Available online at www.ijiit.net

International Journal of Integrative sciences, Innovation and Technology (IJIIT)
(A Peer Review E-3 Journal of *Science Innovation Technology*)
Journal homepage: http://www.ijiit.net/

eISSN 2278-1145
Research Unlimited
Vol. IV Iss 4

Review Paper

Diabetes with Hypertension: Etiology, Pathogenesis and Management

Deepak Bharati*[1], Savita Tauro[1], Swati Rawat[2], Pankaj Sharma[3], B. Shrivastav[3]

[1]*St. John Institute of Pharmacy and Research, Palghar, Thane, Maharashtra- 401404, India*

[2]*S.N.D. College of Pharmacy, Yeola, India.*

[3]*Jaipur National University, Jaipur, India.*

ARTICLE INFO

Article history:
Received 15 July 2015
Received in revised form 02 August 15
Accepted 08 August 2015

Keywords:
Diabetes
Hypertension
Cardiovascular diseases

ABSTRACT

There has been an increase in the predominance of diabetes mellitus over the past 40 years worldwide. The worldwide occurrence of diabetes in 2000 was approximately 2.8% and is estimated to grow to 4.4% by 2030. This data interprets a projected rise of diabetes from 171 million in 2000 to well over 350 million in 2030. The presence of hypertension in diabetic patients substantially increases the risks of coronary heart disease, stroke, nephropathy and retinopathy. Indeed, when hypertension coexists with diabetes, the risk of CVD is increased by 75%, which further contributes to the overall morbidity and mortality of an already high risk population. Patients with type 2 diabetes mellitus have a considerably higher risk of cardiovascular morbidity and mortality, and are disproportionately affected by cardiovascular disease. Most of this excess risk is associated with high prevalence of well-established risk factors such as hypertension, dyslipidaemia and obesity in these patients. Hypertension plays a major role in the development and progression of microvascular and macrovascular disease in people with diabetes. Lifestyle Modifications and pharmacotherapy are the choice for the Management of Hypertension in Patients with Diabetes.

How to cite this article: Deepak Bharati, Savita Tauro, Swati Rawat, Pankaj Sharma and B. Shrivastav (2015). Diabetes with Hypertension: Etiology, Pathogenesis and Management, International Journal of integrative Sciences, Innovation and Technology (IJIIT), 4(4), 7 - 14.

1. Introduction

There has been an increase in the predominance of diabetes mellitus over the past 40 years worldwide. The worldwide occurrence of diabetes in 2000 was approximately 2.8% and is estimated to grow to 4.4% by 2030. This data interprets a projected rise of diabetes from 171 million in 2000 to well over 350 million in 2030.[1] The epidemic of diabetes will continue to rise as there is growing prevalence of obesity in children, which predisposes to diabetes.[2] There is significant evidence for an increased prevalence of hypertension in diabetic persons.[3] In a large prospective cohort study that included 12,550 adults, the development of type 2 diabetes was almost 2.5 times as likely in persons with hypertension than in their normotensive people.[4,5] Similarly, evidence points to increased prevalence of hypertension in diabetic persons. Moreover, each pathophysiological disease conditionworks to aggravate the other. Both hypertension and diabetes predisposes to the development of cardiovascular disease (CVD) and renal disease.[3,5] Subjects with diabetes is at about 60% increased risk of

* Corresponding author. *Tel.:* 09960337398; +91 2525 256486
E-mail address: deepakbharti007@gmail.com

Peer review under responsibility of board members IJIIT

Hosting by AGSI Publications

early mortality. The age adjusted relative risk of death due to cardiovascular events in persons with type 2 diabetes is three-fold higher than in the general population. The presence of hypertension in diabetic patients substantially increases the risks of coronary heart disease, stroke, nephropathy and retinopathy. Indeed, when hypertension coexists with diabetes, the risk of CVD is increased by 75%, which further contributes to the overall morbidity and mortality of an already highrisk population.[4,5] Generally, hypertension in type 2 diabetic persons combined with other CVD risk factors such as microalbuminuria, central obesity, insulin resistance, dyslipidaemia, hypercoagulation, increased inflammation and left ventricular hypertrophy.[5]This clustering risk factor in diabetic patients ultimately results in the development of CVD, which is the major cause of premature mortality in patients with type 2 diabetes.

2. Predominance and Medical Significance of Diabetes Hypertension

According to the International Diabetes Federation there are currently more than 194 million people with diabetes worldwide.[6]The majority of these persons have type 2 diabetes, which has become a worldwide epidemic. More than20 million individuals in the United States have diabetes, and an additional 53 million Americans have impaired fasting glucose.[7,8] The combination of these unadjusted prevalence of total diabetes and impaired fasting glucose in patients older than 20 years is 14.4%, and because it is the leading cause of blindness, end-stage renal disease, dialysis treatment, and nontraumatic amputations, its medical importance cannot beunderestimated.[8,9] It is well-known that the course of microvascular and macrovascular complications are accelerated by hypertension.[10] In hypertensive diabetics, the mortality risk due to cardiovascular events is 4 times more than that of subjects in whom these 2 diseases are absent.[11]

When compare with the overall population Hypertension is a common comorbid condition in patients with type1 or type 2 diabetes [12] Although hypertension may be present at the time of diagnosis of type 2 diabetes, hypertension often precedes diabetes onset,[13] suggesting that it is either an independent process or part of the metabolic syndrome.[14] Hypertensive subjects have a 2.5 times greater risk of developing diabetes within 5 years than normotensives matched for age, sex, and race. The tendency for hypertensives to develop diabetes may be due in part to insulin's reduced ability to promote relaxation and glucose transport in vascular and skeletal muscle tissue.[15,16]on the other hand, type 2 diabetes [17,18] and insulin resistance[38] are strongly associated with increased prevalence of hypertension. Hypertension is 1.5 to 3 times more prevalent in the diabetic population than in non diabetic age-matchedsubjects.[19]This further supports the perception that these 2 common chronic diseases are frequently concordant.[20]The association between hypertension and diabetes is specifically different depending on the type of diabetes. In patients with type 1 diabetes, the lifetime risk of elevated blood pressure (BP) is approximately 60%.[21] The majority of type 1 diabetics are not hypertensive at beginning of microalbuminuria, but its presence accelerateshypertension.[22] While 15% to 25%of microalbuminuric type 1 diabetic patients are hypertensive, the prevalence of hypertension increases to 75%to 85% in patients with diabeticnephropathy.[23]These 2 diseases present a major public health risk. Hypertension occurs in 75% of type 2 diabetics.[24]In a recent cross-sectional study of German primary care practices, the copresentation was 10.4% in men and 8.1% in women who had both of these conditions. Complicating diseases were also found in 81% of cases,.[25,26] Cardiovascular disease is the same in diabetic women as in men, indicating that diabetes removes the normal sex difference in the prevalence of coronary heart disease.[27], the mortality risk of cardiovascular events is 4 times higher in hypertensive diabeticsthan that of subjects in whom these 2 diseases are absent.[12]In the United States Type 2 diabetes constitutes more than90% of diabetes and is associated with a 70% to 80% risk of premature death from cardiovascular disease and stroke.[28] The presence of components of the metabolic syndrome increases oxidative stress leads to endothelial dysfunction, which is a key component of the pathogenesis of hypertension.[29,30] 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.[31]

In reality, diabetes and hypertension are found in the same individual more often than would occur by chance, whereas the overlap between dysglycemia and raised blood pressure is even more significant than that between diabetes and hypertension [32]. This suggests either shared genetic or environmental factors in the etiology [33].

This is a brief review which provides idea of the overlapping between hypertension and type 2 diabetes that suggests there is a spectrum ranging from hypertension without dysglycemia to type 2 diabetes without high blood pressure.

3. Etiology of Diabetes Hypertension

3.1 Genetics

Genetic variants in the gene encoding angiotensinogen, adrenomedullin, apolipoprotein, and α-adducin have been reported to be associated with common conditions such as diabetes, hypertension, dysglycemia, or metabolic syndrome [34–37]. Along with the genetic aspect, another very important aspect for the onset of diabetes and hypertension is environmental. Environmental factors include the period in utero and lifestyle factors such as diet and physical activity. Gestational diabetes, fetal malnutrition, and high birth weight are three factors that may predispose the fetus to cardiometabolic syndrome in adulthood.[38, 39,40] High intakes of sodium, alcohol, and unsaturated fat, smoking, lack of physical activity, and mental stress are examples of an unhealthy lifestyle. It is now understood that insulin resistance, which predicts type 2 diabetes, also has a role in the development of hypertension [41].Hypertension and diabetes significantly share common pathways such as obesity, inflammation, oxidative stress, insulin resistance, and mental stress.

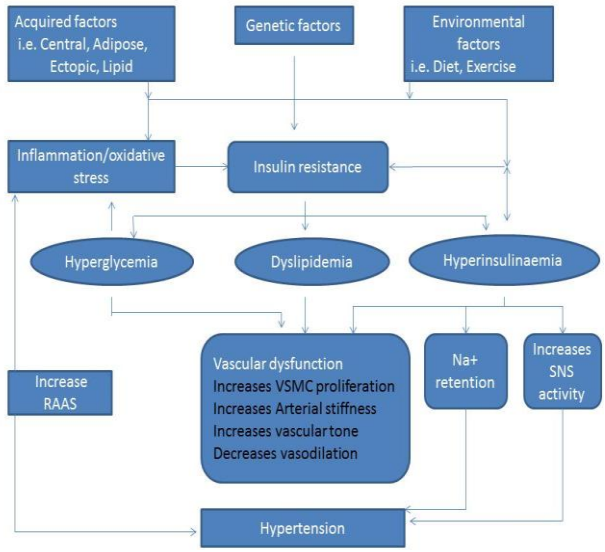
3.2 Obesity

It has been identified that Obesity, a global health problem is the most important risk factor for hypertension and diabetes [42]. Obese persons have a significantly higher risk of hypertension and type 2 diabetes.[43]Studies of obesity in Western countries where there is a high incidence have led to a greater understanding of the phenomenon of risk factor clustering and of the pathophysiologic links among hypertension, obesity, diabetes. Obesity is generally considered as the combined result of dysfunction of feeding center in the brain, imbalance in energy intake and expenditure, and genetic variations. Obesity is largely determined by genes; approximately 50% to 90% of the variation in weight is the result of genetic predisposition according to twin studies [44, 45]It is not surprising to find that diabetes and obesity share some common susceptibility genes. As obesity is a common factor in the etiology of hypertension and diabetes, we would expect that hypertension, diabetes, and obesity not only share common pathophysiologic pathways but also common susceptibility genes. Gene regulatory network analysis has revealed oxidative stress as a key underlying molecular mechanism in diabetes and hypertension. The oxidative stress-mediated regulation cascade is the common

mechanistic link among the pathogenesis of diabetes, hypertension, and other related inflammatory diseases [46].

3.3 Insulin Resistance

In the development of hypertension, diabetes, and the metabolic syndrome Insulin which is a pleiotropic hormone plays a pivotal role. The main metabolic actions of insulin are to stimulate glucose uptake in skeletal muscle and heart and to suppress the production of glucose and very low-density lipoprotein (VLDL) in the liver [47]. Under fasting conditions, insulin secretion is suppressed, leading to increased glucose synthesis in the liver and kidneys (gluconeogenesis) and increased conversion of glycogen to glucose in the liver (glycogenolysis) [48]. After a meal, insulin is released from pancreatic β-cells and inhibits gluconeogenesis and glycogenolysis[48]. Insulin increase cardiac outputby stimulating the sympathetic nervous system (SNS) and so the delivery and utilization of glucose in the peripheral tissues [49]. Other metabolic effects of insulin include inhibition of glucose release from the liver, inhibition of the release of free fatty acids (FFAs) from adipose tissue, and stimulation of the process by which amino acids are incorporated into protein [46,47].In insulin resistance condition, where the defects in the action of insulin are such that normal levels of insulin do not trigger the signal for glucose absorption, denotes an impaired response to insulin in skeletal muscle, liver, adipose, and cardiovascular tissue [48]. Insulin resistance arises due to various genetic, acquired, and environmental factors, including obesity [50]. In muscles insulin-mediated glucose uptake varies more than sixfold in apparently healthy individual[51], with approximately half of the variability in insulin action which is genetically determined and the other half is due to differences in the degree of adiposity and physical fitness [52, 53]. Most patients with type 2 diabetes are insulin resistant and about half of those with essential hypertension are insulin resistant [54]. Therefore, insulin resistance is an important common link between diabetes and hypertension



RAAS—renin-angiotensin- aldosterone system; SNS—sympathetic nervous system; VSMC—vascular smooth muscle cell.

Fig 1 Summary of recognized pathophysiologic mechanisms in the development of hypertension in diabetes mellitus [58]

3.4 Mental Stress and Sympathetic Nervous System

Stress which may be due to intrinsic or extrinsic stimuli leads to disturbances in physiology and psychology, and may threaten health. Compared with physical stress, modern stressors arising from psychological threat (eg, work stress, domestic violence, and natural disasters) are more persistent. Physiologic and psychological disturbances are frequently associated withchronic mental stress, resulting from the modern lifestyle,and may indirectly lead to diabetes and hypertension [55]. Although epidemiologic investigations have demonstrated that mental stress is associated with hypertension, cardiovascular disease, obesity, and the metabolic syndrome (which includes diabetes as a component) [56], the effect of mental stress on the whole body is not completely understood. Animal experiments taught us that the mechanisms include renal sympathetic nerve activity (RSNA) and blood pressure control in which baroreflex function [57] is involved.

3.5 Physical Activity

The risk of developing diabetes and hypertension is reduced due to physical activity. Along with other factors, changes in body weight and glucose tolerance are the mechanism involves. Physical activity influences the effect of obesity susceptibility genes on the onset of obesity in the individual. The potential benefits of physical activity in the prevention and treatment of diabetes and hypertension are well recognized but regular physical activity is difficult and sometimes impossible to carry out in real life. Public health efforts still aim to raise public awareness and facilitate regular physical activity to prevent against diabetes, hypertension, and other related diseases.

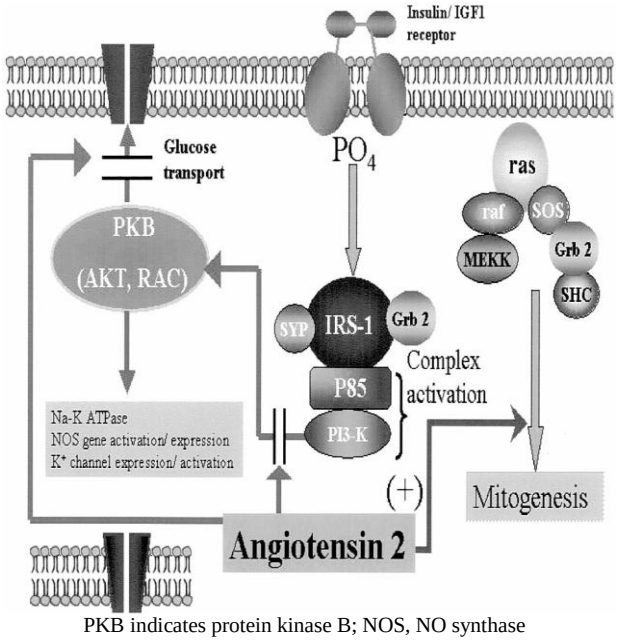
3.6 Pathophysiology of hypertension in diabetic patient

Epidemiologic studies provide evidence for co-existence of hypertension and diabetes and possibly point towards a common genetic and environmental factor promoting both diabetes and hypertension. Similarly, clustering of hypertension, insulin resistance or frank type 2 diabetes, hyperlipidaemia and central obesityin several populations have been documented.[59] Insulin resistance, increased tissue inflammation and reactive oxygen species (ROS) production resulting in endothelial dysfunction, increased tissue renin–angiotensin–aldosterone system (RAAS) and increased sympathetic nervous system (SNS) activity have all been implicated in this complex pathophysiology of diabetes and hypertension.

3.7 A complex interrelated process and the Decisive Role of RAAS in Diabetes, Insulin resistance and Hypertension

It is estimated that about 25–47% of persons with hypertension have insulin resistance or impaired glucose tolerance[59].There are impaired biological and physiological tissue responses to insulinwith insulin resistance. There is complex and interrelated relationship of insulin resistance, diabetes and hypertension. A direct correlation between plasma insulin levels and blood pressure (BP) exists.Untreated patients with essential hypertension have higher fasting and postprandial insulin levels than age- and sex-matched normotensive persons, regardless of body mass;.[59,60] Interestingly, the relationship between hyperinsulinaemia and hypertension is not seen in secondary hypertension.[60] This indicates that insulin resistance and hyperinsulinaemia are not consequences of hypertension, but rather a genetic predisposition that acts as a fertile soil for both diseases. This notion is supported by the observation that there is abnormal glucose metabolism in the progenies of hypertensive parents.[60,61] Thus, there is a strong association between hypertension, diabetes and insulin resistance. There is also a strong association between upregulation of RAAS, hypertension and diabetes.[62–64] This upregulation of RAAS results in enhanced generation of ROS and may explain impaired

glucose utilisation as well as hypertension associated with insulin resistance and type 2 diabetes.[65] It has been proposed that increased autocrine/paracrine activity of angiotensin II (ANG II) results in diminished action of insulin and insulin growth factor-1 (IGF-1) resulting in inhibition of mechanisms involved in the vasodilator and glucose transport properties of insulin and IGF-1 [65,66]
Similar RAAS-mediated increases in oxidative stress are likely contributed to insulin resistance in skeletal muscles.[67] Activation of the RAAS also results in increased aldosterone secretion from the adrenal gland and resultant salt retention and volume expansion and resulting in hypertension. Further, aldosterone also contributes to hypertension by enhancing SNS activity, decreasing parasympathetic activity, and reducing baroreceptor sensitivity.[68] Other effects of aldosterone in kidney, besides the salt retension, include increased extracellular matrix deposition by glomerular cells, leading to glomerulosclerosis and hypertension.[68] Other possible causes of hypertension with diabetes and insulin resistance/hyperinsulinaemia include activation of the sympathetic nervous system, increased renal tubular sodium retention, elevated intracellular calcium concentration and vascular smooth muscle cell proliferation and atherosclerosis, and impaired NO metabolism in skeletal muscle.[69–74] Another mechanism is the upregulation of vascular AT1Rs by post-transcriptional mechanisms enhancing the vasoconstrictive and volume-expanding actions of the RAAS[75] Some studies even suggest that excess levels of insulin can interfere with compliance of the great vessels and decrease the ability of the aorta to reflect aortic waves.[76] Therapy targeted at insulin resistance, such as aerobic exercise or thiazolidinedione drugs, results in a decrease in BP.[77,78]



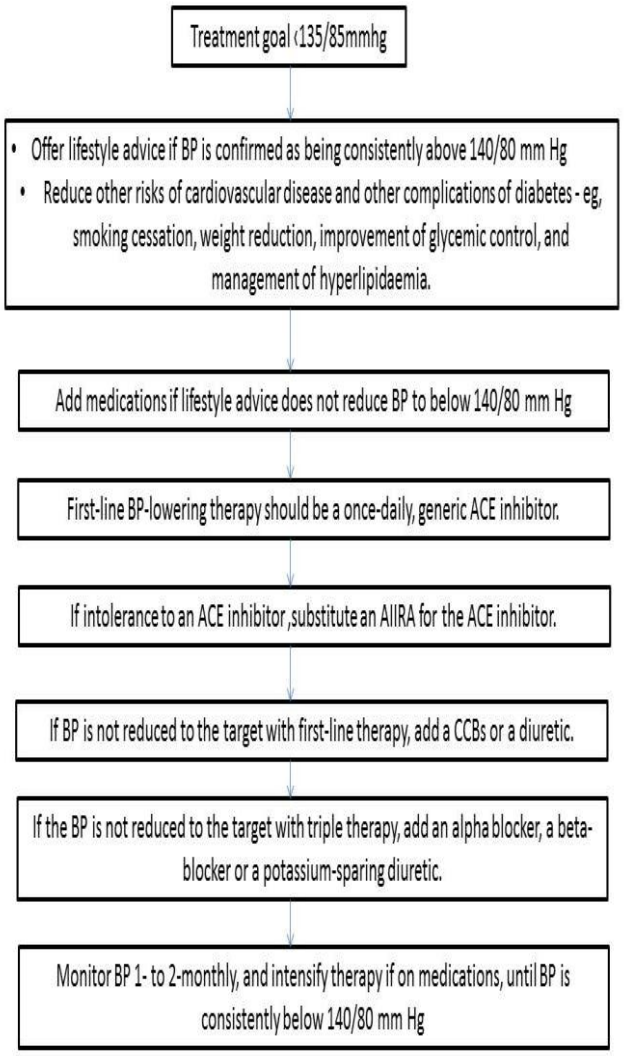
PKB indicates protein kinase B; NOS, NO synthase

Fig 2 Intracellular signaling pathways of insulin/IGF-1[79]

3. 7 People with diabetes are more at risk of developing high blood pressure if they:

- Are of African-Caribbean origin.
- Are from the Indian sub-continent.
- Have a family history of high blood pressure.
- Have certain lifestyle factors - those who are overweight, eat a lot of salt, do not eat much fruit and vegetables, do not take much exercise, or drink a lot of alcohol.

Algorithm for antihypertensive therapy in the diabetic individual [86]



*An adequate response indicates that goal blood pressure is achieved or considerable progress is made.

AIIR: Angiotensin II receptor blockers

3.8 Pharmacotherapy

The JNC 7 recommendations are consistent with guidelines from the American Diabetes Association (ADA), which has also recommended that BP in diabetics be controlled to levels of 130/80mmHg or lower.[83,84] Whatever the goal level, rigorous control of BP is utmost for reducing CVD mortality and morbidity.[27]To achieve goal BP in diabetics, two or more drugs are usually required.[85]There is convincing evidence regarding a certain class of drugs that seems to offer certain beneficial effects over others in hypertensive diabetics.

Table I. Lifestyle Modifications for the Management of Hypertension in Patients with Diabetes [80,81,82]

Sr.No.	*Modification*	*Recommendation*
1	Alcohol Restriction	Limit alcohol consumption to two drinks per day for men or one drink per day for women.
2	Diet	Implement the DASH diet; eat four or five servings of fruits, four or five servings of vegetables, and six to eight servings of whole grains each day; increase intake of calcium (1,250 mg daily), magnesium (500 mg daily), and potassium (4,700 mg daily); Limit intake of cholesterol to 150 mg daily and saturated fat to 6 percent of daily calories.
3	Physical activity	Engage in 30 to 45 minutes of moderate-intensity activity most days of the week
4	Smoking Cessation	Stop smoking to improve overall cardiovascular health.
5	Sodium Restriction	Restrict sodium intake to 2.4 g per day.
6	Weight loss	Lose weight, if necessary, to maintain a healthy body weight (i.e., body mass index of 19 to 25 kg per m2).

DASH = Dietary Approaches to Stop Hypertension.

Table II. Pharmacotherapy for the Management of Hypertension in Patients with Diabetes

Sr. No.	*Class of drug*	*Effects in management of hypertension in diabetes*
1	A C E – I	Improve insulin sensitivity, Retard the progression of diabetes Prevent the development of diabetes in hypertensive patients by inhibiting RAAS.[6,27]
2	ARBs	Effects in reducing the progression of diabetes and carry other cardiovascular and renal benefits Beneficial effects on glucose metabolism that are likely independent of bradykinin-mediated mechanisms.[31–34] Reduced the relative risk of developing type 2 diabetes
3	Beta blockers	induce vasodilatation and improve insulin sensitivity
4	Thiazide Diuretics	First-line therapy for many diabetic patients with hypertension, Cause electrolyte, imbalances, metabolic changes and volume contraction. Combining a diuretic with an ACE-I or an ARB can be an effective
5	CCB	Combination of an ACE-I and a calcium antagonist is effective for the management of hypertension in diabetic patients

4. Summary

Diabetes is a growing epidemic in both the developing and developed world and more so in the developing countries. Diabetes is known to be associated with hypertension. The presence of one increases the risk of having the other. This close relationship between diabetes and hypertension suggests a possible common genetic or pathophysiological process or both. Hypertension and diabetes are associated with increased risk of CVD and renal disease. The risk is aggravated when both are present. It is therefore imperative that hypertension is controlled rigorously to prevent or decrease the risk of CVD and renal disease. Insulin resistance, RAAS, endothelial dysfunction, and autonomic nervous system dysfunction play an important role in the pathogenesis of hypertension and diabetes. Pharmacotherapy must aim at improving insulin sensitivity and RAAS blockade to offer survival benefits to diabetics with hypertension. Further work in identifying the mechanism of hypertension, diabetes and insulin resistance would shed more light on them issing link that connects these seemingly different disease processes.

Acknowledgements

Authors are thankful to Mr. Albert W. D'souza, Chairman, Aldel Education Trust for his motivation and encouragement. Authors are also thankful to St. John Institute of Pharmacy & Research, Palghar and Jaipur National University, Jaipur for providing platform to carry out this work.

REFERENCES

1. Wild S, Roglic G, Green A, Sicree R, King H, "Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030", Diabetes Care (2004);27(5): pp. 1,047–1,053.

2 .Pinhas-Hamiel O, Zeitler P, "The global spread of type 2 diabetes mellitus in children and adolescents", J. Pediatr. (2005);146(5): pp. 693–700.

3. National High Blood Pressure Education Program Working Group report on hypertension in diabetes, Hypertension (1994);23(2): pp. 145–158.

4. Gress T W, Nieto F J, Shahar E, Wofford M R, Brancati F L, "The Atherosclerosis Risk in Communities S. Hypertension and Antihypertensive Therapy as Risk Factors for Type 2 Diabetes Mellitus", N. Engl. J. Med. (2000);342(13): pp. 905–912.

5. Sowers J R, Epstein M, Frohlich E D, "Diabetes, hypertension, and cardiovascular disease: an update", Hypertension (2001);37(4): pp. 1,053–1,059.

6.International Diabetes Federation Web site. Facts & Figures: Diabetes Prevalence. Available at: http://www.idf.org/home/index. cfm?node=264. Accessed August 11, 2006.

7.Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and impaired fasting glucose in adults in the US population. National Health and Nutrition Examination Survey 1999– 2002.Diabetes Care.2006;29:1263–1268.

8.King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. DiabetesCare.1998;21:1414–1431.

9.Eknoyan G, Hostetter T, Bakris GL, et al. Proteinuria and other markers of chronic kidney disease: a position statement of the National Kidney Foundation (NKK) and the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK). Am J KidneyDis. 2003;42:617–622.

10.Collins AJ, Kasiske B, Herzog C, et al. Excerpts from the United States Renal Data System 2001 Annual Data Report: atlas of end-stage renal disease in the United States. Am J Kidney Dis. 2001;38:S7–S247.

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

12.2003 European Society of Hypertension. European Society of Cardiology guidelines for the management of arterial

hypertension.European Society of Hypertension.JHypertens.2003;21:1011–1053.

13.US Department of Health and Human Services (DHHS). National Center for Health Statistics.Second National Health and Nutrition Examination Survey, (NHANES II), 1976- 1980. Hyattsville, MD: Centers for DiseaseControl and Prevention.

14Marks JB, Raskin P. Cardiovascular risk in diabetes: a brief review. J Diabetes Complications. 2000;14:108–115.

15.Newton CA, Raskin P. Blood pressure control— effects on diabetic nephropathy progression: how low does blood pressure have to be? CurrDiab Rep. 2002;2:530–538.

16.Sowers JR. Insulin resistance and hypertension. Am J Physiol Heart Circ Physiol. 2004;286:H1597–H1602.

17.Gress TW, Nieto FJ, Shahar E, et al. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study.N Engl J Med. 2000;342:905–912.

18.Sowers JR, Bakris GL. Antihypertensive therapy and the risk of type 2 diabetes mellitus. N Engl J Med. 2000;342:969–970.

19.Nathan DM, Lachin J, Cleary P, et al, for the Diabetes Control and Complications Trial. Epidemiology of diabetes interventions and complications research group. Intensive diabetes
therapy and carotid intima-media thickness in type 1 diabetes mellitus. N Engl J Med. 2003;348:2294–2303.

20.Wingard DL, Barrett-Connor E. Heart disease and diabetes. In: National Diabetes Group, ed. Diabetes in America. Washington, DC: National Institutes of Health Publication No. 95–1468. National Institutes of Health; 1995:429–448.
21Sowers JR, Epstein M. Diabetes mellitus and associated hypertension, vascular disease, and nephropathy: an update. Hypertension.1995;26(pt 1):869–879.

22Warram JH, Gearin G, Laffel L, et al. Effect of duration of type 1 diabetes on the prevalence
of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. J Am SocNephrol. 1996;7:930–937.

23Bakris GL, Williams M, Dworkin L, et al, for the National Kidney Foundation Hypertension
and Diabetes Executive Committees Working Group. Preserving renal function in adults with hypertension and diabetes: a consensus approach.Am J Kidney Dis. 2000;36:646–661.

24.Mogensen CE, Hansen KW, Pedersen MM, et al. Renal factors influencing blood pressure
threshold and choice of treatment in IDDM. Diabetes Care.1991;14(suppl 4):13–26.

25.Arauz-Pacheco C, Parrott MA, Raskin P; American Diabetes Association. Treatment of hypertension in adults.Diabetes Care. 2003;26:S80–S82.

26.Sharma AM, Wittchen HU, Kirch W, et al, for the HYDRA Study Group. High prevalence and poor control of hypertension in primary care: cross-sectional study. J Hypertens. 2004;22:479–486.

27.Pittrow D, Wittchen H, Kirch W. Hypertension and diabetes care among primary care doctors in Germany: results from an epidemiologic cross-sectional study. In: Kirch W, ed. Public Health in Europe. New York, NY: Springer; 2003:203–218.

28 Sowers JR, Haffner S. Treatment of cardiovascular and renal risk factors in the diabetic hypertensive. Hypertension.2002;40:781–788.

29 Moore WV, Donaldson DL, Chonko AM, et al. Ambulatory blood pressure in type 1 diabetes mellitus: comparison to presence of incipient nephropathy in adolescents and young adults. Diabetes.1992;41:1035–1041.

30 Lurbe A, Redon J, Pascual JN, et al. Altered blood pressure during sleep in normotensive subjects with type 1 diabetes. Hypertension.1993;21:227–235.

31 Lurbe E, Redon J, Kesani A, et al. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes.N Engl J Med. 2002;347:797–805.

32. Cheung BM, Wat NM, Tso AW, et al. Association between raised blood pressure and dysglycemia in Hong Kong Chinese. Diabetes Care. 2008;31:1889–91.

33. Cheung BM. The hypertension-diabetes continuum.JCardiovasc Pharmacol.2010; 55: 333–9.

34. Ong KL, Tso AW, Leung RY, et al. A genetic variant in the gene encoding adrenomedullin predicts the development of dysglycemia over 6.4 years in Chinese. Clin Chim Acta. 2011;412:353–7.

35. Ong KL, Jiang CQ, Liu B, et al. Association of a genetic variant in the apolipoprotein A5 gene with the metabolic syndrome in Chinese. Clin Endocrinol (Oxf). 2011;74:206–13.

36. Cheung CY, Tso AW, Cheung BM, et al. Genetic variants associated with persistent central obesity and the metabolic syndrome in a 12-year longitudinal study. Eur J Endocrinol. 2011;164:381–8.

37. Ong KL, Li M, Tso AW, et al. Association of genetic variants in the adiponectin gene with adiponectin level and hypertension in Hong Kong Chinese. Eur J Endocrinol. 2010;163:251–7.
38. Moore TR. Fetal exposure to gestational diabetes contributes to subsequent adult metabolic syndrome. Am J Obstet Gynecol. 2010;202:643–9.

39. • Xita N, Tsatsoulis A. Fetal origins of the metabolic syndrome. Ann N YAcad Sci. 2010; 1205: 148–55. This article argued that consequences of fetal adaptive responses might be evident later in life rather than at birth. Risk factors in pregnancy mightpredispose the fetus to hypertension, diabetes, or the metabolic syndrome in adulthood.

40. Guerrero-Romero F, Aradillas-Garcia C, Simental-Mendia LE, et al. Birth weight, family history of diabetes, and metabolic syndrome in children and adolescents. J Pediatr. 2010;156:719–23, 723 e1.

41. Sowers JR. Insulin resistance and hypertension. Am J Physiol Heart Circ Physiol. 2004;286:H1597–1602.

42. Davy KP, Hall JE. Obesity and hypertension: two epidemics or one? Am J PhysiolRegulIntegr Comp Physiol. 2004;286:R803–813.

43. • He YH, Jiang GX, Yang Y, et al. Obesity and its associations with hypertension and type 2 diabetes among Chinese adults age 40 years and over. Nutrition.2009; 25: 1143–9. This was a crosssectional study of over 5000 people in the community in Shanghai showing that obesity was associated with a higher risk of both hypertension and type 2 diabetes.

44. Loos RJ, Bouchard C. Obesity–is it a genetic disorder? J Intern Med. 2003;254:401–25.

45. Maes HH, Neale MC, Eaves LJ.Genetic and environmental factors in relative body weight and human adiposity.Behav Genet. 1997;27:325–51.

46. Jesmin J, Rashid MS, Jamil H, et al. Gene regulatory network reveals oxidative stress as the underlying molecular mechanism of type 2 diabetes and hypertension. BMCMed Genomics. 2010;3:45.

47. Yki-Järvinen H. Nonglycemic effects of insulin. Clin Cornerstone. 2003; Suppl 4: S6-12.

48. Jellinger PS. Metabolic consequences of hyperglycemia and insulin resistance. Clin Cornerstone. 2007;8Suppl 7:S30–42.

49. Deedwania P. Hypertension, dyslipidemia, and insulin resistance in patients with diabetes mellitus or the cardiometabolic syndrome: benefits of vasodilating beta-blockers. J Clin Hypertens (Greenwich). 2011;13:52–9.

50. Stump CS, Clark SE, Sowers JR. Oxidative stress in insulinresistant conditions: cardiovascular implications. Treat Endocrinol. 2005;4:343–51.

51. Yeni-Komshian H, Carantoni M, Abbasi F, et al. Relationship between several surrogate estimates of insulin resistance and quantification of insulin-mediated glucose disposal in 490 healthy nondiabetic volunteers. Diabetes Care. 2000;23:171–5.

52. Lillioja S, Mott DM, Zawadzki JK, et al. In vivo insulin action is familial characteristic in nondiabetic Pima-Indians. Diabetes. 1987;36:1329–35.

53. Zoratti R, Godsland IF, Chaturvedi N, et al. Relation of plasma lipids to insulin resistance, nonesterified fatty acid levels, and body fat in men from three ethnic groups: relevance tovariation in risk of diabetes and coronary disease. Metabolism. 2000;49:245 52.

54. Reaven GM. Relationships among insulin resistance, type 2 diabetes, essential hypertension, and cardiovascular disease: similarities and differences. J Clin Hypertens (Greenwich). 2011;13:238–43.

55. Morimoto K, Morikawa M, Kimura H, et al. Mental stress induces sustained elevation of blood pressure and lipid peroxidation in postmenopausal women. Life Sci. 2008;82:99–107.
56. Chapuis B, Vidal-Petiot E, Orea V, et al. Linear modelling analysis of baroreflex control of arterial pressure variability in rats. J Physiol. 2004;559:639–49.

57. Barrett CJ, Ramchandra R, Guild SJ, et al. What sets the longterm level of renal sympathetic nerve activity: a role for angiotensin II and baroreflexes? Circ Res. 2003;92:1330–6.

58. Mugo MN, Stump CS, Rao PG, Sowers JR. Chapter 34: Hypertension and Diabetes Mellitus. Hypertension: A Companion to Braunwald's Heart Disease.

59.GurushankarGovindarajan, James R Sowers and C r a i g S S t u m p; Hyper tension and Diabetes Mellitus; E u r o p e a n c a r d i o v a s c u l a r d i s e a s e 2 0 0 6;Reference Section, pg no 1-7

60. Sechi L A, Melis A, Tedde R, "Insulin hypersecretion: a distinctive feature between essential and secondary hypertension", Metabolism (1992);41(11): pp. 1,261–1,266.

61. Sowers J R, Bakris G L, "Antihypertensive Therapy and the Risk of Type 2 Diabetes Mellitus", N. Engl. J. Med. (2000);342(13): pp. 969–970.

62. Richey J M, Ader M, Moore D, Bergman R N, "Angiotensin II induces insulin resistance independent of changes in interstitial insulin", Am. J. Physiol. Endocrinol. Metab. (1999);277(5): pp. E920–926.

63. Ogihara T, Asano T, Ando K, Chiba Y, Sakoda H, Anai M et al., "Angiotensin II-Induced Insulin Resistance Is Associated With Enhanced Insulin Signaling", Hypertension (2002);40(6): pp. 872–879.

64. Brenner B M, Cooper M E, de Zeeuw D, Keane W F, Mitch W E, Parving H-H et al., "Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy", N. Engl. J. Med. (2001);345(12): pp. 861–869.

65. Sowers J R, "Insulin resistance and hypertension", Am. J. Physiol. Heart Circ. Physiol. (2004);286(5):H pp. 1,597–1,602.

66. Sloniger J A, Saengsirisuwan V, Diehl C J, Dokken B B, Lailerd N, Lemieux A M et al., "Defective insulin signaling in skeletal muscle of the hypertensive TG(mREN2)27 rat", Am. J. Physiol. Endocrinol. Metab. (2005);288(6): pp. E1,074–1,081.

67. Blendea M C, Jacobs D, Stump C S, McFarlane S I, Ogrin C, Bahtyiar G et al., "Abrogation of oxidative stress improves insulin sensitivity in the Ren-2 rat model of tissue angiotensin II overexpression", Am. J. Physiol. Endocrinol. Metab. (2005);288(2): pp. E353–359.

68. McFarlane S I, Sowers J R, "Cardiovascular endocrinology 1: aldosterone function in diabetes mellitus: effects on cardiovascular and renal disease", J. Clin. Endocrinol.Metab. (2003);88(2): pp. 516–523

69. Modan M, Halkin H, "Hyperinsulinemia or increased sympathetic drive as links for obesity and hypertension", Diabetes Care (1991);14(6): pp. 470–487.

70. DeFronzo R A, Ferrannini E, "Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease", Diabetes Care (1991);14(3): pp. 173–194.

71. DeFronzo R A, "The effect of insulin on renal sodium metabolism. A review with clinical implications", Diabetologia (1981);21(3): pp. 165–171.

72. Anderson E A, Hoffman R P, Balon T W, Sinkey C A, Mark A L, "Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans", J. Clin. Invest. (1991);87(6): pp. 2,246–2,252.
73. Berne C, Fagius J, Pollare T, Hjemdahl P, "The sympathetic response to euglycaemic hyperinsulinaemia. Evidence from microelectrode nerve recordings in healthy subjects", Diabetologia (1992);35(9): pp. 873–879.

74. Rowe J W, Young J B, Minaker K L, Stevens A L, Pallotta J, Landsberg L, "Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man", Diabetes (1981);30(3): pp. 219–225.

75. Nickenig G, Roling J, Strehlow K, Schnabel P, Bohm M, "Insulin Induces Upregulation of Vascular AT1 Receptor Gene Expression by Posttranscriptional Mechanisms", Circulation (1998);98(22): pp. 2,453–2,460.

76. Westerbacka J, Vehkavaara S, Bergholm R, Wilkinson I, Cockcroft J, Yki-Jarvinen H, "Marked resistance of the ability of insulin to decrease arterial stiffness characterizes human obesity", Diabetes (1999);48(4): pp. 821–827.

77. Raji A, Seely E W, Bekins S A, Williams G H, Simonson D C, "Rosiglitazone improves insulin sensitivity and lowers blood pressure in hypertensive patients", Diabetes Care (2003);26(1): pp. 172–178.

78. Dengel D R, Hagberg J M, Pratley R E, Rogus E M, Goldberg A P, "Improvements in blood pressure, glucose metabolism, and lipoprotein lipids after aerobic exercise plus weight loss in obese, hypertensive middle-aged men", Metabolism (1998);47(9): pp. 1,075–1,082.

79. James R. Sowers, Murray Epstein, Edward D. Frohlich; Diabetes, Hypertension, and Cardiovascular Disease An Update; *Hypertension*. 2001;37:1053-1059.)

80. Arauz-Pacheco C, Parrott MA, Raskin P, for the American Diabetes Association. Hypertension management in adults with diabetes.*DiabetesCare*. 2004;27(suppl 1):S65-S67.

81. Chobanian AV, Bakris GL, Black HR, et al., for the National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report [published correction appears in *JAMA*. 2003;290(2):197]. *JAMA*. 2003;289(19):2560-2572.

82. Your guide to lowering your blood pressure with DASH. http://www. nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf. Accessed August 11, 2008.

83. Sowers JR. Diabetes mellitus and cardiovascular disease in women. Arch Intern Med. 1998;158:617–621.

84. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart 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.

85 Sowers JR. Recommendations for special populations: diabetes mellitus and the metabolic syndrome. Am J Hypertens.2003;16:41S–45S.

86. James R. Sowers, Murray Epstein, Edward D. Frohlich; Diabetes, Hypertension, and Cardiovascular Disease An Update; *Hypertension*. 2001;37:1053-1059.