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DIABETES & HYPERTENSION: THE SIAMESE TWINS

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INTRODUCTION: Globally type 2 diabetes is in increasing trend with projected 366 million by 2030. The number of adults with hypertension is predicted to increase by 60% to a total of 1.56 billion people by 2025. 70% patients with DM have hypertension and hypertension is approximately twice as common in persons with diabetes as in those without. In the Hong Kong Cardiovascular Risk Factor Prevalence Study, 58% of people with diabetes had HTN and 44% of people with hypertension had dysglycemia.

Diabetes and hypertension constitute the Siamese twin in the tragic story cardiovascular forum. In type 2 DM, HTN dictates the story of metabolic syndrome where as in type 1 it fingers at the onset of nephropathy. Hypertension increases the risk of DM and vice versa explaining the symbiotic lethal chemistry between two. Hypertension substantially increases the risk of both macro vascular and micro vascular complications, including stroke, coronary artery disease, peripheral vascular disease, retinopathy, nephropathy, and possibly neuropathy in diabetes mellitus.

Coexistence of hypertension and diabetes can pose serious risks in subpopulations like pregnant women being at risk for pre-eclampsia and children being particularly vulnerable to end-organ disease and accelerated atherosclerosis with aging. Diabetes carries 2 fold risk of CVD in men and four fold risk of CVD in post-menopausals. Diabetes and HTN in combination has 2 fold more CVD than hypertension alone. They potentiate the complication of each other. In UKPDS study 10 mmHg decrease in SBP decreased any complication by 12%, mortality by 13%, MI by 11% and micro vascular complication by 13%.

PATHOPHYSIOLOGY: As the disease progress the diabetics acquire HTN, dyslipidemia, atherosclerosis and CVD. Obesity, inflammation, oxidative stress and insulin resistance are the common to the duos. DM and HTN share common pathways of SNS, RAAS, oxidative stress, adipokines, insulin resistance, PPARs and both cause a vicious cycle. They may, therefore, develop one after the other in the same individual.

Physical activity plays an important protective role in both of them. Both share the common genetic or environmental factors as evidenced in Hong Kong and Columbia studies of single nucleotide polymorphisms (SNPs), SNPs that predict the development of diabetes were also found also to predict the development of hypertension.

DIABETIC VASCULOPATHY CAUSING HYPERTENSION:

Endothelium:

- ↑NF-κ β activation
- ↓Nitric oxide-production
- ↓Prostacyclin bioavailability

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- ↑Endothelin1activity ↑Angiotensin 2 activity
- ↑Cyclooxygenase 2 activity
- ↑Thromboxane A 2 activity
- ↑Reactive oxygen species
- ↑Lipid peroxidation products
- ↓Endothelium-dependent relaxation
- ↑RAGE expression

Vascular smooth muscle cells and vascular matrix:

- ↑Proliferation and migration into intima
- ↑Increased matrix de-gradation
- Altered matrix components

Inflammation:

- ↑IL-1 β , IL-6, CD36, MCP-1
- ↑ICAMs, VCAMs, and selections
- ↑Activity of protein kinase C
- ↑ AGEs and AGE/RAGE interactions

Triad of sodium retention, endothelial dysfunction and over activity of the renin-angiotensin system (RAS) leads to hypertension. Excessive RAAS and SNS activity is the principal mechanism behind. HTN develops secondary to metabolic syndrome mechanics i.e. insulin resistance, endothelial dysfunction, hyperglycemic wave front mediated endothelial injury, RAGE – AGE axis stimulation, IGF mediated smooth muscle hyperplasia, leptin induced oxidative stress, PPAR γ mediated endothelin release. Nephropathy, renal scarring due to recurrent pyelonephritis, coincidental essential HTN and drugs like OCP, steroids all contribute an additive effect.

HYPERINSULINEMIA & HYPERTENSION: Epidemiologic studies correlate insulin resistance/hyperinsulinemia with hypertension demonstrating Insulin having sympathetic effect. However paradox lies in the fact that chronic hyperinsulinemia, in absence of obesity does not increase BP, neither chronic insulin infusion does increase BP and insulinoma patients are non-hypertensive.

INSULIN RESISTANCE & HYPERTENSION: Insulin resistance, independent of hyperinsulinemia, can increase BP but humans with leptin mutation having severe insulin resistance with no increased BP. However, abnormalities of glucose & lipid metabolism, associated with insulin resistance may lead to vascular and renal injuries to cause increase BP. Enhanced FFA mobilization in DM leads to atherosclerosis which increases the BP and insulin resistance with dysglycemia cause glycosylation of glomerular and extracellular matrix proteins leading in nephron hypofunction and genesis of HTN.

PATHOGENESIS OF DIABETES IN HYPERTENSION: Hypertensive subjects have a 2.5 times greater risk of developing diabetes within 5 years than normotensives matched for age, sex, and race. The predilection for hypertensive to develop diabetes may be due in part to insulin's

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diminished ability to promote relaxation and glucose transport in vascular and skeletal muscle tissue. Decreased tissue blood flow secondary to increased peripheral vascular resistance produce vascular rarefaction and decreased delivery of insulin and glucose to peripheral cells creating a state of insulin resistance. However, caveat lies behind the fact that increased PVR does not always lead to tissue under perfusion and as long as liver sensitivity to insulin is normal, tissue perfusion can't explain insulin resistance and hyperinsulinemia.

CLASSIFICATION OF HYPERTENSION IN DIABETES

Insulin-dependent (Type I) diabetes

- Hypertension associated with nephropathy
- Essential hypertension
- Hypertension secondary to other causes

Non-insulin-dependent (Type II) diabetes

- Hypertension associated with obesity
- Hypertension associated with nephropathy
- Essential hypertension
- Secondary Hypertension

Endocrine causes of glucose intolerance and hypertension

- Pheochromocytoma
- Cushing's syndrome
- Steroid therapy
- Acromegaly

NORMOTENSIVE HYPERTENSION IN DM: Vasculopathy starts 5 years before development of hypertension. A today's normotensive diabetic is tomorrow's hypertensive. Care the microvascular dysfunction (VP) today, prevent the hypertension of tomorrow.

DIABETICS ARE DIFFERENT DIPPERS: The common absence of normal nocturnal "dipping" of BP in diabetics is associated with other cardiovascular disease surrogates such as microalbuminuria and left ventricular hypertrophy.

DIFFICULT HYPERTENSIVES: Systolic HTN more common in DM which is a stronger predictor of CVE while 65% of Type 2 DM have systolic HTN. Depression is more in DM leading to decreased adherence to treatment. "Clinician Inertia" is a big problem. Glycemic control only is the focus; not the vascular protection- is the goal of many physicians caring the diabetes capital.

COMPLICATIONS:

Microvascular:

- Nephropathy
- Autonomic neuropathy
- Retinopathy

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Macrovascular:

- Cardiovascular disease
- Cerebrovascular disease
- Peripheral vascular disease
- Reduced survival and recovery rates from stroke

RELATIVE RISK OF EVENTS BETWEEN DIABETES AND HTN VERSUS DIABETES:

- Neuropathy 1.6
- Nephropathy 2.0
- Retinopathy 2.0
- Stroke 4.0
- CHD 3.0
- Mortality 2.0

DM AND HTN: A CUMULATIVE RISK: Each 20/10 mmHg increase in SBP increase CVD risk by two fold. There is a linear association between SBP and CV mortality in diabetics along with increased hazard ratio as evidenced in SHEP study, Syst EUR study, HOT study and Meta analytic reports. HTN is associated with more morbidity and mortality in Diabetics as compared to non-diabetics.

MANAGEMENT: It begins with a global approach towards hyperglycemia, HTN and hyperlipidemia. Begins with regular blood pressure monitoring, BMI maintenance, micro albuminuria, albumin creatinine ratio estimation along with Serum Cr, screening for metabolic syndrome, CAD, ABI, ophthalmopathy, HbA1c, full lipid profile, Lp(a) and hs-CRP.

LIFESTYLE MODIFICATION:

- Regular 30min of moderately intense exercise decrease SBP by 10 mmHg
- No tobacco and alcohol
- Believe DASH diet plan
- Na restriction to < 6 g of NaCl per day decrease DBP by 5mmHg.
- Avoiding high salt foods – pickles, savouries.
- Use of K containing foods – fruits, vegetables.
- Weight reduction – goal ideal weight (1 kg weight loss translate into 1 mmHg fall in MAP (mean arterial pressure).
- Reducing coffee consumption.

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BENIFITS OF LIFESTYLE MODIFICATION (↓SBP)

- Weight Reduction
5-20 mmHg/10kg
- DASH diet eating
8-14 mmHg
- Sodium Restriction
2-8 mmHg
- Physical Activity
4-9 mmHg
- Alcohol Abstinence
2-4 mmHg
- All put together
20-55 mmHg

DASH Diet Plan:

Type of Food	Servings (1600 K cal)
Grains (whole grains)	6 per day
Vegetables	3 per day
Fruits (not tinned juices)	4 per day
Low fat milk	2 per day
Lean meat, poultry	3 per day
Nuts, seeds (dry roast, soak)	3 per week
Fats and oils	2 per day
Sweets and pastries	0 per day
Salt at table & salted foods	None

BENEFIT OF QUITTING SMOKING IN DM&HTN (↓CAD INCIDENCE (%) OVER 5 YEARS):

Cigarettes/day	Men	Women
10	19	24
20	34	40
40	57	64

THE EVIDENCE BASE FOR MANAGEMENT OPTIONS: The UKPDS and the Hypertension Optimal Treatment (HOT) trial both demonstrated improved outcomes, especially in preventing stroke, in patients assigned to lower blood pressure targets. HTN control translates into micro vascular complication reduction and micro albuminuria as seen in UKPDS. Optimal outcomes in the HOT study were achieved in the group with a target diastolic blood pressure of 80 mmHg (achieved 82.6 mmHg). Study of 61 randomized prospective trials in one million adults showed every 2 mmHg reduction in SBP decrease IHD by 7% and 10% reduction in stroke mortality.

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The UKPDS-Hypertension in Diabetes Study showed no significant difference in outcomes for treatment based on an ACE inhibitor compared with a β -blocker further more there were slightly more withdrawals due to side effects and there was more weight gain in the β -blocker group. In post myocardial infarction patients, β -blockers have been shown to reduce mortality.

ACE inhibitors have a favorable effect on cardiovascular outcomes, as demonstrated in the MICROHOPE study. This cardiovascular effect of ACEI may be mediated by mechanisms other than blood pressure reduction. In (ALLHAT) study ACE inhibitors and β blockers appeared to be superior to DCCBs in reducing myocardial infarction and heart failure. Therefore, DCCBs appear to be appropriate agents in addition to, but not instead of ACE inhibitors and β -blockers.

LESSON FROM LANDMARK TRIALS:

UKPDS¹ Study: 1148 patients were randomized to tight BP control defined as BP < 150/85 mm Hg or less tight control of BP defined as BP < 180/105 mm Hg. Half of tight control group were given ACE inhibitors (captopril) and another half beta blockers (atenolol) with a mean follow-up of 8.4 years with larger part followed up every 3-4 months. Mean blood pressure during follow-up in the tight control group was 144/82 mm Hg and in less tight control group it was 154/87 mm Hg. 1/3 patients in tight control group required 3 or more medications. It demonstrated every 10 mmHg decrease in SBP decreased any complication by 12%, mortality by 13%, MI by 11% and micro vascular complication by 13%. Tight BP control was more important than blood sugar control to obtain CV outcome.

HOT² Study: Enrolled 18, 790 patients from 26 countries with age 50 -80 years with diastolic blood pressure 100-115 mm Hg. Patients were randomized to 3 groups based on diastolic pressure goal (<90, <85, and <80 mm Hg). Primary endpoint was composite macrovascular outcome of non-fatal MI, non-fatal stroke, or CV death. Major finding was that patients with diabetes had a 51% reduction in primary endpoint and DBP reduction <80 mmHg improved CV outcome only in Diabetics.

ADVANCE³: Conducted across 215 centers in 20 countries with 11, 140 patients with type 2 diabetes randomized to fixed combination of perindopril and indapamide or matching placebo. Primary endpoints were composites of major macro and microvascular events i.e. death from CV disease, non-fatal stroke, non-fatal MI and new or worsening renal or diabetic eye disease with 4.3 years of follow-up. Compared to placebo, there was a drop in pressure of 5.6/2.2 mm Hg with perindopril and indapamide or matching placebo.

There was a 9% decrease in micro and macro vascular complication in combination ($p=0.04$); also decrease in CV death ($p = 0.03$) and death from any cause ($p = 0.03$). After 5 years of treatment with Indapamide and Perindopril combination one MACE will be prevented in 66 patients, one death in 79 patients, one coronary event in 75 patients and one renal event in 20 patients. Routine treatment with this combination reduced total mortality by 14%, cardiovascular mortality by 18%, major vascular event by 9%, total coronary event by 14% and total renal event by 21%.

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ACCORD⁴: It was based on the hypothesis that targeting normal systolic blood pressure (<120 mm Hg) in patients with type 2 diabetes and at high risk for cardiovascular events will reduce major cardiovascular events. 4733 patients were randomized to intensive therapy (systolic BP <120 mm Hg) or standard therapy (systolic BP <140 mm Hg) with primary composite outcome was nonfatal MI, nonfatal stroke, or death from CV causes with mean follow-up of 4.7 years

There was no difference between groups, in terms of reaching the primary outcome. But there was a decrease in rates of stroke and lesser rates of progression of albuminuria in intense therapy group. In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg as compared with less than 140 mmHg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events; yet intensive therapy (Less than 120 mmHg) BP resulted in more complications in form of hypotension, bradycardia and hyperkalemia.

ABCD⁵ TRIAL: APPROPRIATE BLOOD PRESSURE CONTROL IN DIABETES: It compared intensive (DBP <75 mmHg) versus moderate blood pressure (DBP: 80 – 89 mm Hg) control on the incidence and progression of complications in type 2 diabetes in 470 patients with entry diastolic blood pressure > 90 mm Hg with follow up for 5.3 years. It also compared the effect of CCB vs. ACE inhibitor. Endpoints were change in creatinine clearance as primary and development of microvascular complications and CV disease as secondary. BP attained for last 4 years was 132/78 mm Hg for intensive and 138/86 mm Hg for moderate control group.

There was no difference in creatinine clearance, microalbuminuria, and progression of retinopathy or neuropathy between moderate and intensive control group; also there was no difference between ACEI or CCB. Intensive therapy had a lower overall incidence of death (5.5 vs. 10.7%, $p = 0.037$).

ONTARGET⁶: It compared telmisartan (ARB) with ramipril (ACEI), as well as combination of telmisartan plus ramipril vs ramipril alone, as treatment for prevention of vascular events in patients with CVD and patients with diabetes and known micro vascular complications, but no CHF. It was a noninferiority trial with primary endpoint of death from CV causes, MI, stroke, or hospitalization for CHF in 25, 620 patients. Telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes. The combination of telmisartan plus ramipril vs ramipril alone was no better, but there were more adverse events associated with the combination.

HOPE Trial: This landmark study constituted 3577 diabetes comparing Ramipril vs placebo. Ramipril-treated patients reached primary endpoint at a rate lower than placebo (14.0 vs 17.8%, $p < 0.001$). Ramipril reduced rate of death from any CV cause (6.1 vs. 8.1%, $p < 0.001$), decreased rate of MI (9.9 vs 12.3%, $p < 0.001$), decreased stroke (3.4 vs. 4.9%, $p < 0.001$) and death from any cause (10.4 vs. 12.2%, $p = 0.005$). In addition revascularization, rate of heart failure, cardiac arrest and complications related to diabetes were all reduced by Ramipril.

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ACEI – GOLDEN DRUG FOR VASCULAR PROTECTION (VP):

- ACEI are antihypertensive, vasoprotective, anti-thrombotic and anti-inflammatory.
- Inevitable in DM, more so in DM and HTN in combination.
- Reduce atherosclerosis & CV events.
- Reduce nephropathy - a strong CV risk factor.
- Metabolically „friendly“ with drugs in DM and improve HbA1C.
- Well-tolerated with few side effects.

ACEI OR ARB:

- HOPE (Ramipril vs Placebo): Ramipril Decreased cardiovascular MACE.
- Micro HOPE: Ramipril decreased CV mortality
- CALM (Lisinopril vs. Candesatran): Lisinopril decreased HTN and microalbuminuria.
- RENAAL7 (Losartan vs. Placebo): Losartan decreased progression to nephropathy.
- MARVEL: Irbesatran and Valsartan decreased nephropathy; Amlodipine was not superior to placebo.
- So far as renal protection is concerned studies are merging towards ARB and 20 meta-analysis demonstrated ACEI/ARB slowed down the progression of renal disease.
- Paradox is seen when AMI and HF concerned, ACEI works better i.e. in ELITE II, Losartan was not superior to captopril in HF, in OPTIMAAL Captopril reduced CV death compared to Losartan.
- ACEI and ARB combination although initially encouraged from CALM8 and COOPERATIVE9 study, ONTARGET clearly ignores it.
- These are of dramatic benefit in renal impairment; improve e-GFR, microalbuminuria, LV dysfunction (along with new β blocker) and previous MI (along with new β blocker).
- Contraindicated in pregnancy with relative contraindications in bilateral renal artery stenosis, severe renal impairment (Cr >3.0) or patients with angioedema, ACEI induced cough.

CARVEDILOL: It Improve HbA1C, improves insulin resistance and metabolic syndrome, lipid neutral, adds on to RAAS blockade in DM, improves microalbuminuria, albumin creatinine ratio and endothelial dysfunction and plays best role in diabetic cardiomyopathy and HF.

VASCULAR PROTECTION (VP) IN DM & HTN:

- Statin (Lipid management)
- ASA (Acetyl Salicylic Acid)
- ACE inhibitors or ARBs
- A₁ Ccontrol (HbA1C<7%)
- Blood pressure goal (<140/90)
- Control of microalbuminuria (MAU)
- Cigarette smoking cessation
- Weight and waist management
- 2 km/day walking x 5 days per week

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STEPS TO FOLLOW OF JNC 8¹⁰: TARGET BP IS <149/90 mmHg: Irrespective of the presence or absence of CKD the target BP in DM is <140/90 mmHg and any drug out of ACEI, ARB, CCB or thiazide type of diuretic can be chosen for initiation. It is based on evidence from 3 quality trials (SHEP, Syst-Eur, and UKPDS) that treatment to an SBP goal of lower than 150mmHg improves cardiovascular and cerebrovascular outcomes and lowers mortality in adults with diabetes and hypertension, also supported by the ACCORD-BP trial.

ADVANCE trial did not meet the ACC/AHA panel's inclusion criteria because participants were eligible irrespective of baseline BP and there were no BP treatment goals. SBP goal of lower than 130mmHg is not supported by any RCTs. There are also no good quality RCTs that compared a DBP goal of lower than 90 mm Hg with a lower goal of <80 mmHg. HOT trial frequently cited to support a lower DBP of 80mmHg or lower was a small subgroup post hoc analysis that was not pre specified and the evidence in it was graded as low quality.

UKPDS was a mixed systolic and diastolic BP goal study (combined SBP and DBP goals), so it was difficult to derive whether the benefits were due to lowering SBP, DBP, or both. Contrary to this evidence ESC 2013 guideline recommends blood pressure goal <140/85mmHg and ADA 2013 guideline recommends it to be <140/80 mmHg and this jigsaw puzzle goes on. Assimilating all these facts JNC8 ultimately now recommends a target BP of 140/90 mmHg irrespective of age and CKD.

THERAPEUTIC RISK REDUCTION IN DM: 4mmHg reduction in SBP reduce CV event by 12.5%, 1 mmol reduction in LDL reduce CV event by 8.2% and 0.9% reduction in HbA1C reduce it by only 2.9%; hence BP reduction is utmost important in Diabetes Mellitus.

CONCLUSION: HTN, DM and CVD constitute the tripod of a fatal sink the present race is moving towards. Timely intervention towards dysglycemia, hypertension and dyslipidemia can candle a bright outcome in future. Treat blood pressure to below 140/90 mmHg, HbA1C below 7% and use moderate or high intensity statin; the epic will come to an end. No intensive; it is the conventional strategy to win the game. Thanks to the age old saying:

“Slow and steady wins the race”

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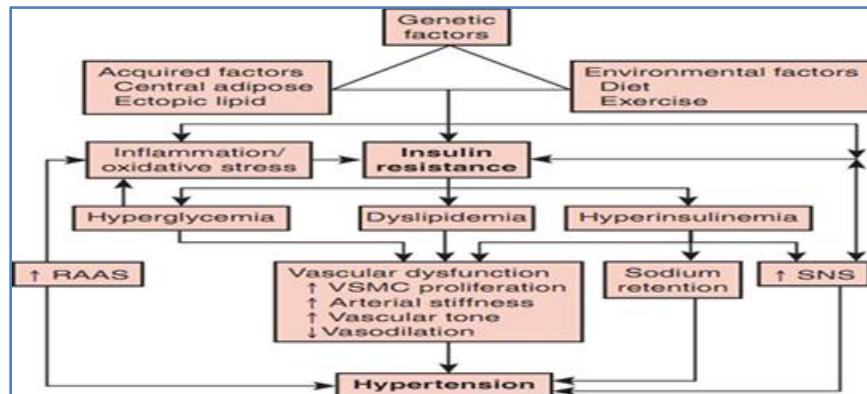


Fig. 1: Pathogenesis of hypertension in diabetes mellitus

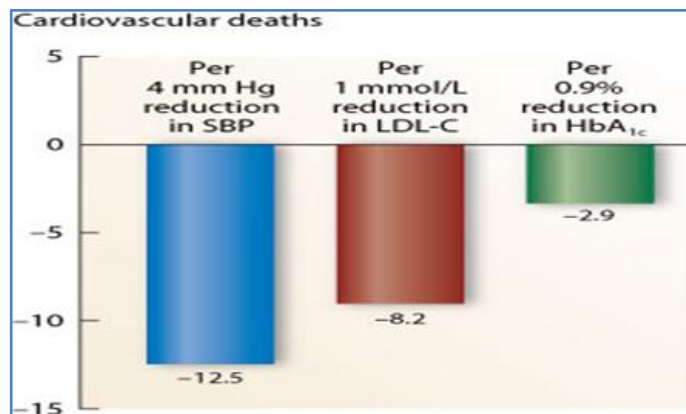


Fig. 2: BP reduction most important

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