A COMPARATIVE STUDY ON THE PREVALENCE OF MICRO AND MACRO VASCULAR COMPLICATIONS AMONG TYPE 2 DIABETIC PATIENTS WITH AND WITHOUT HYPERTENSION

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERISTY

CHENNAI – 600 032

In partial fulfillment of the regulations
For the Award of the Degree of

M.D. (GENERAL MEDICINE)

BRANCH -1, PART - II

KILPAUK MEDICAL COLLEGE
CHENNAI – 600 010

MARCH - 2007

CERTIFICATE

This is to certify that **Dr. K. SELVARAJ,** Postgraduate Student (2004 to 2007) in the Department of Medicine, Kilpauk Medical College, Chennai – 600 010, has done this dissertation **"A COMPARATIVE STUDY ON THE PREVALENCE OF MICRO AND MACRO VASCULAR COMPLICATIONS AMONG TYPE 2 DIABETIC PATIENTS WITH AND WITHOUT HYPERTENSION"** under my guidance and supervision in partial fulfillment of the regulation laid down by **THE TAMILNADU DR M.G.R MEDICAL UNIVERSITY** for the award of MD Degree in General Medicine.

Prof. THIAGAVALLI KIRUBAKARAN, M.D,
Dean,
Kilpauk Medical College and Hospital, Chennai.

Prof. S.R. SAKUNTALA, M.D.,
Professor and HOD,
Department of Medicine,
Kilpauk Medical College and Hospital, Chennai.

Date :

Place : Chennai

ACKNOWLEDGEMENT

I greatfully acknowledge and sincerely thank **Prof. THIAGAVALLI KIRUBAKARAN, M.D.,** Dean, Kilpauk Medical College, Chennai, for permitting me to utilize the facilities available in the institution for my study.

I owe my sincere gratitude to my Chief **Prof. S.R. SAKUNTALA, M.D.,** Professor and Head, Department of Medicine, Kilpauk Medical College, for her constant encouragement and guidance in all stages of this study.

I whole heartedly express my sincere thanks to **Prof. C. R. ANAND MOSES, M.D.,** Head of the Department, Dr. Ambedkar Institute of Diabetology, Kilpauk Medical College, Chennai, for his valuable guidance and support throughout my dissertation work.

I wish to thank **Dr. R. KULOTHUNGAN, M.D.,** and **Dr. N. GUNASEKARAN, M.D.,** Assistant Professors, Department of Medicine, Kilpauk Medical College, for their valuable suggestions and help rendered throughout this work.

I extend my thanks to Department of Ophthalmology, Kilpauk Medical College & Hospital, for their valuable guidance and support throughout my dissertation work.

I also extend my thanks to Technicians in Diabetic Foot Clinic, Laboratory Technicians and Statistician for their valuable support throughout my dissertation work.

I also thank my parents, colleagues, friends and staffs of our hospital, for their support of this work.

Last but not least, with sincere gratitude, I thank all the patients who contributed so much to this study, without whom the study could not have been possible.

CONTENTS

ABBREVIATIONS

ABPI	-	Ankle Brachial Pressure Index
ACE	-	Angiotensin Converting Enzyme
ADA	-	American Diabetes Association
AER	-	Albumin Excretion Rate
AGEs	-	Advanced Glycation End products
ALLHAT	-	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
ARBs	-	Angiotensin Receptor Blockers
ATP	-	Adenosine Triphosphate
BMI	-	Body Mass Index
BP	-	Blood Pressure
CABG	-	Coronary Artery Bypass Grafting
CAD	-	Coronary Artery Disease
CHD	-	Coronary Heart Disease
CNS	-	Central Nervous System
CRP	-	C-Reactive Protein
CVA	-	Cerebrovascular Accident
CVD	-	Cardiovascular Disease
DAG	-	Diacylglycerol
DM	-	Diabetes Mellitus
ECG	-	Electrocardiogram

eNOS	-	endothelial Nitric Oxide Synthase
ESRD	-	End Stage Renal Disease
Fruc-6-p	-	Fructose-6-phosphate
HDL	-	High Density Lipoprotein
HOT	-	Hypertension Optimal Treatment
ICAM	-	Inter Cellular Adhesion Molecule
JNC	-	Joint National Committee
LDL	-	Low Density Lipoprotein
LV	-	Left Ventricle
LVH	-	Left Ventricular Hypertrophy
MI	-	Myocardial Infarction
NO	-	Nitric Oxide
NPDR	-	Non Proliferative Diabetic Retinopathy
NSAIDs	-	Non-Steroidal Anti Inflammatory Drugs
OPD	-	Out Patient Department
PAI-1	-	Plasminogen Activator Inhibitor – 1
PDR	-	Proliferative Diabetic Retinopathy
PCI	-	Percutaneous Coronary Intervention
PKC	-	Protein Kinase C
PLA_2	-	Phospholipase A_2
PTCA	-	Percutaneous Transluminal Coronary Angioplasty
PVD	-	Peripheral Vascular Disease
RAAS	-	Renin Angiotensin – Aldosterone System

RBC	-	Red Blood Cell
ROS	-	Reactive Oxygen Species
RR	-	Relative Risk
SD	-	Standard Deviation
TIA	-	Transient Ischemic Attack
UKPDS	-	United Kingdom Prospective Diabetes Study
VCAM	-	Vascular Cell Adhesion Molecule
VPT	-	Vibration Perception Threshold
WBC	-	White Blood Cell

INTRODUCTION

Diabetes mellitus (DM) comprises a group of common metabolic disorders that share the phenotype of hyperglycemia. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with Diabetes and on the health care system. DM is one of the leading cause of end stage renal disease (ESRD), non traumatic lower extremity amputations and adult blindness. Diabetes is one of the leading cause of cardiovascular and cerebrovascular diseases. With increasing incidence Worldwide, DM will be a leading cause of morbidity and mortality for foreseeable future.

Hypertension is a very common comorbid condition in Diabetes. In type 2 Diabetes, Hypertension usually clusters with other components of cardiometabolic syndrome such as microalbuminuria, central obesity, insulin resistance, dyslipidemia, hypercoagulation, increased inflammation, LVH and hyperuricemia.

Hypertension, as an independent risk factor for atherogenesis, synergizes with effects of diabetes and significantly increases the development and progression of coronary artery disease, cerebrovascular disease and peripheral vascular disease. Hypertension also predisposes to the development of certain microvascular complications of diabetes such as nephropathy and retinopathy.

Diabetes and hypertension are the 2 important causes of morbidity and mortality and imposing a tremendous burden on health care system.

AIM OF THE STUDY

- To compare the prevalence of Micro and Macrovascular complications of diabetes mellitus among type 2 DM patients, with and without hypertension.

- To study the influence of hypertension on the vascular complications of type 2 DM.

REVIEW OF LITERATURE

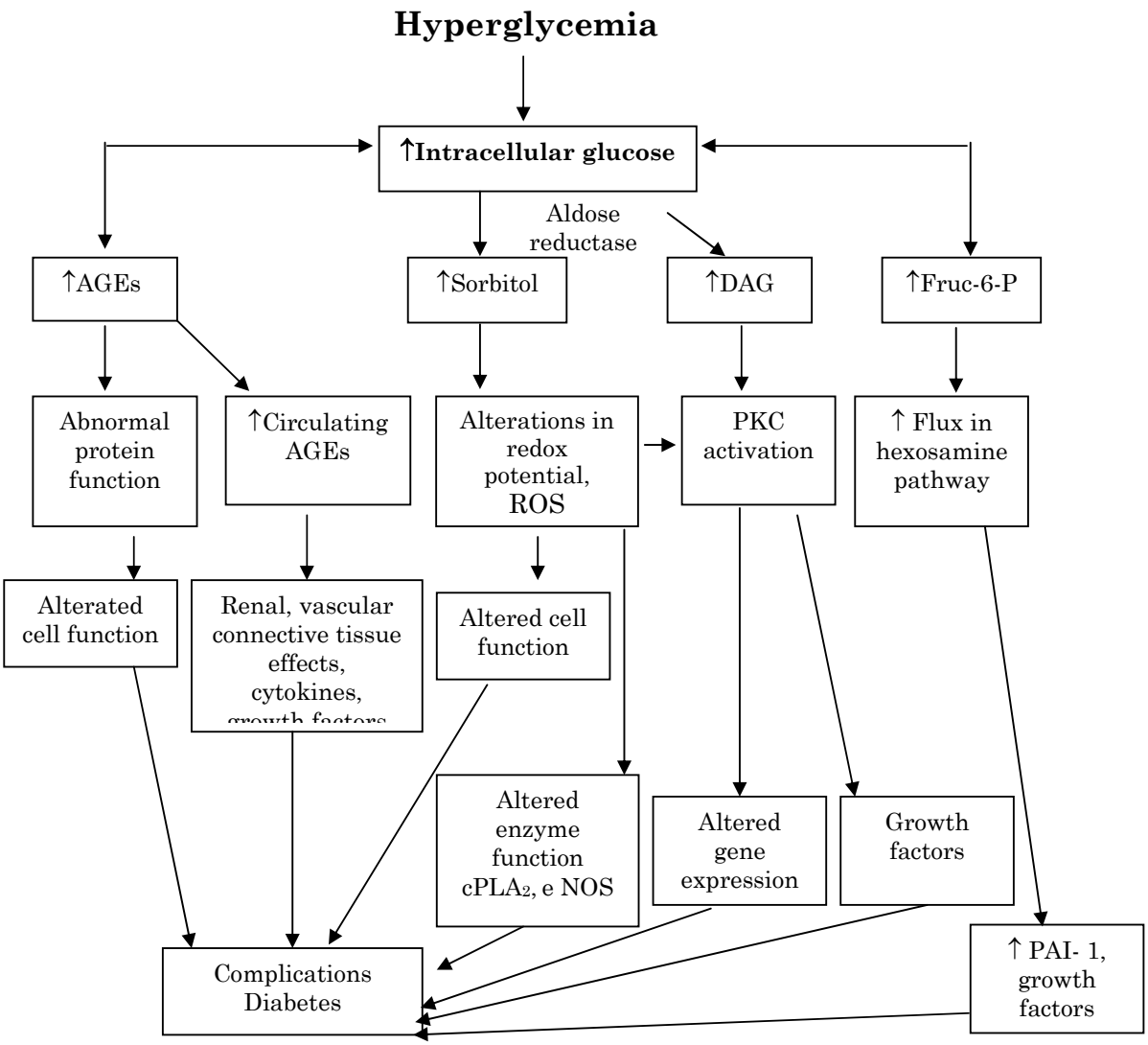
CHRONIC COMPLICATIONS OF DIABETES MELLITUS

The chronic complications of DM affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease.

Chronic complications can be divided into vascular and non-vascular complications

Vascular	Non Vascular
Microvascular Eye Disease - Retinopathy (Non proliferative / proliferative) - Macular Edema Neuropathy - Sensory and Motor - Autonomic Nephropathy **Macrovascular** Coronary Artery Disease Peripheral Vascular Disease Cerebrovascular Disease	- Gastrointestinal (Gastroparesis, Diarrhea) - Genitourinary (Uropathy / Sexual Dysfunction) - Dermatologic - Infectious - Cataract - Glaucoma

MOLECULAR MECHANISMS OF DIABETES RELATED COMPLICATIONS



MICROVASCULAR COMPLICATIONS OF DIABETES

Diabetic Neuropathy

Diabetic neuropathy occurs commonly in individuals with long standing Type 1 or Type 2 DM. The development of neuropathy correlates with the duration of diabetes and glycemic control. Both myelinated and unmyelinated nerve fibers are lost.

Pathogenesis of Diabetic Neuropathy

Hyperglycemia is the central factor. Following mechanisms mediates the effects of chronic hyperglycemia in the pathogenesis of diabetic neuropathy :-

- Genetic predisposition
- Nerve hypoxia / ischemia[1]
- Oxidative stress[2]
- Overactivity of polyol pathway[3]
- Increased advanced glycation end products[4]
- Deficiency of γ- linolenic acid
- Protein Kinase C, especially increase in β - isoform.
- Growth factors deficiency
- Dysimmune mechanism

Classification of Diabetic Neuropathy

Symmetric Neuropathies	Focal and multifocal neuropathies
Distal symmetric sensori motor polyneuropathy	Cranial neuropathy
Autonomic neuropathy	Thoraco abdominal neuropathy
Acute painful neuropathy	Focal limb neuropathy
Hyperglycemic neuropathy	Diabetic amyotrophy
Treatment induced neuropathy	
Symmetric proximal lower extremity neuropathy	

Autonomic Neuropathy

Individuals with long standing type 1 or type 2 DM may develop signs of autonomic dysfunction involving the cholinergic, noradrenergic and peptidergic systems. DM related autonomic neuropathy can involve multiple systems, including the cardiovascular, gastrointestinal, genitourinary, sudomotor, and metabolic systems. Autonomic neuropathy may reduce counter regulatory hormone release, leading to an inability to sense hypoglycemia appropriately, thereby subjecting the patient to the risk of severe hypoglycemia and complicating efforts to improve glycemic control.

Treatment of Diabetic Neuropathy

Treatment of diabetic neuropathy is less satisfactory. Symptoms of diabetic neuropathy improves less even after proper glycemic control. Efforts to improve glycemic control may be confounded by autonomic neuropathy and hypoglycemia unawareness. Avoidance of neurotoxins (alcohol), supplementation for possible deficiencies (B12, B6, Folate) and symptomatic treatment are the mainstays of therapy. Loss of sensation in the foot places the patient at risk for ulceration and its sequelae. Prevention of such problems is important. Chronic painful diabetic neuropathy is difficult to treat, but may respond to tricyclic antidepressants, gabapentin, NSAIDs and other agents such as Mexilitine, phenytoin, Carbamazepine and Capsaicin cream.

Therapy of orthostatic hypotension secondary to autonomic neuropathy is challenging. A variety of agents such as fludrocortisone, midodrine, clonidine, octreotide and yohimbine have been tried. Non pharmacologic maneuvers (adequate salt intake, avoidance of dehydration and diuretics and lower extremity support hose) offer some benefit.

Diabetic Retinopathy

Diabetic retinopathy is one of the leading cause of adult blindness. Duration of DM and degree of glycemic control are the best predictors of the development of retinopathy. Hypertension is one of the most important risk factor. Because diabetic retinopathy is often asymptomatic in its most treatable stages, early detection of retinopathy through regularly scheduled ocular examination is critical. Blindness usually results from non-resolving vitreous haemorrhage, traction retinal detachment or diabetic macular edema. In type 2 DM, most often patients have retinopathy at diagnosis, reflecting its long asymptomatic period of hyperglycemia in type 2 DM.

UKPDS[5,6] enrolled 3,687 patients with newly diagnosed type 2 diabetes. Intensive therapy to control blood glucose, using either sulfonylureas or Insulin resulted in a 17% risk reduction for progression of diabetic retinopathy, a 29% risk reduction in the need for laser photocoagulation surgery, a 23% risk reduction for the development of vitreous haemorrhage and a 16% risk reduction in legal blindness.

Conditions that may affect course of diabetic retinopathy

- Hypertension[7]
- Elevated lipids [8]
- Proteinuria; elevated creatinine level[9]
- Cardiovascular disease

International classification of Diabetic retinopathy[10]

5 Clinical levels of DR :

- No apparent retinopathy (No abnormality).
- Mild non proliferative diabetic retinopathy (NPDR) (Microaneurysms only).
- Moderate NPDR (more than microaneurysms only but less than severe NPDR).
- Severe NPDR (any of the following : > 20 Intraretinal haemorrhages in each 4 quadrants, definite venous beading in 2+ Quadrants, prominent intraretinal microvascular abnormalities in 1+ quadrant and no PDR).
- Proliferative Diabetic retinopathy (PDR) (1 or more of retinal neovascularization, vitreous haemorrhage or preretinal haemorrhage).

International clinical Diabetic macular edema scale[10]

2 broad levels

1. Macular edema apparently absent (No apparent retinal thickening or hard exudates in posterior pole).

2. Macular edema apparently present.

Mild – Some apparent retinal thickening or hard exudates in posterior pole but distant from centre of macula.

Moderate – Retinal thickening or hard exudates approaching centre of macula but not involving centre.

Severe - retinal thickening or hard exudates involving centre of macula.

Treatment of Diabetic Retinopathy

The most effective therapy for diabetic retinopathy is prevention. Intensive glycemic and BP control will delay the development or slow the progression of retinopathy in individuals with either type 1 or type 2 DM. Individuals with known retinopathy are candidates for prophylactic photocoagulation, while initiating intensive therapy. Once advanced retinopathy is present, improved glycemic control imparts less benefit, though adequate ophthalmologic care can prevent most of blindness. Regular,

comprehensive eye examinations are essential for all individuals with DM. Most diabetic eye disease can be successfully treated if detected early. Laser photocoagulation is very successful in preserving vision. Proliferative retinopathy is treated with panretinal laser photocoagulation, whereas macular edema is treated with focal laser photocoagulation.

Diabetic Nephropathy

Diabetic nephropathy occurs in 30-50% of patients with type 1 or type 2 diabetes[11] and is the leading cause of Endstage renal disease worldwide. The increasing incidence of diabetic nephropathy in patients with type 2 DM is in part, the result of greater success in decreasing mortality due to type 2 diabetes. Improved management of cardiovascular complications of type 2 diabetes through better control of lipids and improved and more stringent BP control has significantly increased life expectancy and the time for other complications to develop.

One of the earliest sign of renal involvement in diabetes is an increase in albumin excretion[12] (30-300 mg/day) Albumin excretion rate (AER) varies from 20-200 μg/minute. This stage is referred to as the "Microalbuminuria" stage which is albustix negative. Its therapeutic importance lies on the fact that it is reversible by tight

glycemic control. With further progression of Diabetic nephropathy, persistent albuminuria is referred to as "Macroalbuminuria" heralding the onset of clinical Diabetic nephropathy. At this stage, urinary albumin excretion is > 300 mg/day and AER > 200 μg/min. Macroalbuminuria is albustix positive.

Hypertension plays a critical role in the progression of Diabetic nephropathy. Indeed, the development of proteinuria is paralleled in most cases by a gradual rise in systemic BP. There is a significant correlation between BP levels and rate of decline in glomerular filtration rate[13]. Interventional studies in humans and animals have demonstrated significant renoprotective and antiproteinuric effects of antihypertensive therapy[14].

In diabetic nephropathy, hypertension is not merely the result of relentless kidney damage, there is clinical evidence that elevated BP is also important in genesis of glomerular lesion. Prospective studies in type 1 and type 2 diabetic subjects have demonstrated that mean arterial BP levels are significantly higher in those who progress to microalbuminuria, that in those who do not progress[15].

Under normal conditions, intraglomerular capillary pressure is tightly regulated by pressure adjustments in afferent and

efferent arteriolar resistance. Hyperglycemia induces vasodilatation and in diabetes, there is marked reduction in afferent and a lesser reduction in efferent arteriolar resistance. This leads to an increase in the levels of glomerular capillary pressure and moreover allows ready transmission of any increase in systemic BP to the glomerular capillary network[16].

Diagnosis of Diabetic Nephropathy

100% of patients with Diabetic nephropathy have albuminuria. Its absence should seek an alternate diagnosis.

The urinary sediment is unremarkable – There are usually no casts, no RBCs and no WBCs.

Majority of patients have retinopathy before the onset of diabetic kidney disease.

Duration of the disease is also important. It is unusual to diagnose diabetic nephropathy before 5 years of Diabetes. Deviation from any of the above association should prompt a search for alternative diagnosis in a patient with diabetic kidney disease.

Treatment of Diabetic Nephropathy

The optimal therapy for diabetic nephropathy is prevention. Microalbuminuria should be detected at an early stage, when

effective therapies can be instituted. Interventions effective in slowing the progression from microalbuminuria to overt nephropathy include 1) near normalization of glycemia 2) strict BP control 3) administration of ACE inhibitors or ARBs and 4) treatment of dyslipidemia.

During the phase of declining renal function, insulin requirements may fall as the kidney is a site of insulin degradation. Oral hypoglycemic drugs are contraindicated in advanced renal insufficiency.

Numerous studies in both type 1 and type 2 DM demonstrate the effectiveness of strict BP control in reducing albumin excretion and slowing the decline in renal function. BP should be maintained at < 130/80mmHg in diabetic individuals without proteinuria. A target of < 125/75mmHg should be considered for individuals with proteinuria > 1g/day.

ACE inhibitors and ARBs reduce the progression of overt nephropathy and should be prescribed in individuals with type 1 or type 2 DM and microalbuminuria.

Nephrology consultation should be considered after the diagnosis of early incipient nephropathy. The risk of complications during hemodialysis in Diabetic patients is more when compared to

non diabetic patients. Atherosclerosis is the leading cause of death in diabetic individual on dialysis. Renal transplantation from a living related donor is the preferred therapy. Combined pancreas-kidney transplant offers the promise of normoglycemia.

MACROVASCULAR COMPLICATIONS

Coronary artery disease

Diabetes mellitus is a major independent risk factor for cardiovascular disease[17] (CVD). Increased prevalence of CVD in diabetes has been attributed to the acceleration of coronary atherosclerosis, which occurs at earlier age and advances more rapidly to clinical cardiovascular events in individuals with diabetes than those without diabetes[18]. Coronary heart disease (CHD) in diabetes is diffuse with increase in number of affected vessels. Furthermore, autonomic neuropathy in patients with diabetes reduce the symptoms of CHD[19], delay its detection and worsen the prognosis. Diabetic individuals are faced with increased restenosis and mortality rates following revascularization procedures especially for percutaneous transluminal coronary angioplasty (PTCA).

Hypertension is a major CVD risk factor that often coexists with Insulin resistance and diabetes[20]. The UKPDS[21] has shown that tight BP control substantially reduces the risk of

macrovascular events in patients with type 2 DM. This study showed that for each 10mmHg reduction from ≤ 160 to < 120 mm Hg of systolic BP, there was 11% reduction in myocardial Infarction. Combination of CVD risk factors frequently coexist in individuals with Insulin resistance and diabetes. Because these CVD risk factors can develop years before the onset of type 2 DM, it is likely that pathogenesis of CVD in patients with type 2 DM begins well before the diagnosis of diabetes.

RISK FACTORS FOR CVD IN DIABETES

Metabolic factors	**Coagulation, inflammatory factors**	**Vascular related factors**
Hyperglycemia	↑ PAI – 1	Hypertension
Insulin resistance	↑ Platelet activation	Impaired endothelial dependent vasodilatation
Hyperinsulinemia	↑ Fibrinogen	↑ Arterial calcification
↓ HDL cholesterol	↑ P- selectin, VCAM-1 and ICAM	↓ Arterial compliance
Small dense LDL	↑ Tissue factor and factor VII	
Hyperhomocysteinemia	↓ Nitric oxide bio availability	
	↑ CRP	

Treatment

In general, the treatment of coronary artery disease is no different in the diabetic subjects. Revascularization procedures for coronary artery disease such as percutaneous coronary interventions (PCI) and coronary artery bypass grafting (CABG), are less efficacious in the diabetic individual. Initial success rates of PCI in diabetic patients are similar to those in the non – diabetic patients, but diabetic patients have higher rates of restenosis and lower long-term patency and survival rates. Recent trials indicate that diabetic individuals with multivessel coronary artery disease or recent Q-wave MI have better long term survival with CABG than PCI.

The ADA has emphasized the importance of glycemic control and aggressive cardiovascular risk modification in all individuals with DM. ACE inhibitors and Beta blockers are particularly beneficial and should be considered in individuals with type 2 DM and other risk factors. Antiplatelet therapy reduces cardiovascular events in individuals with DM, who have coronary artery disease. Current recommendations by the ADA include the use of aspirin for secondary prevention of coronary events. Other risk factors such as hypertension, dyslipidemia should be treated properly.

Cerebrovascular Disease

Diabetes is one of the most important risk factor for stroke. Cerebrovascular disease in diabetes usually manifests in the form of transient ischemic attacks and stroke. The cause of stroke in diabetes is mainly due to accelerated atherosclerosis. Stroke contributes significantly to the morbidity and mortality associated with diabetes. Other risk factors which contribute to the development and progression of cerebrovascular disease in type 2 DM include hypertension, smoking and dyslipidemia.

Hypertension significantly increases the risk of developing stroke in type 2 DM[22]. The beneficial effects of strict BP control in reducing the incidence of stroke has been demonstrated by UKPDS[21]. In this study, there was a 44% risk reduction in stroke, in patients assigned to tight BP control (144/82mmHg) compared with patients assigned to less tight BP control (154/87 mmHg). HOT[23] (hypertension optimal treatment) trial demonstrated improved cerebrovascular outcomes in patients assigned to a target diastolic BP of less than 80 mmHg.

Treatment

The treatment of cerebrovascular disease in diabetes is similar to non diabetic individuals. Strict BP control and glycemic control forms the mainstay in the prevention and delaying the progression of cerebrovascular disease. Aspirin, clopidogrel, dipyridamole are the commonly used antiplatelet drugs in the prevention of TIA and stroke. Addressing other risk factors such as smoking, dyslipidemia is also emphasized.

Peripheral Vascular Disease

Lower extremity arterial disease is more common among patients with diabetes, than among those without diabetes. The presence of diabetes is associated with a two to three fold excess risk of intermittent claudication, compared with its absence[24]. Despite significant advances in the prevention and treatment of peripheral vascular disease, diabetes continues to be the strongest cardiovascular risk factor for the development of critical leg ischemia and limb loss.

The cause of lower extremity ischemia in diabetes is similar to non- diabetic patient and is due to accelerated atherosclerosis. Patients with diabetes are more likely to have atherosclerotic disease affecting infrapopliteal arteries, with sparing of foot

arteries[25] which allows for successful arterial reconstruction to these distal vessels. Conversely, the superficial femoral or popliteal artery is less likely to be affected by the occlusive process, allowing these vessels to serve as a possible inflow source for bypass grafting.

Because the foot vessels are often patent in diabetes and because of success of bypass grafting to these vessels, an appropriate evaluation for ischemia is essential in patients with diabetes. The complex milieu of motor and sensory neuropathy, thickening of capillary basement membrane, loss of neurogenic inflammatory response and endothelial abnormalities, all result in a biologically compromised foot. Unless ischemia is recognized and corrected, limb salvage efforts with diabetic foot will fail, even if infection and neuropathy have been appropriately treated.

Treatment

The optimal therapy for foot ulcers and amputation is prevention through identification of high risk patients, education of the patient and institution of measures to prevent ulceration. Attention to other risk factors for vascular disease such as smoking, dyslipidemia, hypertension and improved glycemic control is important. Patient education should emphasize : 1. Careful

selection of footwear 2. Daily inspection of the feet to detect early signs of poor – fitting footwear or minor trauma, 3. Daily foot hygiene to keep the skin clean and moist, 4. Avoidance of self – treatment of foot abnormalities and walking bare foot 5. Prompt consultation with a health care provider if an abnormality arises. The ADA identified six interventions with demonstrated efficacy in diabetic foot wounds. 1. Off loading 2. Debridement 3. Would dressings 4. Appropriate use of antibiotics 5. Revascularization and 6. Limited amputation.

DIABETES AND HYPERTENSION

Hypertension is a very common comorbid condition in diabetes. Conversely patients with hypertension are more prone to develop diabetes than normotensive patients[26]. Hypertension is upto twice as common in diabetic people as in general population[27], affecting 10-30% of type I diabetic patients and 30-50% of those with type 2 DM[28]. Hypertension is also present in 20-40% of people with impaired glucose tolerance[29].

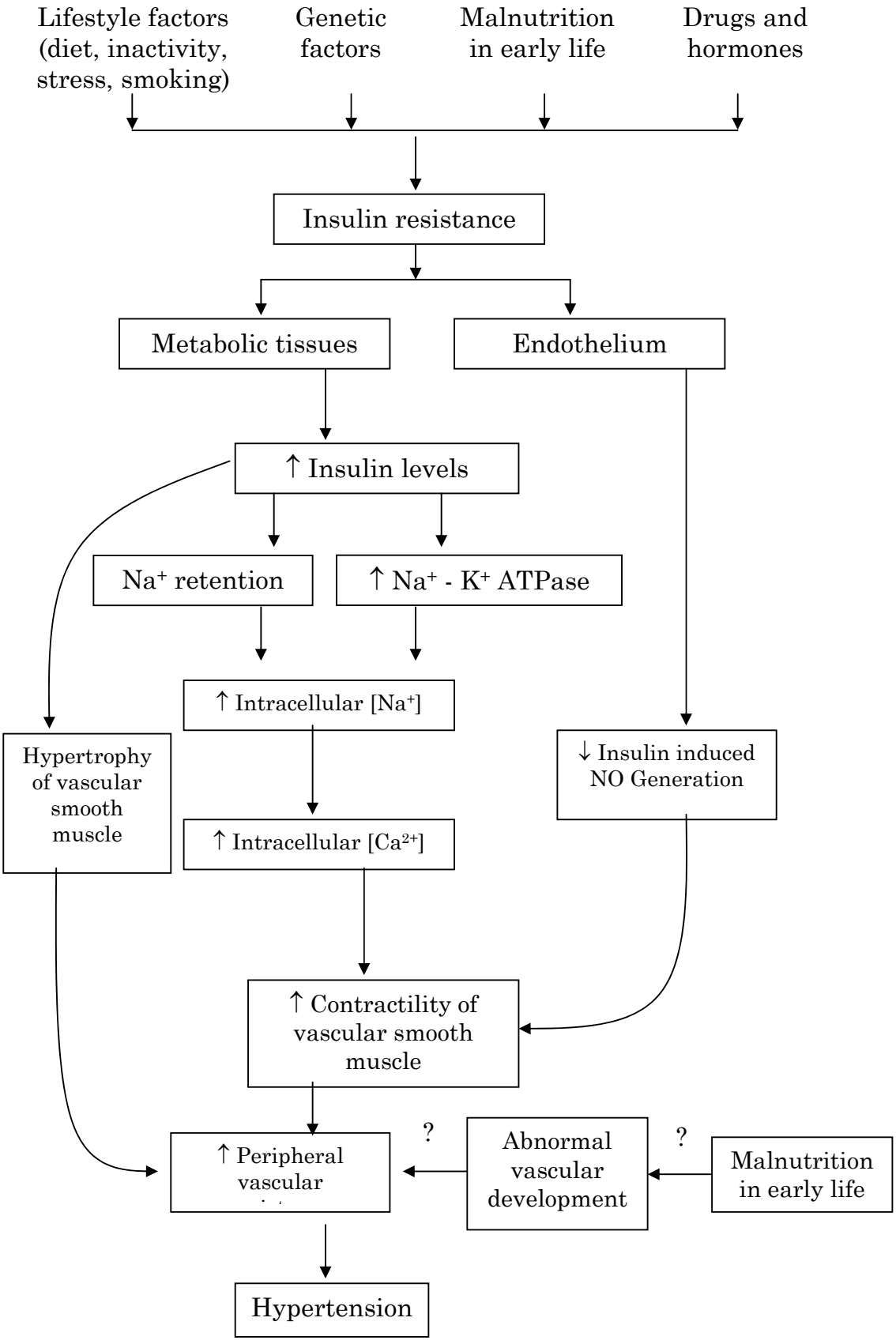
MECHANISMS OF HYPERTENSION IN INSULIN RESISTANCE

Hypertension is associated with insulin resistance, type 2 diabetes and other features of the metabolic syndrome. Insulin resistance is closely associated with high blood pressure in both humans and animals. There is some evidence that insulin is an

endothelium dependent vasodilator, releasing nitric oxide (NO) from the endothelium, which relaxes vascular smooth muscle[30,31]. Blunting of this effect, due to insensitivity of Insulin's action on the endothelium as well as on metabolically important tissues, could contribute to the increased peripheral resistance that is the hallmark of hypertension in obesity and type 2 DM. Impaired endothelium mediated vasodilatation is associated with insulin resistant states and may play a key role in the initiation and progression of atherosclerosis[32].

Insulin also has several actions that tend to raise BP and these are accentuated in insulin- resistant states, because sensitivity is preserved to the effects of the raised insulin levels. Insulin acts on the distal renal tubule to retain Na^+ ions and water[32,33] – an effect that still operates in insulin-resistant subjects[34] and so could contribute to the rise in total body sodium content that occurs in obesity and type 2 DM[35]. Insulin also stimulates cell membrane Na^+ - K^+ ATPase which would raise intracellular Na^+ concentrations in vascular smooth muscle and, by increasing systolic calcium levels, would enhance contractility and increase peripheral resistance. Through its effects on the CNS, insulin may stimulate the sympathetic outflow; this could also increase blood pressure[36]. Finally, insulin may stimulate the proliferation of vascular smooth muscle cells, which could lead to medial hypertrophy and increased peripheral resistance[37].

POSSIBLE MECHANISMS OF HYPERTENSION IN CONDITIONS OF INSULIN RESISTANCE



RELATIONSHIP BETWEEN HYPERTENSION AND DIABETES

The major cause of mortality in patients with diabetes is CVD[38]. Risk factors for CVD that cluster in diabetes include hypertension, central obesity, dyslipidemia, microalbuminuria, coagulation abnormalities, loss of nocturnal dipping of BP and pulse, and LVH[26].

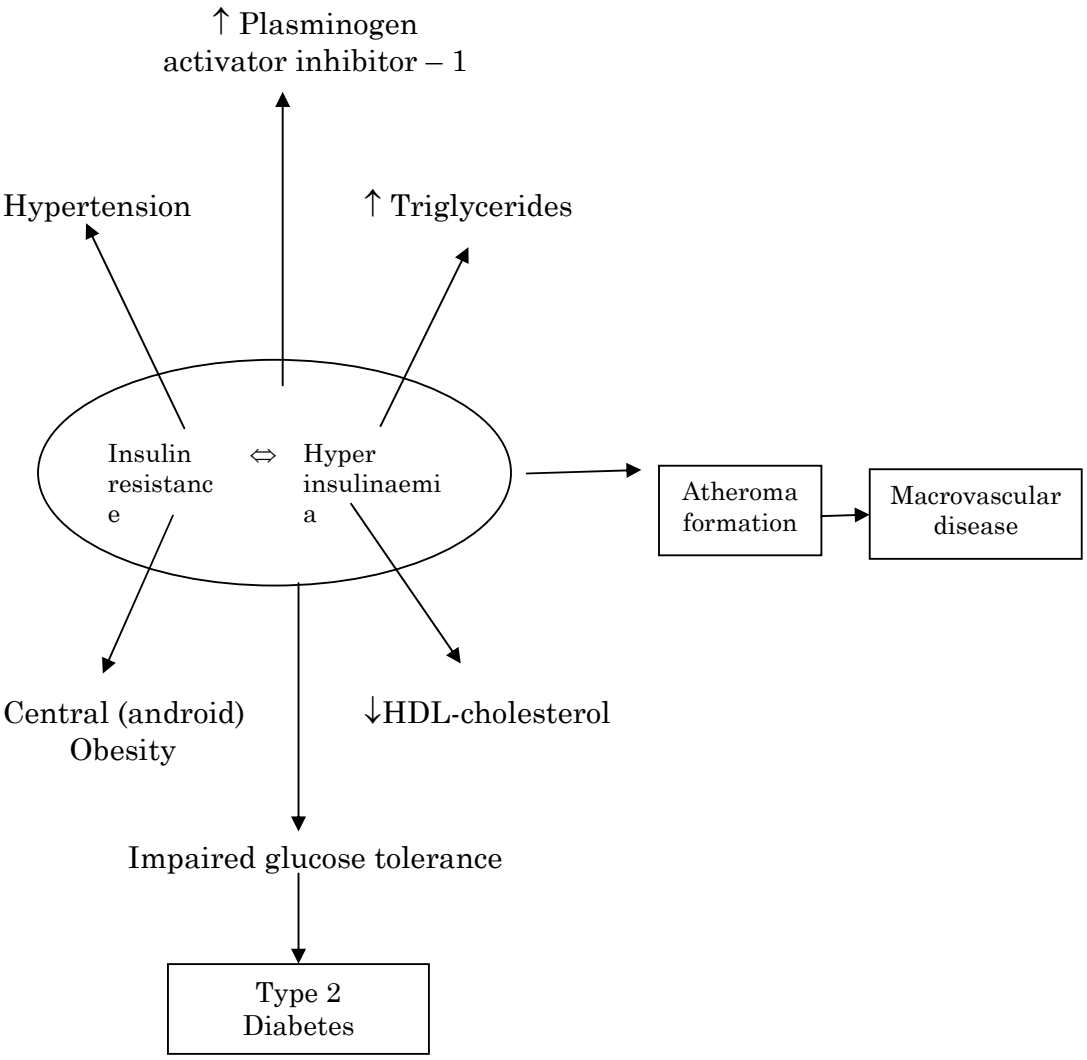
Hypertension is approximately twice as frequent in patients with diabetes as in those without diabetes[27] and accounts for upto 85% of the CVD risk. In a large prospective study of 12,550 adults, type 2 DM was almost 2.5 times as likely to develop in patients with hypertension as in their normotensive counterparts after adjustment for age, sex, race, education, adiposity, family history with respect to diabetes, physical activity level and other related behaviour[39].

The association between hypertension and insulin resistance is well established. In untreated patients with essential hypertension, fasting and postprandial insulin levels were higher than in normotensive controls, regardless of the body mass index, with a direct correlation between plasma insulin concentrations

and blood pressure. On basis of these results, it was concluded that essential hypertension is an insulin resistance state[40].

Another study of 24 adults documented that patients with hypertension treated or untreated are insulin resistant, hyperglycemic and hyperinsulinemic compared with a well matched control group[41]. Insulin resistance and hyperinsulinemia are also present in rats with genetic hypertension, such as Dahl hypertensive and spontaneously hypertensive rat strains[42,43]. On the other hand, association of insulin resistance and essential hypertension does not occur in secondary hypertension[44]. These data suggest a common genetic predisposition for essential hypertension and insulin resistance, a concept that is supported by finding of altered glucose metabolism in normotensive off spring of hypertensive patients[45].

THE METABOLIC SYNDROME / SYNDROME X



METABOLIC DISORDERS ASSOCIATED WITH HYPERTENSION AND DIABETES

- Central obesity
- Microalbuminuria
- Low HDL – cholesterol levels
- High triglyceride levels
- Small, dense LDL cholesterol particles
- Hyperinsulinemia / Insulin resistance
- Endothelial dysfunction
- Increased apolipoprotein B levels
- Increased fibrinogen levels
- Increased PAI-1 levels
- Increased C-reactive protein and other inflammatory markers
- Absent nocturnal dipping of BP and pulse.
- Left ventricular hypertrophy
- Increased uric acid levels
- Premature coronary artery disease.

HEMODYNAMIC AND METABOLIC CHARACTERISTICS OF HYPERTENSION IN DIABETES

Salt sensitivity and volume expansion

Alterations in sodium balance and extracellular fluid volume have heterogeneous effects on blood pressure in both normotensive and hypertensive subjects[46]. Increased salt intake does not raise BP in all hypertensive subjects, and sensitivity to dietary salt intake is greatest in the elderly; those with diabetes, renal insufficiency, and low renin status[47,48].

Studies demonstrated that salt sensitivity in normotensive subjects is associated with a greater age-related increase in BP[49]. This is particularly important to consider in the management of hypertension in patients with diabetes, especially elderly persons, since the prevalence of both diabetes and salt sensitivity increases with age. Thus, a decreased salt intake along with other aspects of diet such as reductions in fat and free carbohydrates and increase in potassium are important for these patients[26].

Loss of nocturnal decline in blood pressure

Normotensive individuals and most patients with hypertension have a reproducible circadian pattern to blood pressure and heart rate during 24 hour ambulatory monitoring[50]. Typically, the BP is highest while the patient is awake and lowest during sleep, a pattern called "dipping", in which blood pressure decreases by 10% to 15%. Patients with loss of nocturnal decline in BP, "non-dippers", have a less than 10% decline in BP during the night compared with their day time BP[51].

Patients with diabetes and many of those with the cardiometabolic syndrome have a loss of nocturnal dipping, as demonstrated by 24hour ambulatory monitoring of blood pressure. This is particularly important, since the loss of nocturnal dipping conveys excessive risk for stroke and myocardial infarction. Infact, ambulatory BP has been reported to be superior to office BP in predicting target organ involvement such as LVH[52]. About 30% of episodes of MI and 50% of strokes occur between 6.00 am and noon. This is particularly important in deciding strategies for the optimal dosing of antihypertensive medications, for which drugs that provide consistent and sustained 24- hour blood pressure control will be advantageous[53].

Microalbuminuria

Hypertension in type 1 diabetes is a consequence, rather than a cause, of renal disease and that nephropathy precedes the rise in BP[54]. Hypertension and nephropathy appear to exacerbate each other. In type 2 diabetes, microalbuminuria is associated with insulin resistance, salt sensitivity, loss of nocturnal dipping of BP and LVH. Elevated systolic BP is a significant determining factor in the progression of microalbuminuria[55,56]. Indeed, there is increasing evidence that microalbuminuria is an integral component of the metabolic syndrome associated with hypertension[57]. This concept is important to consider in selecting pharmacologic therapy for hypertension in patients with diabetes, for which medications that decrease both proteinuria and blood pressure, such as ACE inhibitors and AR blockers are used for reducing progression of nephropathy.

Isolated systolic hypertension

With the progression of atherosclerosis in patients with diabetes, the larger arteries lose elasticity and become rigid. The systolic pressure increases disproportionately because the arterial system is incapable of expansion for any given volume of blood ejected from left ventricle, leading to isolated systolic hypertension,

which is more common and occurs at a relatively younger age in patients with diabetes[58].

Orthostatic Hypotension

Pooling of blood in dependent veins when an individual rises from a recumbent position normally leads to a decrease in stroke volume and systolic blood pressure with concomitant increase in systemic vascular resistance, diastolic BP and heart rate.

In patients with diabetes and autonomic dysfunction, excessive venous pooling can cause immediate or delayed orthostatic hypotension, that might cause a reduction in cerebral blood flow, leading to lightheadedness, fatigue, unsteady gait and syncope[59]. This is important to recognize in patients with diabetes and concomitant hypertension because it has several diagnostic and therapeutic implications; for example, discontinuation of diuretic therapy and volume repletion might be necessary for the treatment of chronic orthostasis. Furthermore, increased propensity for orthostatic hypotension in patients with diabetes renders beta blockers less desirable and second line agents for these patients.

TREATMENT OF HYPERTENSION IN PATIENTS WITH DIABETES

UKPDS[21] and Hypertension optimal treatment (HOT) trial[23] demonstrated improved outcomes, in patients assigned to lower blood pressure targets. In HOT trial, improved outcomes were achieved in the group assigned to a target diastolic BP of less than 80mmHg. A target BP of < 130/80mmHg is currently recommended by the seventh joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (JNC-VII) and American Diabetes Association (ADA).

Dietary and Life style Modification

Both JNC-VII[60] and ADA[61] recommend lifestyle and dietary modifications as an integral part of the management of hypertension in patients with diabetes. Importance of other CVD risk factors such as smoking, physical inactivity, and elevated LDL –cholesterol is also emphasized[62].

Following are the dietary and lifestyle modification approaches in the management of Hypertension.

1. Weight loss [maintain normal body weight (BMI 18.5 – 24.9)].

2. Exercise (aerobic physical activity) 30-45 min at least 3 times per week.
3. Reduced sodium intake to 100 mmol (2-4g) per day.
4. Cessation of smoking.
5. Adequate intake of dietary potassium, calcium and magnesium.
6. Reduced alcohol intake < 1Oz of ethanol per day.
7. Diet rich in fruits and vegetables but low in fat.

Pharmacotherapy for Hypertension in patients with Diabetes

ACE Inhibitors

These drugs may be used in Diabetic hypertension, even in cases where renin angiotensin system is not activated; instead, the drugs may interfere with local angiotensin action in specific target tissues. Their ability to attenuate albuminuria and the progression of renal disease led to their use as renoprotective agents in diabetic nephropathy[14,63].

Angiotensin converting enzyme inhibitors provide Cardiovascular and microvascular benefits and may also improve insulin resistance and prevent the development of diabetes[64]. In the studies of left ventricular dysfunction (SOLVD) trial, ACE

inhibitors reduced left ventricular mass and left ventricular dilatation and significantly reduced mortality and hospitalization for heart failure[65].

Angiotensin II Receptor Blockers

JNC-VII recommended the use of AR Blockers as one of the several alternative first line therapy for patients with hypertension who do not tolerate or respond to first line medications[60]. AR Blockers were also recommended as an initial therapy for those who could not tolerate ACE inhibitors and in whom ACE inhibitors are recommended[66], such as patients with diabetes and proteinuria, heart failure, systolic dysfunction, post MI and mild renal insufficiency.

Three major studies, reduction of End points in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) study[67], Irbesartan Microalbuminuria Type 2 Diabetes in Hypertensive patients (IRMA II) study[68] and the Irbesartan in Diabetic nephropathy trial[69] (IDNT), showed that AR blockers are effective in reducing the progression of renal disease in patients with type 2 diabetes and hypertension.

Beta Blockers

Beta blockers are very useful antihypertensive agents in the treatment of hypertension in patients with diabetes. In UKPDS[21] atenolol reduced microvascular complications of diabetes by 37%, strokes by 44% and death related to diabetes by 32%. In that study efficacy of beta blocker atenolol was equal to ACE inhibitor Captopril in reducing micro and macrovascular complications of diabetes, most probably secondary to their ability to modulate RAAS. Despite the potentially adverse effects of betablockers, they have significant long term favourable effects on CVD in hypertensive patients with diabetes.

Calcium channel Blockers

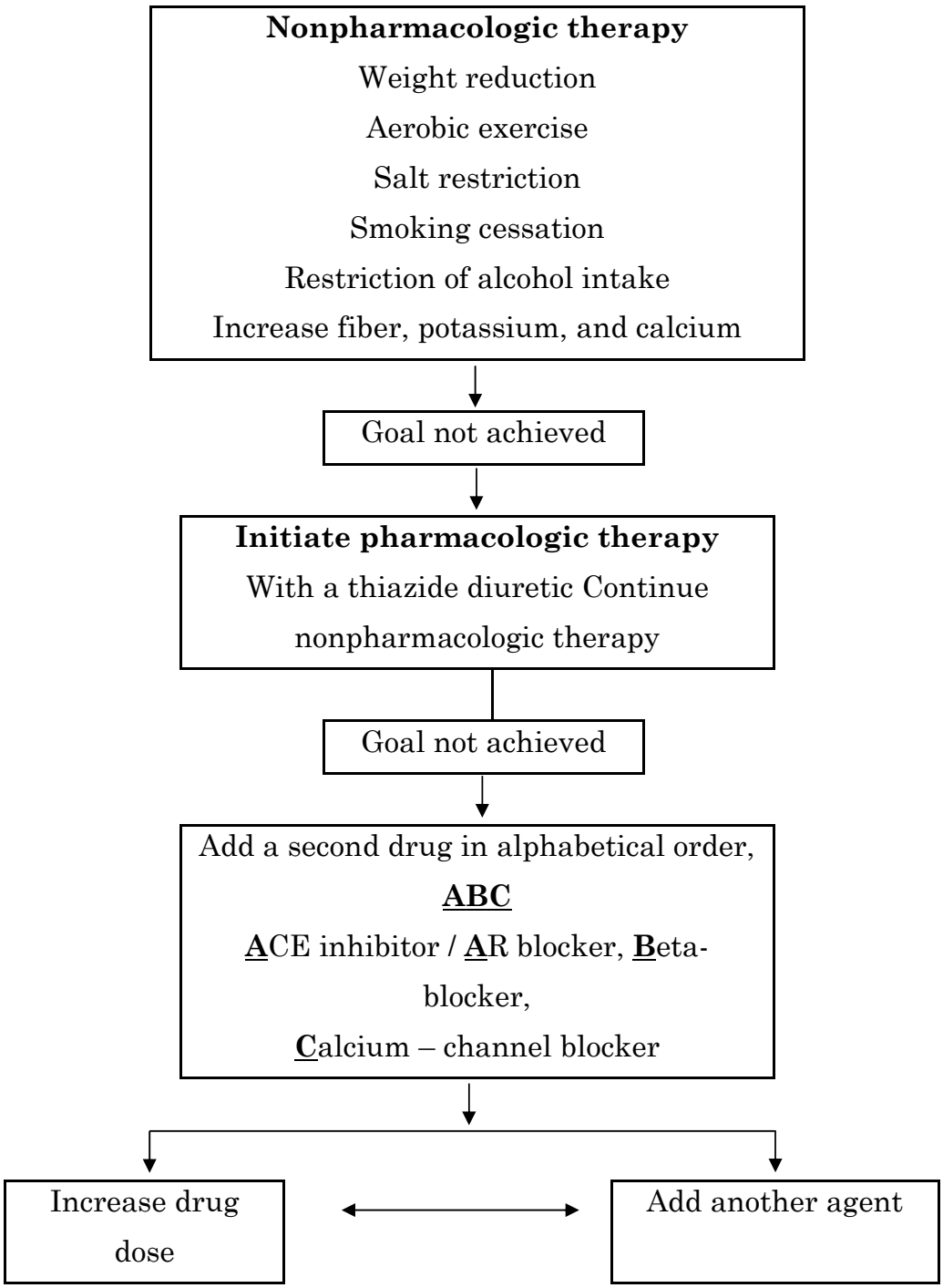
For patients to achieve a target BP of 130/80mmHg, most studies suggest that at least 65% of them require 2 or more different antihypertensive agents[70]. With the use of ACE inhibitor as a first line treatment, together with a diuretic, addition of a long-acting dihydropyridine such as amlodipine, nifedipine or felodipine will reduce both proteinuria and the rate of CVD events.

Diuretics

The diabetic cohort in ALLHAT[71] (Antihypertensive and Lipid-Lowering treatment to prevent Heart attack trial) provided valuable information about the treatment of hypertension in older diabetic patients at risk for CVD. Thiazide diuretics were effective as part of combined therapy that reduced stroke. Therefore, they are recommended as preferred antihypertensive therapy.

TREATMENT OF HYPERTENSION IN PATIENTS WITH DIABETES

Treatment Goal : < 130/80 mmHg



Materials and

Methods

MATERIALS AND METHODS

The study was conducted at the outpatient department, Dr. Ambedkar Institute of Diabetology, Kilpauk Medical College Hospital, during the period from February 2005 to June 2005.

Patients attending diabetology OPD were taken up for the study.

Two groups of patients were selected after proper inclusion and exclusion criteria.

One group in which 50 patients with type 2 DM of various duration of the disease, and of either sex, without hypertension were selected.

Another group of 50 patients with both type 2 DM and hypertension, of various duration and of either sex were selected.

All the patients who were selected in both the groups were on treatment with oral hypoglycemic drugs or insulin for diabetes and antihypertensive drugs in diabetes with hypertension group, for various duration.

In diabetes with hypertension group, hypertensives were selected on the basis of history of treatment for hypertension. In

patients who did not have the history of hypertension, hypertension was diagnosed based on JNC-VII criteria. (Seventh Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure).

Patients, who had systolic BP 140mmHg or more and diastolic BP 90mmHg more were included in diabetic hypertensive group. Patients who had systolic BP <140mmHg and diastolic BP< 90mmHg were included in diabetes without hypertension group.

Smokers were excluded from both the groups.

INCLUSION CRITERIA	EXCLUSION CRITERIA
Patients with type 2 DM	• Patients with type 1 DM • Smokers • Patients with acute illness • Patients with secondary hypertension • Patients who are over weight and obese (BMI 25 or more).

Patient's name, age, sex, duration of DM, duration of hypertension were taken. Treatment history of DM and hypertension were taken. Family history of hypertension and diabetes mellitus were taken. History of complications of DM and treatment for them were taken.

All peripheral pulses were examined. BP was recorded after seating the patients for 5 minutes, with sphygmomanometer. Two recordings were taken at 2 consecutive visits. Clinically patients were examined for vascular bruit.

METHODOLOGY USED TO DIAGNOSE VASCULAR COMPLICATIONS

Neuropathy

10 gm monofilament was used to check the presence or absence of sensation in foot. Vibration perception threshold (VPT) was checked in the foot using a biothesiometer, (6 sites in the foot were examined great toe, 1, 3, 5 metatarsal heads, Instep, heal).

Peripheral neuropathy, if present was graded as mild, moderate and severe (VPT 11-15 V mild, 16-25 V moderate, > 25 V severe).

Nephropathy

History of diabetic nephropathy was taken. Early morning urine sample was analysed for albumin using dip stick method. 2 samples were analysed. Urine for microscopic examination was done to exclude active urinary sediment. Patients having urine

albumin positive for 2 samples using dipstick method, were considered to have diabetic nephropathy.

Retinopathy

Ocular fundus was examined by ophthalmologist after proper dilatation of pupil using mydriatic. Direct ophthalmoscopy method was used. Levels of diabetic retinopathy were noted. (Non proliferative or proliferative diabetic retinopathy with or without macular edema).

Cardiovascular Disease

History of treatment for coronary artery disease was taken. A 12 – lead baseline electrocardiogram was taken. Ischemic changes and infarction were looked for in ECG. Patients having these ECG changes were considered to have coronary artery disease.

Cerebrovascular Disease

History of cerebrovascular accidents, transient ischemic attacks, was taken. Patients were clinically examined for focal neurological deficit. Patients having either history of CVA, TIA or clinical evidence of focal neurological deficit were considered to have cerebrovascular disease.

Peripheral Vascular Disease

History of lower extremity gangrene, amputation was taken. Clinically patients were examined for all peripheral pulses. A hand held Doppler ultrasound probe was used to measure to ankle brachial pressure index. The ankle brachial pressure index is the ratio of systolic pressure at the ankle to that in arm. Pressure recorded in the ankle was taken as numerator. Pressure recorded in the arm is taken as denominator. The resting ABPI is normally about 1.0. Patients with ABPI below 0.9 were considered to have peripheral vascular insufficiency.

Results of the Study

RESULTS OF THE STUDY

TABLE -1

AGE DISTRIBUTION

S.No	Age in years	Diabetes with hypertension		Diabetes without hypertension	
		No. of Cases	Percentage	No. of Cases	Percentage
1	≤ 40	1	2%	1	2%
2	41 – 50	8	16%	7	14%
3	51 – 60	19	38%	21	42%
4	61 – 70	15	30%	17	34%
5	>70	7	14%	4	8%
		50		50	

The most common age interval in diabetes with hypertension group → 51- 60 years.

The most common age interval in diabetes without hypertension group → 51- 60 years.

	Age
	Mean ± S.D
Diabetes with hypertension	60.34 ± 9.7323
Diabetes without hypertension	58.88 ± 8.5228

P = 0. 213393 (Not significant)

(Student t test)

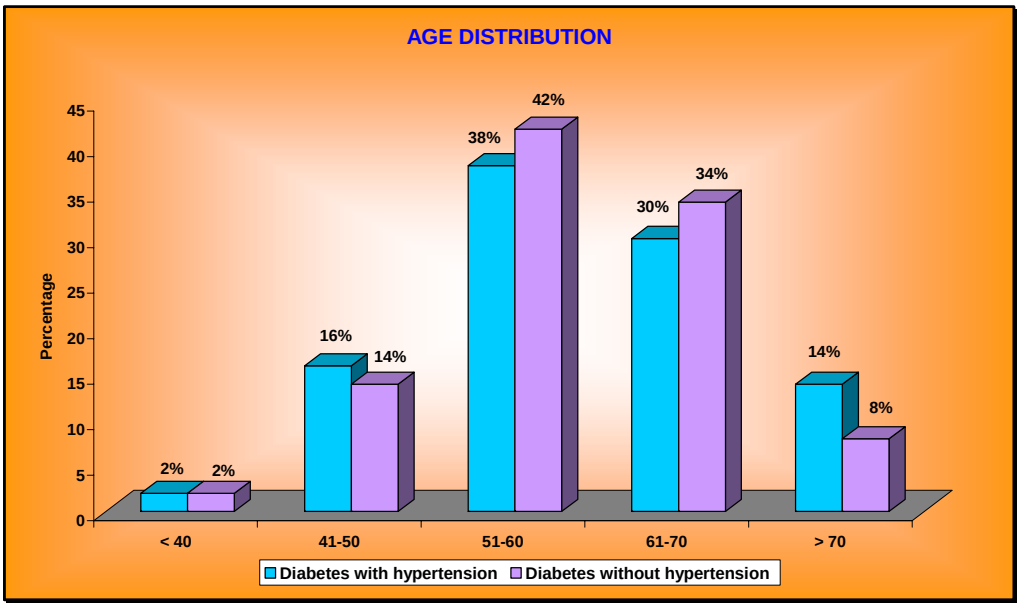

AGE DISTRIBUTION
Percentage
45
40
35
30
25
20
15
10
5
0
2%
2%
16%
14%
38%
42%
30%
34%
14%
8%
< 40
41-50
51-60
61-70
> 70
Diabetes with hypertension
Diabetes without hypertension

TABLE – 2

GENDER

Sex	Diabetes with hypertension		Diabetes without hypertension	
	No of cases	**%**	**No of cases**	**%**
Male	22	44	24	48
Female	28	56	26	52

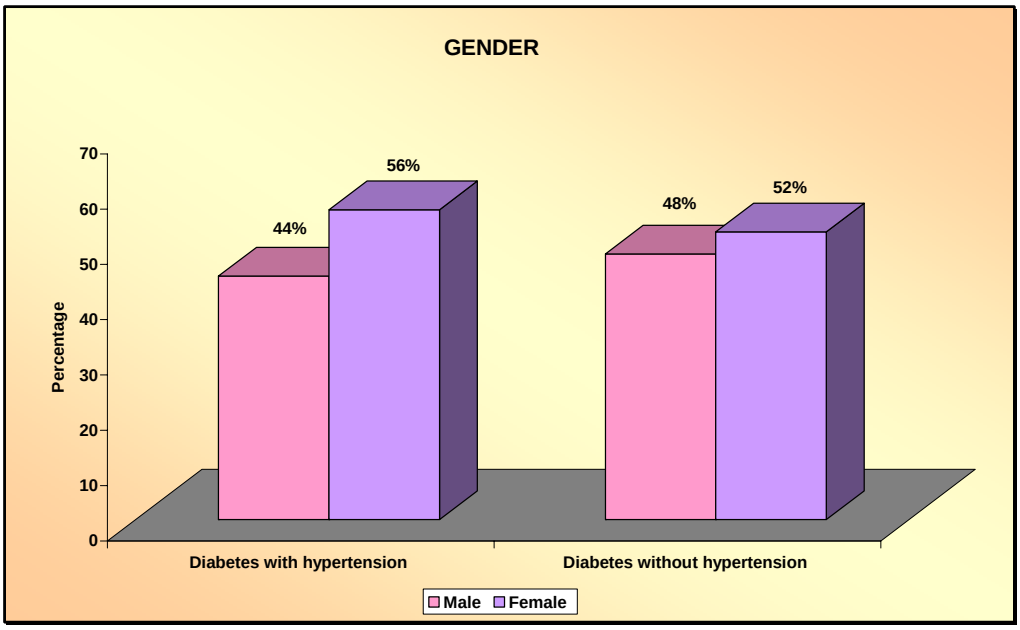

GENDER
70
60
50
40
30
20
10
0
Percentage
44%
56%
48%
52%
Diabetes with hypertension
Diabetes without hypertension
Male
Female

TABLE -3

DURATION OF DIABETES MELLITUS

Duration of DM (years)	Diabetes with hypertension		Diabetes without hypertension	
	No. cases	%	No. cases	%
1-5	5	10	4	8
6-10	21	42	20	40
11-15	15	30	21	42
>15	9	18	5	10

The most common duration of DM in diabetes with hypertension group 6 – 10 years.

The most common duration of DM in diabetes without hypertension group 11-15 years.

	Duration of DM
	Mean ± SD
Diabetes with hypertension	11.66 ± 5.6734
Diabetes without hypertension	11.28 ± 4.7725

P = 0.717811 (Not significant)

(Student t test)

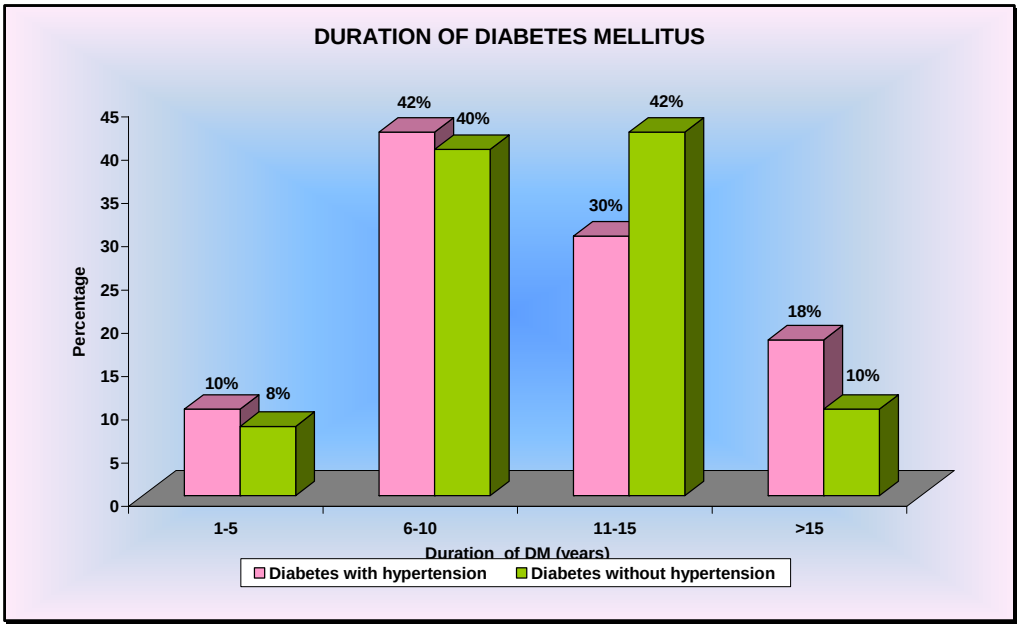
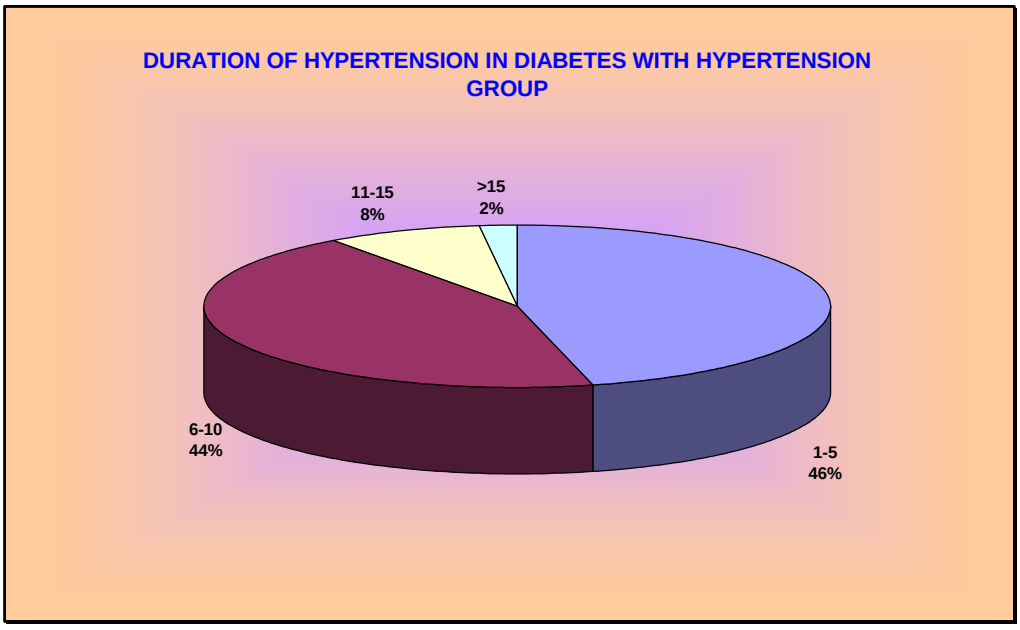

DURATION OF DIABETES MELLITUS
Percentage
45
40
35
30
25
20
15
10
5
0
10%
8%
42%
40%
30%
42%
18%
10%
1-5
6-10
11-15
>15
Duration of DM (years)
Diabetes with hypertension
Diabetes without hypertension

TABLE – 4

DURATION OF HYPERTENSION IN DIABETES WITH HYPERTENSION GROUP

Duration of hypertension (years)	No. of Cases	Percentage
1-5	23	46
6-10	22	44
11-15	4	8
>15	1	2
Total	**50**	**100**

Mean ± SD = 6.46 ± 3.9186


DURATION OF HYPERTENSION IN DIABETES WITH HYPERTENSION GROUP
11-15
8%
>15
2%
6-10
44%
1-5
46%

COMPARISON OF VASCULAR COMPLICATIONS

TABLE – 5

PERIPHERAL NEUROPATHY

Group	Peripheral Neuropathy	
	Yes	**No**
Diabetes with hypertension	32	18
Diabetes without hypertension	24	26
Total	**56**	**44**

P = 0.107039 (Not significant)

(Chi – square test)

Relative risk = 1.33

The prevalence of peripheral neuropathy in diabetes with hypertension group = 64%.

The prevalence of peripheral neuropathy in diabetes without hypertension group = 48%.

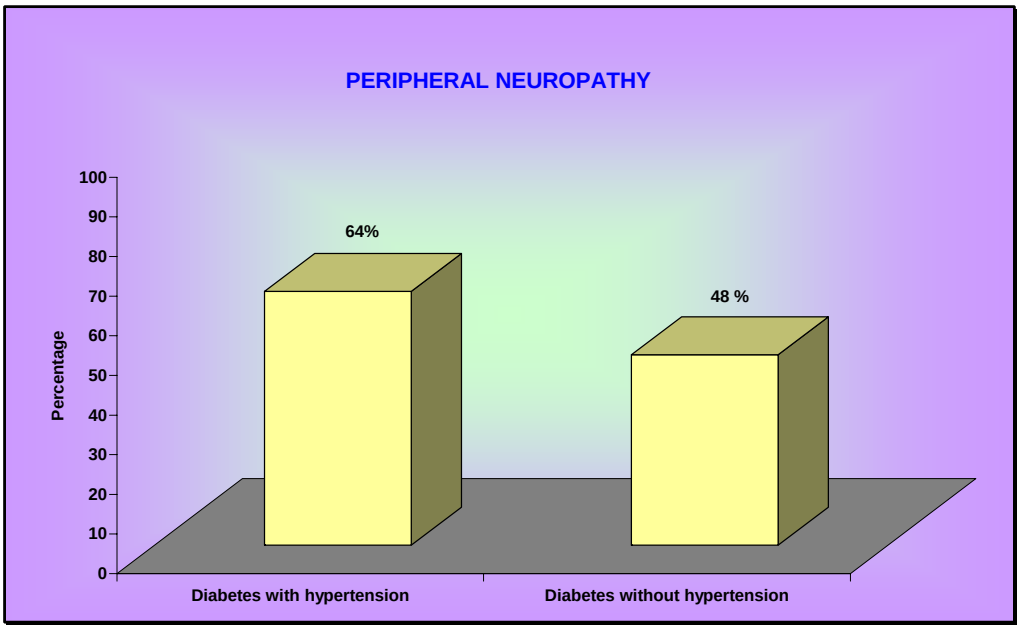

PERIPHERAL NEUROPATHY
Percentage
100
90
80
70
60
50
40
30
20
10
0
64%
48 %
Diabetes with hypertension
Diabetes without hypertension

TABLE - 6

DIABETIC NEPHROPATHY

Group	Diabetic Nephropathy	
	Yes	**No**
Diabetes with hypertension	12	38
Diabetes without hypertension	6	44
Total	**18**	**82**

P = 0.1183498 (Not significant)

(Chi – square test)

Relative risk = 2.00

The prevalence of nephropathy in diabetes with hypertension group = 24%.

The prevalence of nephropathy in diabetes without hypertension group = 12%.

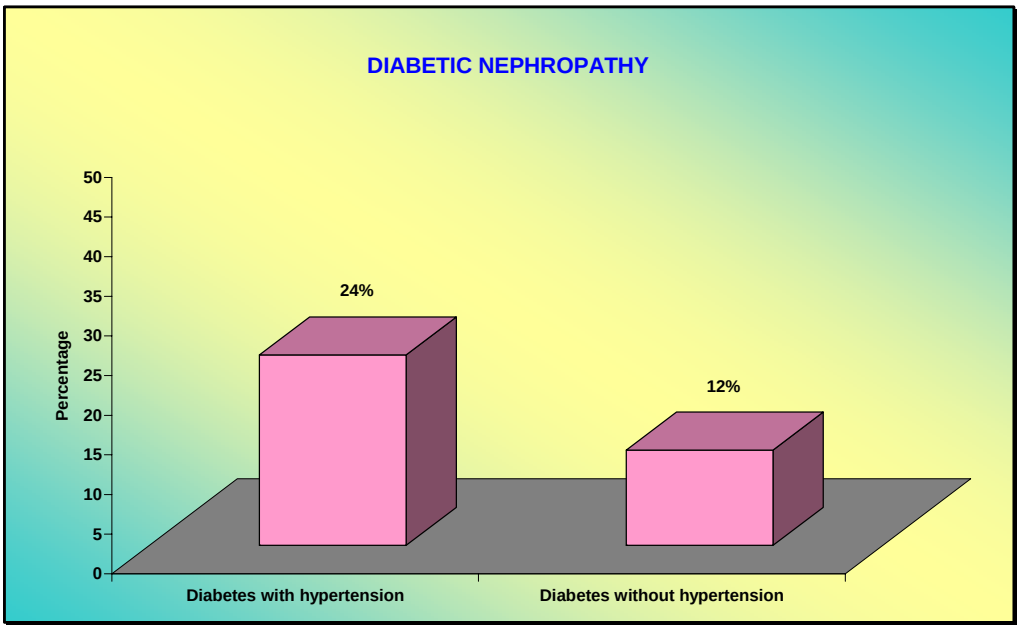

DIABETIC NEPHROPATHY
Percentage
50
45
40
35
30
25
20
15
10
5
0
24%
12%
Diabetes with hypertension
Diabetes without hypertension

TABLE - 7

DIABETIC RETINOPATHY

Group	**Diabetic Retinopathy**	
	Yes	**No**
Diabetes with hypertension	18	32
Diabetes without hypertension	8	42
Total	26	74

P = 0.0226193

(Statistically significant)

Relative risk = 2.25

(Chi – square test)

The prevalence of retinopathy in diabetes with hypertension group = 36%.

The prevalence of retinopathy in diabetes without hypertension group = 16%.

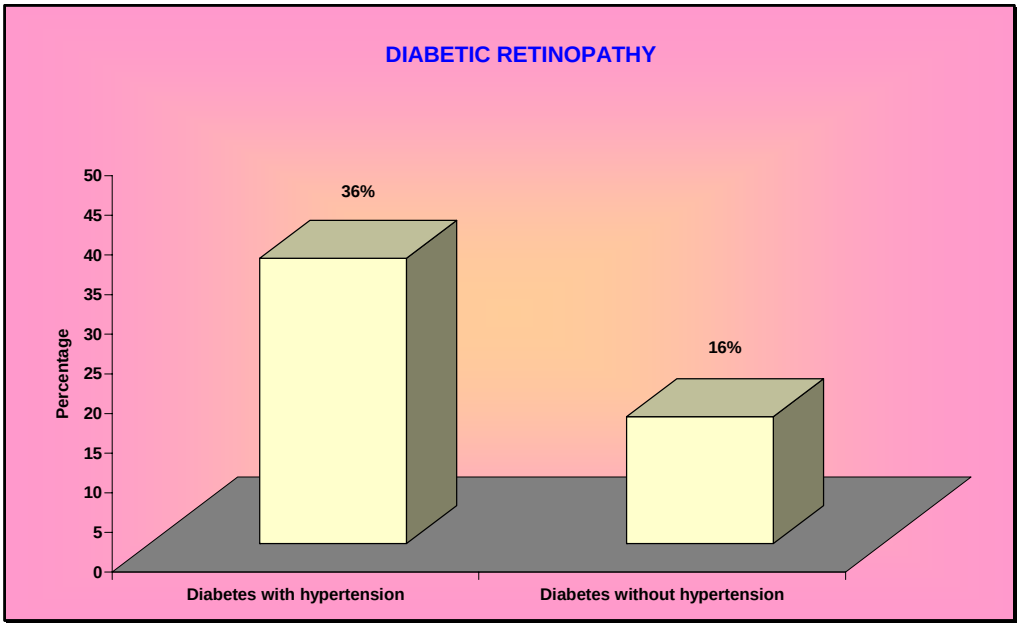

DIABETIC RETINOPATHY
Percentage
50
45
40
35
30
25
20
15
10
5
0
36%
16%
Diabetes with hypertension
Diabetes without hypertension

TABLE - 8

CORONARY ARTERY DISEASE

Group	Coronary Artery disease	
	Yes	**No**
Diabetes with hypertension	17	33
Diabetes without hypertension	5	45
Total	**22**	**78**

P = 0.003769

(Statistically significant)

(Chi square test)

Relative risk = 3.40

The prevalence of coronary artery disease in diabetes with hypertension group = 34%.

The prevalence of coronary artery disease in diabetes without hypertension group = 10%.

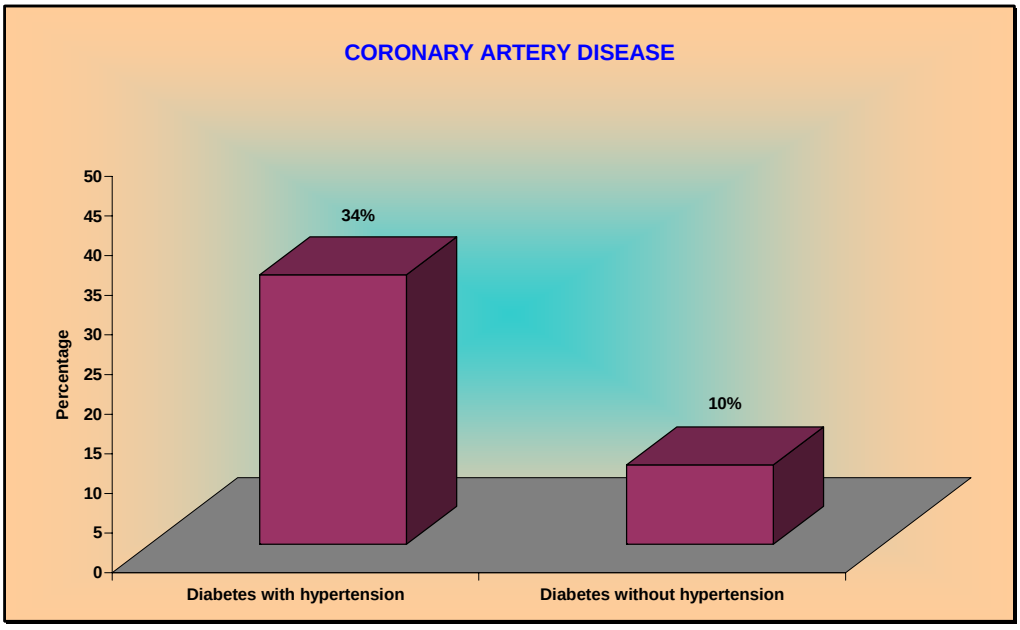

CORONARY ARTERY DISEASE
Percentage
50
45
40
35
30
25
20
15
10
5
0
34%
10%
Diabetes with hypertension
Diabetes without hypertension

TABLE – 9

CEREBROVASCULAR DISEASE

Group	Cerebrovascular disease	
	Yes	**No**
Diabetes with hypertension	4	46
Diabetes without hypertension	1	49
Total	**5**	**95**

P = 0.3621785 (Not significant)

(Fisher exact two tailed test)

Relative risk = 4

The prevalence of cerebrovascular disease in diabetes with hypertension group = 8%.

The prevalence of cerebrovascular disease in diabetes without hypertension group = 2%.

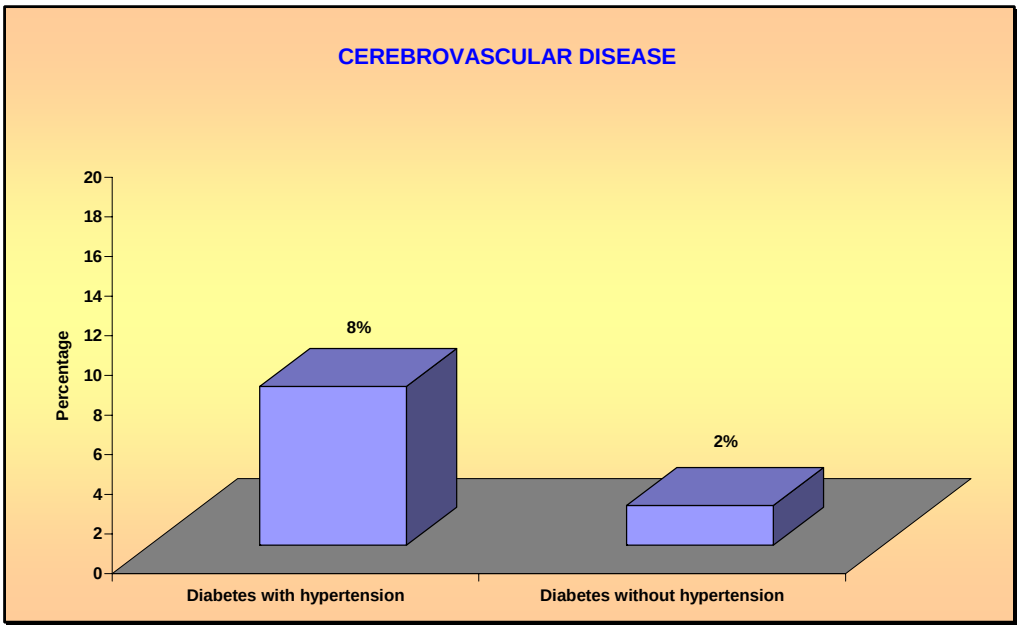

CEREBROVASCULAR DISEASE
Percentage
20
18
16
14
12
10
8
6
4
2
0
8%
2%
Diabetes with hypertension
Diabetes without hypertension

TABLE – 10

PERIPHERAL VASCULAR DISEASE

Group	Peripheral Vascular Disease	
	Yes	**No**
Diabetes with hypertension	3	47
Diabetes without hypertension	1	49
Total	**4**	**96**

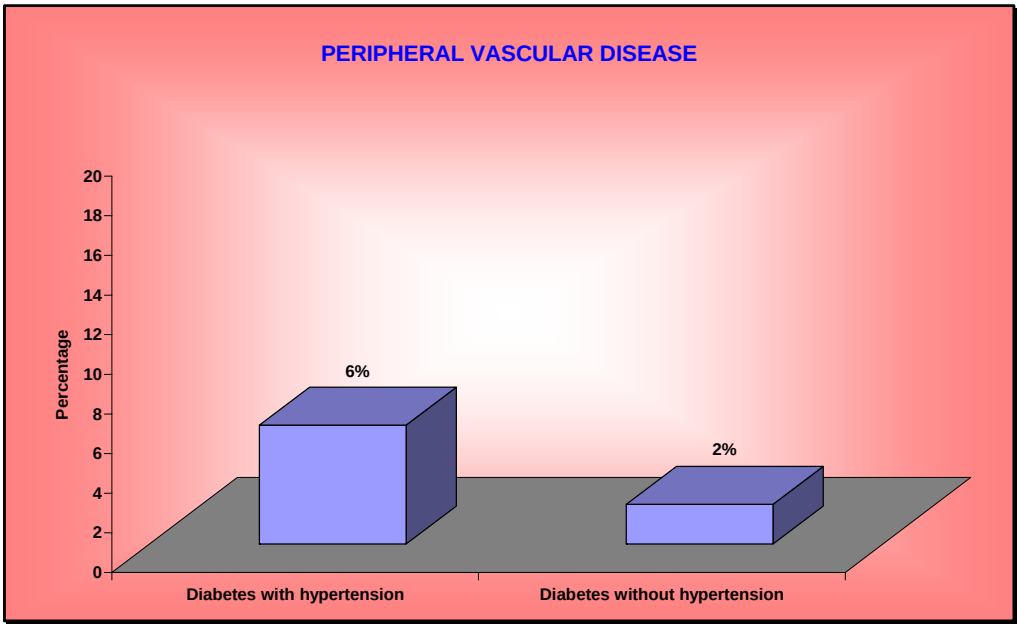
P = 0.6173071 (Not significant)

(Fisher exact two tailed test)

Relative risk = 3

The prevalence of peripheral vascular disease in diabetes with hypertension group = 6%

The prevalence of peripheral vascular disease in diabetes without hypertension group = 2%


PERIPHERAL VASCULAR DISEASE
Percentage
20
18
16
14
12
10
8
6
4
2
0
6%
2%
Diabetes with hypertension
Diabetes without hypertension

Discussion

DISCUSSION

The vascular complications of DM affect many organ systems and are responsible for majority of the mortality and morbidity associated with diabetes. Duration of DM is the Central Factor in the pathogenesis of these complications. Hypertension is a very common co-morbid condition in diabetes. In type 2 Diabetes, hypertension usually clusters with other components of cardiometabolic syndrome such as central obesity, Insulin resistance, dyslipidemia, microalbuminuria, hypercoagulation, increased PAI-1, hyperuricemia. Hypertension in diabetes has its specific characteristics like salt sensitivity and volume expansion, loss of nocturnal decline in BP, microalbuminuria, isolated systolic hypertension, orthostatic hypotension.

Hypertension worsens both microvascular and macrovascular complications, of diabetes. A large proportion of hypertensive diabetic patients show signs of target organ damage[28], particularly affecting cardiovascular system. The deleterious effects of hypertension on left ventricular function are also accentuated by the presence of Diabetes. These include impaired LV relaxation[72] and increased left ventricular mass[73], the later being an independent predictor of premature death from CAD.

The beneficial effects of strict BP control in type 2 diabetic patients has been demonstrated in UKPDS[21]. The most striking implication of UKPDS is the beneficial effects of strict BP control, than glycemic control in reducing microvascular disease as well as on all diabetes related end points. In this study, reduction in risk in the group assigned to tight BP control (144/82mmHg) compared with that assigned to less tight BP control (154/87 mmHg) were 24% reduction in diabetes related end points, 32% in death related to diabetes, 44% in stroke and 37% in microvascular end points (Retinopathy and advanced nephropathy).

The hypertension optimal treatment (HOT) trial[23] has demonstrated improved outcomes in patients assigned to lower blood pressure targets (51% risk reduction in cardiovascular outcomes in target group assigned to diastolic BP of 80mmHg compared with group assigned to a diastolic BP of 90mmHg).

JNC-VII[60] has demonstrated the benefits of lowering BP in reducing the incidence of stroke (35-40%), MI (35-40%) and heart failure (50%). JNC-VII[60] and ADA[61] currently recommends a target BP of <130/80 mmHg in Diabetes and < 125/75mmHg in patients with > 1gm proteinuria per day and renal insufficiency.

Our study compared the prevalence of both the micro and macrovascular complications among type 2 DM between diabetic hypertensive and Diabetes without hypertension groups.

The prevalence of vascular complications in diabetic hypertensive group in our study are peripheral neuropathy 64%, nephropathy 24%, retinopathy 36%, coronary artery disease 34%, cerebrovascular disease 8% and peripheral vascular disease 6%. The prevalence of vascular complications in diabetes without hypertension group are peripheral neuropathy 48%, nephropathy 12%; Retinopathy 16%, coronary artery disease 10%, cerebrovascular disease 2% and peripheral vascular disease 2%.

There is significant increase in the prevalence of coronary artery disease (P=0.003769) (RR=3.40) and retinopathy (P=0.0226193) (RR=2.25) in diabetic hypertensive group compared to diabetes without hypertension group. Though there is no statistical significance, there is increased prevalence of nephropathy (RR=2) in diabetic hypertensive group compared to diabetes without hypertension group. In our study, microalbuminuria was not done. The prevalence of nephropathy would have increased, if we had investigated for microalbuminuria. The prevalence of cerebrovascular disease is increased in diabetic

hypertensive group compared to that of diabetes without hypertension group (RR = 4). The prevalence of peripheral vascular disease is increased in diabetic hypertensive group compared to that of diabetes without hypertension group (RR = 3). The prevalence of peripheral neuropathy in both groups showed no appreciable difference (RR =1.33).

A similar study conducted in Kilpauk Medical College[74], Chennai in 1991 compared the prevalence of Macrovascular disease in type 2 Diabetes between Diabetic hypertensives and diabetic non hypertensives (1200 type 2 diabetic patients were studied). The results of that study are : the prevalence of coronary, cerebral and peripheral vascular events is diabetes with hypertension group were 34.61%, 5.77% and 5.77% respectively compared to 16.33%, 4.59% and 1.53% respectively in diabetes without hypertension. This study concluded that diabetics with hypertension, compared to those without hypertension have a two fold increase in the prevalence of macrovascular events in general, as well as that of CAD and a 4 fold increase in the prevalence of PVD and there is no appreciable difference in the prevalence of cerebrovascular disease.

Our study results are comparable to the above study results.

From the results obtained in our study, diabetic hypertensive group has significant increased prevalence of vascular complications when compared to diabetes without hypertension group. The limitations of our study include smaller sample size, not investigated for micro albuminuria and lipid profile. Our study results signifies that hypertension is a definite risk factor in the development and progression of micro and macrovascular complication, in Type 2 DM. Apart from other factors such as smoking, dyslipidemia, obesity in the progression of vascular complications, hypertension plays a critical role in the progression of complications leading to increased mortality and morbidity in patients with type 2DM. JNC-VII has demonstrated the significance of strict BP control in patients with diabetes and lifestyle modification in diabetic prehypertensive stage in reducing diabetes related end points. Both JNC-VII[60] and ADA[61] recommends a target BP of < 130/80mmHg in diabetic hypertensives and <125/75mmHg in patients with > 1gm proteinuria per day and significant renal disease. Apart from BP control, discontinuation of smoking, correction of dyslipidemia significantly reduces the development and progression of vascular complications of diabetes.

Conclusion

CONCLUSION

The conclusion obtained from the study results are :

- The prevalence of coronary artery disease is significantly increased in diabetic patients with hypertension compared to diabetic patients without hypertension (P=0.003769). Diabetic patients with hypertension have more than three times risk of developing coronary artery disease, compared to diabetic patients without hypertension (RR=3.40).

- The prevalence of diabetic retinopathy is significantly increased in diabetic patients with hypertension, compared to diabetic patients without hypertension (P=0.0226193). Diabetic patients with hypertension have more than two times increased risk of developing retinopathy than diabetic patients without hypertension (RR = 2.25).

- Patients with diabetes and hypertension have 2 times increased risk of developing nephropathy than diabetic patients without hypertension (RR = 2).

- Patients with diabetes and hypertension have 4 times increased risk of developing cerebrovascular disease than diabetic patients without hypertension (RR=4).

- Patients with diabetes and hypertension have 3 times increased risk of developing peripheral vascular disease, than diabetic patients without hypertension (RR=3).

- There is no appreciable difference in the prevalence of peripheral neuropathy between diabetic patients with hypertension and diabetic patients without hypertension.

From the study results obtained, it is concluded that patients with type 2 DM and hypertension have a higher prevalence of micro and macro vascular complications compared to those without hypertension. Hypertension is a definite risk factor in the development and progression of vascular complications. Therefore, meticulous control of hypertension in patients with diabetes is important in the prevention and in reducing the progression of vascular complications of diabetes.

Bibliography

BIBLIOGRAPHY

1. Tuck, RR., Schmelzer JD, Low PA. Endoneurial blood flow and oxygen tension in the sciatic nerves of rats with experimental diabetic neuropathy. **Brain 1984; 107 : 935-950**.

2. Sato Y, Hotta N, Sakamoto N, et al. Lipid peroxide level in plasma of diabetic patients. **Biochem. J. 1979; 21 : 104-107**.

3. Greene DA. A sodium – pump defect in diabetic peripheral nerve corrected by Sorbinil administration : relationship to myo-inositol metabolism and nerve conduction slowing. **Metabolism, 1986; 35 (Suppl 1) : 60-65**.

4. Bucala R, Tracey KJ, Cerami A. Advanced glycosylation end products quench Nitric Oxide and mediate defective endothelium dependent vasodilatation in experimental diabetes. **J. Clin. Invest, 1991 : 87 : 432-438**.

5. Kohner EM, Aldington SJ, Stratton IM, et al. UKPDS, 30 : diabetic retinopathy at diagnosis of non-insulin dependent diabetes mellitus and associated risk factors : **Arch Ophthalmol, 1998 ; 116 : 297-303**.

6. UKPDS group. Effect of Intensive blood glucose control with sulfonylureas or Insulin Compared with conventional

treatment and risk of complications in patients with type 2 Diabetes. (UKPDS 33). **Lancet 1998; 352 : 837-853**.

7. Krolewski AS, Canessa M, Warram J H et al. Predisposition to hypertension and susceptibility to renal disease in Insulin dependent diabetes mellitus. **N. Engl. J. Med. 1988; 318 : 140-145.**

8. Stern MP, Patterson JK, Haffner SM, et al. Lack of awareness and treatment of hyperlipidemia in type II diabetes in a community survey. **JAMA 1989; 262 : 360-364**.

9. Chase HP, Jackson WE, Hoops SL et al., Glucose control in the renal and retinal complications of Insulin-dependent diabetes. **JAMA 1989; 261 : 1155-1160**.

10. Wilkinson CP, Ferris FLIII, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. **Ophthalmology 2003; 110 : 1677-1682**.

11. American Diabetes association. Diabetic nephropathy. **Diabetes Care 2003; 26 (Suppl. 1) : S94-S98**.

12. Schwab SJ, Dunn, FL, Fienglos, MN. Screening for microalbuminuria. A comparison of single sample methods of collection and techniques of albumin analysis. **Diabetes care 1992; 15 : 1581-1584**.

13. Mogensen CE, Christiansen CK. Blood pressure changes and renal function changes in incipient and overt diabetic nephropathy. **Hypertension 1985; 7 : 11-64. 11-73**.

14. Lewis EJ, Hunsicker LG, Bain RP et al. The effect of angiotensin – Converting enzyme inhibition on diabetic nephropathy **N Engl. J. Med. 1993; 329 : 1456-1462**.

15. Ravid M, Brosh D, Ravid - Safron D, et al. Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure and hyperglycemia. **Arch Intern. Med. 1998; 11 : 998-1004**.

16. Hostetter TH, RennkeHG, Brenner BM. The case of intra-renal hypertension in the initiation and progression of diabetic and other glomerulopathies. **Am. J. Med. 1982; 72 : 375-380**.

17. Grundy SM, Benjamin IJ, Burke GL, et al., Diabetes and Cardiovascular disease : a statement for health Care professionals from the American Heart Association**. Circulation 1999; 100 : 1134-1146**.

18. Natali A, Vichi S, Landi, P et al. Coronary atherosclerosis in type II diabetes angiographic findings and clinical outcome. **Diabetologia 2000; 43 : 632-641**.

19. Castells I, Salinas I, Rius F, et al. : Inducible myocardial ischemia in asymptomatic type 2 diabetic patients. **Diabetes Res. Clin. Pract 2000; 49 : 127-133**.

20. Zavaroni I, Bonora E, Pagliara M, et al. Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. **N. Engl. J. Med. 1989; 320: 702-706**.

21. UK prospective diabetic study group. Tight Blood pressure control and risk of microvascular and macrovascular complications in type 2 diabetes. **UKPDS 38. BMJ. 1998; 317: 703-713**.

22. G. Hu and Collegues. The impact of history of hypertension and type 2 diabetes at baseline on the incidence of stroke and stroke mortality. **Stroke 36; 2005 : 2538-2543**.

23. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood- pressure lowering and low dose aspirin in patients with hypertension. Principal results of the Hypertension optimal treatment (HOT) randomized trial. HOT study group. **Lancet 1998; 351 : 1755-1762**.

24. Brand FN, Abbott RD, Kannel WB. Diabetes, intermittent claudication and risk of cardiovascular events. The Framingham Study. **Diabetes 1989; 38 : 504-509**.

25. Menzoian JO, Lamorte WW, Paniszyn CC et al. Symptomatology and anatomic patterns of peripheral vascular disease : differing impact of smoking and diabetes. **Ann. Vasc. Surg. 1989; 3 : 224-228**.

26. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease : an update. **Hypertension 2001; 37 : 1053-1059**.

27. Wiseman MJ, Viberti GC, Mackintosh D, Jarrett RJ, Keen H. Glycemia, arterial pressure and microalbuminuria in type 1 diabetes mellitus. **Diabetologia 1984; 26 : 401-5**.

28. Hypertension in Diabetes study group. Hypertension in Diabetes study (HDS), II. Increased risk of cardiovascular complications in hypertensive type 2 diabetic patients. **J Hypertens, 1993; 11 : 319-25**.

29. Salomaa W, Strandberg TE, Vanhanen H. et al. Glucose tolerance and blood pressure : long term follow up in middle aged men. **BMJ 1991; 302 : 493-6**.

30. Scherrer U, Randin D, Vollenweider P, Vollenweider L, Nicod P. Nitric oxide release accounts for insulin's vascular effects in Humans. **J. Clin. Invest. 1994; 94 : 2511-15**.

31. Rongen GA, Tack CJ. Triglycerides and endothelial function in type 2 diabetes. **Eur. J. Clin. Invest. 2001; 31 : 560-2**.

32. DeFronzo RA, Goldberg M, Azus ZS. The effects of glucose and insulin on renal electrolyte transport. **J. Clin. Invest. 1976; 58 : 83-90**.

33. Natali A, Quinones Galvan A, Santora D et al. Relationship between Insulin release, anti natriuresis and hypokalemia after glucose ingestion in normal and hypertensive man. **Clin. Sci., 1993; 85 : 327-35**.

34. Hall JE, Summers RL, Brands MW, Keen H, Alonso-Galicia M. Resistance to metabolic actions of Insulin and its role in hypertension. **Am. J. Hypertens. 1994; 7 : 772-88**.

35. Morris AD, Petrie JR, Connell JMC. Insulin and Hypertension. **J. Hypertens. 1994; 12 : 633-42**.

36. Anderson EA, Balon TW, Hoffman RP, Sinkey CA, Mark AL. Insulin increases sympathetic activity but not blood pressure in borderline hypertensive humans. **Hypertension, 1992; 19 : 621-7**.

37. Capron L, Jarnet J, Kazandjian S, Housset E. Growth-promoting effects of diabetes and Insulin on arteries : an in vivo study of rat aorta. **Diabetes. 1986; 35 : 973-8**.

38. Haffner SM, Lehto S, Ronnemaa T., et al. Mortality from coronary artery disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. **N. Engl. J. Med. 1998; 339 : 229-234**.

39. Gress TW, Nieto J, Shahar E, et al. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. **N. Engl. J. Med. 2000; 342 : 905-912**.

40. Ferrannini E, Buzzigoli G, Bonadonna R, et al. Insulin resistance in essential hypertension. **N. Engl. J. Med. 1987; 317 : 350-357**.

41. Shen DC, Shieh SM, Fuh MM, et al. Resistance to Insulin – stimulated glucose uptake in patients with hypertension. **J. Clin. Endocrinol Metab. 1988; 66 : 580-583**.

42. Kotchen TA, Zhang HY, Covelli M, et al. Insulin resistance and blood pressure in Dahl rats and in one-kidney, one-clip hypertensive rats. **Am. J. Physiol. 1991; 261 : E692-E697**.

43. Reaven GH, Chang H. Relationship between blood pressure, plasma insulin and triglyceride concentration, and insulin action in spontaneous hypertensive and Wistar-Kyoto rats. **Am. J. Hypertens. 1991; 4 : 34 -38**.

44. Sechi LA, Melis A, Tedde R. Insulin hypersecretion : a distinctive feature between essential and secondary hypertension. **Metabolism 1992; 41 : 1261-66**.

45. Beatty OL, Harper R, Sheridan B, et al. Insulin resistance in offspring of hypertensive parents. **BMJ, 1993; 307 : 92-96**.

46. Semplicini A, Ceolotto G, Massimino M, et al. Interactions between insulin and sodium homeostasis in essential hypertension. **Am. J.Med. Sci. 1994; 307 [Suppl. 1] : S43-S46**.

47. Weinberger MH. Salt Sensitive Human Hypertension. **Endocr. Res., 1991; 17 : 43-51**.

48. Luft FC, Miller JZ, Grim CE, et al. Salt Sensitivity and resistance of blood pressure. Age and race as factors in physiological responses. **Hypertension 1991; 7 : 1102-1108**.

49. Weinberger MH, Fineberg NS. Sodium and volume sensitivity of blood pressure. Age and pressure change over time. **Hypertension, 1991; 18 : 67-71**.

50. Verdecchia P, Porcellati C, Schillaci G, et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. **Hypertension 1994; 24 : 793-801**.

51. Nakano S, Kitazawa M, Tsuda S, et al. Insulin resistance is associated with reduced nocturnal falls of blood pressure in normotensive, non obese type 2 diabetic subjects. **Clin. Exp. Hypertens 2002; 24 : 65-73**.

52. Ohkubo T, Hozawa A, Yamaguchi J, et al. Prognostic significance of the nocturnal decline in blood pressure in

individuals with and without high 24-h blood pressure : the Ohasama study. **J. Hypertens. 2002; 20 : 2183-2189**.

53. White WB. A Chronotherapeutic approach to the management of hypertension. **Am. J. Hypertens. 1996; 9 : 29S-33S**.

54. Arun CS, Stoddart J, Mackin P, et al. Significance of microalbuminuria in long duration type 1 diabetes. **Diabetes Care 2003; 26 : 2144-2149**.

55. Mogensen CE. Microalbuminuria and hypertension with focus on type 1 and type 2 diabetes. **J. Intern. Med. 2003; 254 : 45-66**.

56. Tagle R, Acevedo M, Vidt DG. Microalbuminuria : is it a valid predictor of cardiovascular risk? **Cleve Clin. J. Med. 2003; 70 : 255-261**.

57. Mitchell TH, Nolan B, Henry M, et al. Microalbuminuria in patients with non-insulin-dependent diabetes mellitus relates to nocturnal systolic blood pressure. **Am. J. Med. 1997; 102:531-535**.

58. McFarlane SI, Farag A, Sowers J. Calcium antagonists in patients with type 2 diabetes and hypertension. **Cardiovasc. Drug Rev. 2003; 21 : 105-118**.

59. Streeten DH, Anderson GH Jr. The role of delayed orthostatic hypotension in the pathogenesis of chronic fatigue. **Clin. Auton Res. 1998;8 : 119-124**.

60. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure : the JNC 7 report. **JAMA 2003; 289:2560-2572**.

61. Arauz-Pacheco C, Parrott MA, Raskin P. Treatment of hypertension in adults with diabetes. **Diabetes Care 2003; 26 [Suppl 1] : S80-S82**.

62. Bakris CL, Williams M, Dworkin L et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. **Am J Kidney Dis. 2000; 36 : 646-661.**

63. Bakris GL, Sowers JR. Microalbuminuria in diabetes : focus on cardiovascular and renal risk reduction. **Curr Diab. Rep. 2002; 2 : 258-262**.

64. McFarlane SI, Kumar A. Sowers JR. Mechanisms by which angiotensin converting enzyme inhibitors prevent diabetes and cardiovascular disease. **Am. J. Cardiol. 2003; 91 : 30H-37H**.

65. Shindler DM, Kostis JB, Yusuf S, et al. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) trials and registry. **Am. J. Cardiol. 1996, 77 : 1017-1020**.

66. Kendall MJ. Therapeutic advantages of AT1 blockers in hypertension. **Basic Res. Cardiol. 1998; 93 [Suppl 2] : 47-50**.

67. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. **N. Engl J. Med. 2001; 345 : 861-869**.

68. Parving HH, Lehnert H, Brochner – Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. **N. Engl. J. Med. 2001; 345 : 870-878**.

69. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. **N. Engl. J.Med. 2001; 345 : 851-860**.

70. Black HR, Elliott WJ, Neaton JD, et al. Baseline characteristics and early blood pressure control in the CONVINCE trial. **Hypertension 2001; 37 : 12-18**.

71. Major outcomes in high-risk hypertensive patients randomized to angiotensin converting enzyme inhibitor or

calcium channel blocker vs diuretic. The Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). **JAMA 2002; 288 : 2981-2997**.

72. Lin JE, Palmieri V, Roman NJ et al. The impact of diabetes in left ventricular filling pattern in normotensive and hypertensive adults : the strong heart study. **J. Am. Coll. Cardiol. 2001; 37 : 1943-9**.

73. Kuperstein R, Hanly P, Niroamand M, Fasson Z. The importance of age and obesity on the relation between diabetes and left ventricular mass. **J. Am. Coll. Cardiol. 2001; 37 : 1957-62**.

74. Hariharan R.S., Anand Moses C.R., Udhaya Shankar D. Influence of hypertension on the prevalence of macrovascular disease in diabetics. **"The Antiseptic" 1991, Vol.88(12) : P656-658**.

CASE PROFORMA

Name :

Age :

Sex :

Duration of DM : Family H/o. DM :

Duration of Hypertension : Family H/o. Hypertension:

Which came first DM/Hypertension ?

H/o. Complications

Neuropathy : Coronary Artery Disease :

Nephropathy : Cerebrovascular Disease :

Retinopathy : Peripheral Vascular Disease :

Clinical Examination

BP - 1. :

- 2. :

Pulse Rate :

Peripheral pulses :

Vascular Bruit :

Vascular Complications

Neuropathy

Monofilament :

Biothesiometry :

Neuropathy : Mild / Moderate / Severe

Nephropathy

Urine albumin – 1 :

- 2 :

Urine Microscopy :

Retinopathy

Fundus Examination :

Level of Retinopathy :

Coronary artery disease

ECG

Cerebrovascular disease

Focal neurological deficits :

Peripheral vascular disease

Ankle brachial pressure index :
(Doppler Method)

MASTER CHART

Diabetes with Hypertension

S.No	Age	Sex	Duration of DM (Years)	Duration of Hypertension (Years)	Peripheral Neuropathy	Nephropathy	Retinopathy	Cardio Vascular Disease	Cerebro Vascular Disease	Peripheral Vascular Disease
1	61	M	1	2	+ (Moderate)	-	+ (Mild NPDR)	-	-	-
2	50	F	5	3	-	-	-	-	+ (H/o. TIA)	-
3	58	F	5	5	+ (Severe)	-	-	-	-	-
4	58	F	5	6	-	-	-	+ (IW Ischemia)	-	-
5	60	F	6	4	+ (Moderate)	-	+ (Severe NPDR)	+ (AW Ischemia)	-	-
6	63	F	8	1	+ (Severe)	-	-	-	-	-
7	60	F	10	5	+ (Moderate)	+	+ (PDR)	+ (LW Ischemia)	-	+ (ABPI Lt. = 0.59)
8	75	M	7	7	-	-	-	-	-	-
9	44	F	7	7	+ (Moderate)	-	-	-	-	-
10	55	F	10	2	-	-	-	+ (IW Ischemia)	-	-
11	63	M	6	6	+ (Severe)	-	-	+ (IW Ischemia)	-	-
12	45	F	10	7	+ (Moderate)	-	-	-	-	-
13	65	F	9	2	+ (Severe)	+	+ (Mild NPDR)	-	-	-
14	65	M	8	8	-	-	-	-	-	-
15	55	F	10	5	+ (Moderate)	-	+ (PDR)	+ (AL Ischemia)	-	-
16	60	F	10	8	+ (Moderate)	-	-	+ (AS Ischemia)	-	-
17	39	M	8	8	-	+	+ (Mild NPDR)	+ (Old ASMI)	+ (H/o. CVA/Lt. Hemiparesis)	-

18	70	F	10	10	+ (Moderate)	-	+ (Moderate NPDR)	-	-	-
19	64	F	8	7	+ (Severe)	-	+ (PDR)	-	-	-
20	45	F	10	20	+ (Severe)	-	+ (Mild NPDR)	+ (IW Ischemia)	-	-
21	56	M	11	2	+ (Mild)	-	+ (Mild NPDR)	-	-	-
22	61	M	13	6	-	-	-	-	-	-
23	50	F	12	7	+ (Severe)	-	-	-	-	-
24	61	M	15	10	-	-	+ (Mild NPDR)	+ (IW Ischemia)	-	-
25	60	M	11	4	-	+	+ (PDR)	-	-	-
26	70	F	13	13	-	-	-	-	-	-
27	77	M	15	10	+ (Severe)	-	-	-	-	-
28	58	M	13	13	-	+	+ (Mild NPDR)	-	-	-
29	52	M	11	8	+ (Severe)	-	-	-	-	-
30	50	F	15	1	-	+	-	-	-	-
31	70	M	12	5	+ (Moderate)	-	-	+ (IW Ischemia)	-	-
32	57	F	12	6	-	-	-	-	-	-
33	53	F	12	3	+ (Moderate)	-	-	-	-	-
34	60	F	10	3	+ (Moderate)	-	-	-	-	-
35	69	M	10	10	-	+	+ (Moderate NPDR)	+ (Old IWMI)	-	-
36	60	F	11	3	+ (Moderate)	-	-	+ (AL Ischemia)	-	-
37	71	M	10	6	-	-	-	+ (LW Ischemia)	-	-
38	45	F	8	13	+ (Severe)	-	-	-	-	-
39	76	M	18	15	+ (Severe)	-	-	-	-	-
40	56	M	12	5	+ (Moderate)	-	-	+ (Old IWMI)	-	-
41	56	M	18	4	+ (Severe)	+	+ (PDR)	+ (AL & IW Ischemia	-	-

42	58	F	16	2	+ (Moderate)	+	-	-	-	-
43	47	F	10	10	+ (Severe)	-	-	-	-	-
44	79	M	20	10	+ (Severe)	-	-	-	+ (H/o. CVA/Lt. Hemiparesis)	-
45	79	M	20	10	-	-	-	-	-	-
46	51	F	23	6	+ (Severe)	+	+ (Moderate NPDR)	-	-	-
47	70	M	24	5	-	-	-	-	-	+ (H/o. Amputation 3rd Toe)
48	72	M	32	4	-	-	+ (PDR)	-	+ (H/o. TIA)	+ (ABPI B/L = 0.5)
49	68	F	20	3	+ (Severe)	+	+ (Mild NPDR)	-	-	-
50	70	F	3	3	+ (Moderate)	+	-	Recent ASMI	-	-

NPDR - Non Proliferative Diabetic Retinopathy, PDR - Proliferative Diabetic Retinopathy, IW - Inferior wall,
IL - Inferolateral wall, AL - Anterolateral, ASMI - Anteroseptal Myocardial Infarction, LW - Lateral wall,
ABPI - Ankle Brachial Pressure Index, TIA - Transient Ischemic Attack, CVA - Cerebrovascular accident,
IWMI - Inferior Wall Myocardial Infarction, AS - Antero Septal; + Presence of complications; - Absence of complications

MASTER CHART

Diabetes without Hypertension

S. No.	Age	Sex	Duration of DM (Years)	Peripheral Neuropathy	Nephropathy	Retinopathy	Cardiovascular Disease	Cerebrovascular Disease	Peripheral Vascular Disease
1	55	F	3	+ (Moderate)	-	-	-	-	-
2	45	M	3	-	-	-	-	-	-
3	40	F	4	+ (Moderate)	-	-	-	-	-
4	45	F	5	+ (Mild)	-	-	-	-	-
5	65	F	6	-	-	-	-	-	-
6	50	F	6	-	-	-	-	-	-
7	64	M	6	-	-	-	-	-	-
8	74	M	7	+ (Moderate)	-	-	-	-	-
9	79	M	6	-	-	-	-	-	-
10	68	M	9	-	-	-	-	-	-
11	48	M	10	-	-	-	-	-	-
12	63	F	10	+ (Moderate)	-	-	-	-	-
13	54	M	10	+ (Moderate)	-	-	-	-	-
14	62	M	10	-	-	-	-	-	-
15	60	M	7	-	-	-	+ (IW Ischemia)	-	-

16	75	M	10	-	+	-	-	+ (CVA / Lt. Hemiparesis)	-
17	66	F	12	+ (Severe)	-	-	+ (IL Ischemia)	-	-
18	57	F	12	+ (Mild)	-	-	-	-	-
19	56	M	13	-	-	-	-	-	-
20	63	M	13	+ (Moderate)	-	-	+ (AL Ischemia)	-	+ (ABPI Lt.= 0.7)
21	53	M	14	+ (Moderate)	+	+ (PDR)	-	-	-
22	66	M	14	-	-	-	-	-	-
23	50	F	12	-	-	-	-	-	-
24	67	M	13	+ (Moderate)	-	+ (Mild NPDR)	-	-	-
25	63	F	13	+ (Severe)	+	-	-	-	-
26	54	M	13	-	-	-	-	-	-
27	60	M	12	+ (Severe)	+	-	-	-	-
28	53	M	15	-	-	-	-	-	-
29	65	M	12	-	-	-	-	-	-
30	54	F	13	-	-	-	-	-	-
31	64	M	8	+ (Mild)	-	-	+ (IW Ischemia)	-	-
32	63	F	11	-	-	-	-	-	-
33	53	F	15	+ (Moderate)	-	+ (Mild NPDR)	-	-	-
34	63	F	10	-	-	-	-	-	-
35	53	F	10	+ (Moderate)	-	-	-	-	-

36	54	F	10	-	-	-	-	-	-
37	58	F	10	-	-	-	-	-	-
38	55	F	12	-	-	-	+ (Old ASMI)	-	-
39	67	F	12	+ (Mild)	-	-	-	-	-
40	55	M	13	+ (Severe)	-	+ (Severe NPDR)	-	-	-
41	47	M	11	+ (Moderate)	+	+ (Moderate NPDR)	-	-	-
42	60	F	9	+ (Moderate)	-	-	-	-	-
43	60	F	10	-	-	-	-	-	-
44	42	F	13	-	-	+ (Mild NPDR)	-	-	-
45	57	F	18	+ (Mild)	-	+ (Moderate NPDR)	-	-	-
46	53	M	20	-	-	-	-	-	-
47	64	M	21	+ (Moderate)	-	-	-	-	-
48	59	F	19	+ (Severe)	+	-	-	-	-
49	70	F	9	-	-	-	-	-	-
50	73	F	30	+ (Moderate)	-	+ (Mild NPDR)	-	-	-

NPDR - Non Proliferative Diabetic Retinopathy, PDR - Proliferative Diabetic Retinopathy, IW - Inferior wall, IL - Inferolateral wall, AL - Anterolateral, ASMI - Anteroseptal Myocardial Infarction, ABPI - Ankle Brachial Pressure Index

+ Presence of complications; - Absence of complications