enalapril treatment in 9 hypertensive diabetics, despite improved glycosylated haemoglobin levels.

Baba et al (1993) and Allemann et al (1992) did not find any change in insulin sensitivity in insulin-sensitive, hypertensive and normotensive patients. Many other studies with different ACE inhibitors and treatment periods have demonstrated that ACE inhibitors have no appreciable effect on insulin sensitivity and glucose tolerance in individuals who have no obvious insulin resistance (Seghien et al 1992, Seefeldt et al 1990, Shionoiri et al 1987, Santoro 1992, Chan et al 1992).
Captopril 25 mg twice daily for 3 months in hypertensive patients significantly reduced total cholesterol levels, LDL cholesterol levels, total cholesterol: HDL cholesterol ration and apo C-III levels (Catalano et al 1992). In another study, enalapril 20 mg/Kg for 10 weeks did not alter the serum total and lipoprotein lipid fractions, or apolipoprotein AI and B (Ferrier et al 1992). On the other hand, Libertti and Catalano (1993) have demonstrated that enalapril significantly reduces total cholesterol, triglycerides and LDL cholesterol in patients with essential hypertension. Lisinopril (Sevak and Goyal 1996) and spirapril (Parulekar et al 1997) have been reported to prevent hyperlipidemia in STZ-diabetic Wistar rats.

ACE inhibitors are excellent for patients with CCF and effectively improve LVH (Bohlen et al 1994, Cruickshank et al 1992). ACE inhibitors have been shown to prevent LVH in animal models of hypertension (Hansson and Dahlof 1990). ACE inhibitors prevent cardiac remodelling after myocardial infarction (Pfeffer et al 1988). In STZ diabetic Wistar rats enalapril (Goyal et al 1997) and lisinopril (Sevak and Goyal 1996) have been shown to prevent LVH and cardiomyopathy.

Because of their vasodilating action ACE inhibitors may improve arterial compliance and blood flow in the limbs of hypertensive patients with claudication.

ACE inhibitors are the first choice for treating microalbuminuria or overt proteinuria in normotensive or hypertensive diabetics since they exert direct intrarenal actions, such as lowering the intraluminal pressure and the permeability to albumin of the glomerular capillaries, and this can decrease proteinuria even without a concomitant systemic reduction in blood pressure. Some ACE inhibitors can markedly reduce the progression from incipient to overt diabetic nephropathy (Ravid et al 1993, Lebowitz et al 1994, Viberti et al 1994). In patients with already established overt diabetic nephropathy, ACE inhibitors preserve the glomerular filtration rate (GFR) better than conventional antihypertensives (Weidmann et al 1995).

There are also a few potential disadvantages to ACE inhibitors. Very rarely, proteinuria may be induced (Vidt et al 1982) and falsely suggest diabetic nephropathy. The individual dosage needs to be adjusted to renal function, and since most IDDM patients become hypertensive with the onset of nephropathy, this means continuous
control of renal parameters (as well as serum potassium levels) becomes essential because renal function may be further aggravated by the drug. Renal artery stenosis or reversible kidney damage may occur (Hricik et al 1983).

Thus although ACE inhibitors appear to be better choice in treating a hypertensive diabetic, much long term clinical research remains to be done. However, it is certain that it would be preferred to try an ACE inhibitor as first line monotherapy rather than a diuretic or beta-blocker, especially with declining cardiac performance. Renal artery stenosis should be ruled out before and renal function and potassium monitored closely in patients with early nephropathy.

Conclusions: All the major classes of antihypertensives can be used in diabetics, but the thiazide diuretics and beta-blockers have metabolic side effects which make them less appropriate as first line agents. Use of beta-blockers should be avoided in diabetic hypertensives and if intended for other reasons then they should be used with extreme caution. If advising such treatment, patients, as well as their families, should be instructed about possible alterations during hypoglycemia, and serum lipid levels should be regularly monitored. The calcium antagonists and ACE inhibitors have better metabolic effects and may reduce insulin resistance. ACE inhibitors may have a renal protective effect in incipient nephropathy although the studies have been fairly short term and with small patient numbers. The alpha blockers appear to be better choice when it comes to improving the lipid profile and insulin sensitivity, however, more long term trials with these agents are also necessary before they can be used frequently in hypertensive diabetics.
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