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Hypertension and Type 2 Diabetes Mellitus
Metabolic Interface & Vascular Biology

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Abstract

The association of essential hypertension and type 2 diabetes mellitus (T2DM) is well recognized. This combination of co-morbidities, with the constellation of common risk factors, results in considerable disease burden with consequent loss of quality adjusted life years (QUALY). To the generally known mechanisms, particularly insulin resistance, underlying obesity, T2DM, hypertension and cardiovascular disease, has now been added the contributory role of low-grade inflammatory process. New insights into endocrine-metabolic interactions with vascular biology have highlighted the role of adiponectin and renin-angiotensin-aldosterone system. While adiponectin acts as an integrator of metabolic and inflammatory signals, its low levels are associated with obesity, T2DM and coronary heart disease. There is also negative correlation between circulating level of adiponectin and markers of inflammation including CRP, PAI-1 and tissue plasminogen activator (tPA). In contrast to anti-inflammatory role of adiponectin, angiotensin II is proinflammatory resulting in upregulation of inflammatory transcriptor factors such as NF-kappa B (NF-κB). These in turn lead to endothelial dysfunction and vascular injury. Advances in the understanding of molecular mechanisms may lead to rational development of new therapeutic interventions.

Key Words : Quality adjusted life years, inflammatory transciptor factors, endothelial dysfunction, vascular injury

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Introduction

The association between hypertension and T2DM is well recognized. More than 80% of patients with T2DM develop hypertension and approximately 20% of patients with hypertension develop diabetes. Combined together, these account for a large proportion of cardiovascular morbidity and mortality. Whilo tho pathophysiology of medium and large vessel diseases is multifactorial, there is strong suggestive evidence that metabolic profile along with low-grade inflammatory process constitute the base and basis of pathogenic mechanism(s).

Metabolic Interface

Subjects with hypertension (HT) have higher risk of developing insulin resistance. Systolic blood pressure is a significant predictor of subsequent development of T2DM irrespective of age and gender. In our own study at the AIIMS, New Delhi wherein 38 young healthy non-obese (mean BMI ~ 22.74) normotensive offspring of hypertensive parents were investigated, higher levels of insulin *both* in the fasting state and during oral GTT were observed in 23 (62%) of the subjects (1). Hyperinsulinemia indicates insulin resistance as was well documented in earlier studies. Reaven has suggested that adiposity and physical fitness each account for approximately 25% of the variability in insulin sensitivity, with genetic factors responsible for an additional 50% of the variation (2). Our data of hyperinsulinemia in non-obese normotensive offspring of hypertensive parents supports the partially genetic basis of insulin resistance.

Subjects with HT, newly diagnosed and prior to the administration of any antihypertensive treatment, showed during OGTT a high AUC glucose, alongwith significant hyperinsulinemia, suggestive of insulin resistance. Indeed, there seems to be a correlation between mean BP (mmHg) and insulin sensitivity (ml/min/Kg): Insulin sensitivity is inversely related to severity of hypertension. Those subjects with more severe hypertension are more likely to have greater insulin resistance (3).

Equally significant is the observation that level of blood glucose at any point in time may be predictive of developing hypertension several years later. In a landmark study of public health importance, blood glucose concentration one hour after a glucose load, blood pressure and body weight were measured in a cohort of men at 5-7 years interval in 1968, 1974, 1979 and 1986. Regression

analysis showed that the higher the blood glucose concentration after a glucose load in 1968, the higher the blood pressure during the following years. Those men between the second and third tertiles of blood glucose concentration in 1968 had a significantly higher risk of developing hypertension (odds ratio 1.71, 95% confidence interval 1.05 to 2.77) compared with those below the first tertile (4).

The possibility that obesity, especially visceral fat, may provide the link between diabetes mellitus and hypertension is strongly supported by available data. While the association of visceral adipose tissue (VAT) with glucose intolerance, dyslipidemia and hypertension is well recognized and constitutes the phenotype of metabolic syndrome, there is strong evidence for an independent association of increase in VAT with hypertension and insulin resistance.

Studies in children show that rise in blood pressure is associated with hyperinsulinemia and VAT excess (5). Likewise, in hypertensive women with central adiposity, accumulation of fat in abdominal viscera is associated with insulin resistance and also with higher levels of blood pressure (6). In a recent study of 13 nondiabetic men with newly detected untreated essential hypertension, VAT and subcutaneous fat were estimated using multiscan MRI. Age and BMI-matched normotensive subjects were taken as controls. In both groups, insulin secretion was measured during oral glucose tolerance test, and dynamics of β-cell function were calculated by mathematic modeling. The study confirmed that abdominal VAT, insulin resistance, and blood pressure were quantitatively interrelated. While VAT excess was quantitatively related to both the height of blood pressure and severity of insulin resistance, there was no demonstrable impact on the dynamics of β-cell function (3).

In view of the association of insulin resistance, hyperinsulinemia and dyslipidemia, the role of lipids in pathogenesis of cardiovascular disease needs consideration. Small, dense LDLs, and excess triglyceride-rich remnants, which are highly atherogenic, are increased in the insulin-resistant state (7). There is also an overproduction of very low-density lipoproteins (VLDLs) which can accelerate the atherosclerotic process in several ways, including direct effect on the metabolism and growth of endothelial cells. Low HDLs, associated with insulin resistance, are unable to reduce the inhibitory effect of LDL on endothelium-mediated vasodilation. Finally, hypercholes-

terolemia increases the expression of endothelial adhesion molecules. Visceral adiposity, insulin resistance, and hypertension constitute the metabolic interface underlying cardiovascular morbidity and mortality associated with type 2 diabetes mellitus (T2DM) and essential hypertension.

Insulin Resistance, Vascular Biology, and Cardiovascular Disorders

It took nearly sixty years following the discovery of insulin to convincingly demonstrate its direct effects on the vasculature in dogs, and another decade to establish similar vascular effects in humans (8). Insulin, in concentration at the high physiological range, as observed in the postprandial phase, produces a nearly two-fold increase in skeletal muscle blood flow in non-obese insulin-sensitive subjects. The vasodilatory effect of insulin occurs within about 30 minutes of administration coinciding temporally with its effects on glucose uptake in the muscle. The mechanism underlying the vasodilatory effect of insulin is through the release of endothelium derived nitric oxide (eNO). Such release of eNO is mediated through signaling pathways involving tyrosine kinase, PI3K, and Akt, downstream from the insulin receptor (9). Thus the metabolic and vascular actions of insulin share common signaling pathways.

In addition to enhancing blood flow in the skeletal muscle, insulin also augments stroke volume, increases heart rate, as well as cardiac output (10). Furthermore, insulin causes antinatriuresis, antikaliuresis, and antiuricosuria in healthy human volunteers. Insulin also modulates the response to vasopressor hormones i.e. norepinephrine, vasopressin, and angiotensin II both at the level of vascular endothelium, as well as at vascular smooth muscle cell *independent* of the endothelium (11). Taken together, there is a net effect of insulin on blood pressure. Thus, any imbalance between the vasodilatory effects of insulin and the opposite effects of other vasoconstrictor hormones, may result in elevation of blood pressure and accelerated development of macrovascular disease.

Obesity causes a shift to the left in the vasodilatory response to insulin. The medium effective dose (ED_{50}) for insulin to increase leg blood flow in the obese was approximately four times (~ 160 μU/ml) that in the lean subjects (44 μU/ml). Subjects with T2 diabetes showed a more pronounced impairment of insulin-mediated vasodilation : only supraphysiologic

hyperinsulinemia (~ 2000 μU/ml) resulted in a 33% increase in blood flow (12). Similar observations were made when subjects with essential hypertension were studied. It was surmised that the impaired insulin-induced vasodilation as observed in obesity, type 2 diabetes and hypertension was a result of impaired production of NO.

A sound conceptual framework for the understanding of molecular linkage between insulin resistance, hyperinsulinemia, and increase risk of cardiovascular diseases or atherosclerosis in T2DM, has been provided in recent studies. Insulin receptors have been demonstrated on the vascular cells; these receptors are identical with those on the nonvascular cells with respect of structure, affinity, binding kinetics, capacity for tyrosine phosphorylation, and activation of tyrosine kinase (13). As in other cells, insulin binding with its receptors on vascular cells results in the activation of two separate signal transduction pathways: (i) the phosphatidylinositol (PI) 3-kinase pathway; and (ii) the Ras-mitogen-activated protein (MAP) kinase pathway. Under physiological concentrations of insulin, the vascular effects are mainly mediated by PI3-kinase pathway. However, in insulin resistant states with resultant hyperinsulinemia and persistent elevation of plasma insulin concentrations, MAP-K pathway is continuously activated, leading to proliferation and migration of smooth muscle cells in aorta and large blood vessels, alongwith a marked increase in the synthesis of extracellular matrix proteins in the arterial wall (14). In addition to these direct effects, insulin may also enhance the mitogenic effect of more potent growth factors, such as platelet-derived growth factor, and insulin-like growth factors.

It has already been mentioned that PI3-kinase pathway is involved in the release of endothelium derived nitric oxide, and that the vasodilatory effects of insulin are considerably impaired in insulin-resistant states. The role and place of PI3-kinase and ras-AMP kinase pathways in vascular endothelial cells can now be succinctly conceptualised. At physiological concentrations, insulin-mediated vasodilation is mainly through PI3-kinase activation, leading to NO production (acute effect) and enhanced gene expression of eNOS (delayed effect). These effects are antiatherogenic. In contrast, insulin-mediated effects through ras-MAP kinase pathway, resulting in vascular smooth muscle cell growth, proliferation and

migration, along with stimulation of extracellular matrix production, are atherogenic requiring persistently elevated concentrations of insulin as encountered in insulin-resistant states. Thus, accelerated atherosclerosis in T2DM is due to a combined effect of impaired insulin effects mediated by PI3-kinase pathway *without* the inhibition of insulin effects mediated by ras-MAP kinase pathway. The differential effects of insulin resistance on the PI3-kinase and MAP kinase-mediated signaling in human muscle, are major determinants of alteration of vascular biology in insulin resistant states such as type 2 diabetes and obesity. The subject has been recently reviewed (15).

Experimental evidence, generated in recent years, does show that mice with gene disruption of endothelial nitric oxide synthase (eNOS) (16) or neuronal nitric oxide synthase (nNOS) exhibit insulin resistance, hypertension, and dyslipidemia. Induction of iNOS by endotoxin is associated with impaired insulin-stimulated glucose uptake. In contrast, targeted disruption of iNOS protects against obesity-linked insulin resistance in muscle (17). Recent clinical studies indicate marked impairment of insulin activation of IRS-1/PI3-kinase pathway in the muscle of normal-glucose-tolerant insulin-resistant offspring of two diabetic parents. Thus, both the metabolic effects of insulin and its vasodilatory effects are linked together through IRS-1/PI3-kinase pathway and insulin resistance even at an early stage, when glucose tolerance is normal, results in impairment of both metabolism and vasodilation.

Vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM) are established cardiovascular risk markers. It has also been shown that NO modulates leucocyte adhesions to the endothelium by regulating the production/release of ICAM and VCAM by endothelial and vascular smooth muscle cells. In a recent study, NOS activity in skeletal muscle of well controlled T2 diabetics, who were on diet and/or sulphonylurea therapy, was investigated under basal condition and during a 80 mU/m^2 min euglycaemic clamp. Healthy age-matched, sex matched, BMI matched, and ethnicity matched subjects served as controls. Basal and insulin-stimulated muscle NOS activity was impaired in well controlled type 2 diabetic subjects. The defect in insulin-stimulated NOS activity correlated closely with the severity of insulin resistance as assessed by measurements of insulin-stimulated glucose

disposal. In addition, there was a significant increase in plasma ICAM and VCAM concentrations, with an inverse correlation between the increased plasma ICAM and VCAM levels and the reduced muscle NOS activity (9).

Hormone-Metabolic Interactions

In addition to the key role of insulin resistance and hyperinsulinemia, recent work tends to highlight the role of leptin, adiponectin, and rennin-angiotensin system. Plasma adiponectin and leptin levels had opposite and characteristic association with adiposity, insulin resistance, and inflammation. In a recent study aimed to measure coronary artery calcium (CAC), leptin but not adiponectin showed a significant correlation with CAC (18). Furthermore, plasma leptin was positively associated with higher CAC after adjustment for age, gender, and traditional cardiovascular risk factors. Combined with HOMA-IR index (homeostasis model assessment of insulin resistance), leptin had a strong predictive value for CAC, indicating possible association with coronary artery disease. Leptin has been shown to possess prothrombotic effects as it activates human platelet aggregation and adhesion, and limits transendothelial cell diffusion (19).

In contrast, adiponectin increased the integrity of diffusion barrier formed by a monolayer of human microvascular endothelial cells. Low adiponectin levels also correlate with increased inflammatory markers. Adiponectin, which is predominantly of adipocyte origin, is low in obesity possibly due to expression of transcription factors that negatively regulate the adiponectin gene. Association of low adiponectin with visceral adiposity and the risk of T2DM is well recognized. Clinical studies provide interesting data linking the metabolic and anti-inflammatory roles of adiponectin. In a study of 77 subjects who had diabetes or were at high risk to develop diabetes, there was a significant negative correlation between circulating levels of adiponectin and CRP, PAI-1, and tissue plasminogen activator (tPA) (20). These negative associations remained significant after adjusting for gender and BMI. This study reinforces earlier observation regarding the protective role of adiponectin against inflammation and endothelial dysfunction, and provides evidence of its negative association with tPA, which is known to play a role in impaired fibrinolysis. A similar study in women with prior gestational diabetes mellitus (pGDM) who are known to be at higher risk of

developing T2DM and associated cardiovascular complications, showed that plasma adiponectin was significantly lower in pGDM as compared to women with normal glucose tolerance during pregnancy. The differences remained statistically significant even after adjustment for body fat mass. Equally significant were the differences in the levels of PAI-1 and ultrasensitive CRP which were higher in the pGDM group. It was concluded that lower plasma adiponectin concentrations characterize women with previous GDM independently of the prevailing glucose tolerance, insulin sensitivity or the degree of obesity and are associated with subclinical inflammation and atherogenic parameters (21).

In a recent study of 3640 male nondiabetic subjects aged 60-79 years, there was a significant negative correlation between serum adiponectin, obesity, insulin resistance, markers of inflammation, and endothelial dysfunction (22): these factors are also known to increase the risk of T2DM. Thus the role of adiponectin as an integrator of metabolic and inflammatory signals underlying obesity, T2DM, and coronary heart disease has assumed considerable significance, both in terms of its potential as a part of preventive strategies, and also as a prototype molecule for the development of new analogues and related compounds aimed at therapeutic intervention.

Renin-angiotensin-aldosterone system (RAAS) has received considerable attention as a key mediator of cardiovascular dysfunction in diabetes, in addition to its well recognized role in the regulation of blood pressure. Angiotensin II has been shown to have direct effects on endothelial dysfunction, oxidative stress, inflammation, and adipocyte function. Of considerable relevance is the data from clinical trials demonstrating not only the antihypertensive effect of RAAS inhibitors, but also a positive effect in reducing the risk of cardiovascular and renal complications in diabetes mellitus.

The Captopril Prevention Project (CAPPP) randomized nearly 11,000 hypertensive patients to treatment with captopril or conventional antihypertensive therapy (beta blockers or thiazide diuretics). Among the 10,413 study participants who did not have DM at the time of study entry, risk for incident DM (a pre-specified secondary end point) was reduced 11% in the captopril group relative to the conventional therapy group after a mean follow-up period of 6.1 years (23).

The Heart Outcomes Prevention Evaluation (HOPE) trial compared ramipril with placebo in 9,297 patients with or at high risk for cardiovascular disease and demonstrated a 22% relative reduction in the composite end point or cardiovascular death, MI and stroke with ramipril treatment. Ramipril was also observed to prevent the development of DM, a prospectively planned secondary end point. Among the 5,720 patients without DM at study entry, 102 (3.6%) assigned to ramipril developed DM compared with 155 (5.4%) of the placebo group. The relative risk reduction in the HOPE study for incident diabetes (34%) was notably similar to that observed with metformin (31%) in the DPP study (24).

The Losartan Intervention For Endpoint Reduction (LIFE) study randomized 9,193 patients with hypertension and left ventricular hypertrophy to receive either losartan or atenolol. In this study, compared with atenolol, losartan was associated with a 25% reduction in incident DM. However, in the absence of a placebo control, it is unknown whether losartan decreased the risk of DM or atenolol increased the risk (or both) (25). Recently, a meta-analysis of 13 major trials, including the ACE-I and ARB trials described above, was performed in an attempt to evaluate the effect of inhibiting the RAAS system on incident DM. The meta-analysis found an overall decrease in the incidence of DM from 9% to 7.1% when ACE-Is or ARBs were used (26).

How does RAAS inhibition benefit metabolic and vascular outcomes? Experimental evidence suggests that ACE inhibitors (ACE-Is) as well as Angiotensin Receptor Blockers (ARB) promote recruitment and differentiation of insulin resistant preadipocytes into small insulin sensitive adipocytes (27). Thus while the overall body fat content may remain unchanged, insulin sensitivity is enhanced. A reference has already been made to insulin signaling pathway. Angiotensin II has been shown to reduce IRS-1 tyrosin phosphorylation and PI3-kinase activity via the AT_1 receptor (28). Thus ACE-Is and ARBs may inhibit angiotensin II generation and action respectively, with resultant enhancement of insulin signaling and glucose transport. Furthermore inhibition of RAAS may enhance glucose-stimulated insulin release by reducing potassium loss; preventing hypokalemia with a potassium clamp enhances glucose-stimulated β-cell insulin secretion in both healthy subjects and in patients with hypertension (29).

In addition to the endocrine-metabolic interactions described above, there is growing evidence implicating markers of low-grade inflammation as independent predictors of atherosclerotic progression, coronary heart disease (CHD), and incident T2DM (30). While ACE-Is favourably affect markers such as PAI-1, endothelin-1 and nitric oxide, ARBs have been shown to produce similar effects on VCAM-1 and CRP. Thus chronic blockade of RAAS may decrease underlying subclinical inflammatory response thereby reducing risk of incident T2DM (31) as well as CHD (32).

Perspectives

The role of hypertension, hyperlipidemia and hyperglycemia in causing arterial damage and accelerating atherosclerosis is well recognized in clinical practice. Evidence-based therapeutic management is essentially focused on normalizing these factors, in addition to incorporating appropriate life style changes and normalization of body weight.

Recent evidence points to the adverse effects of circulating peptide hormones, especially originating from adipose tissue, on constituents of blood as well as on blood vessels and resulting in an increase in the inflammatory markers in circulation along with the causation of vascular inflammation. Molecular mechanisms underlying metabolic alterations and linked with changes in vascular biology provide new insight into the understanding of the role of vascular inflammation in hypertension and T2DM. This may lead to identification of new molecular targets that may enhance the scope and range of possible therapeutic interventions.

References

1. Misra A, Cherukupalli R, Reddy KS, Mohan A, Bajaj JS (1998). Hyperinsulinemia and dyslipidemia in non-obese, normotensive offspring of hypertensive parents in Northern India. *Blood Pressure* **8**: 1-5.
2. Reaven G. The insulin resistance syndrome: past, present, and future. Presented at the First Annual World Congress on the Insulin Resistance Syndrome; November 20-22, 2003; Los Angeles, California.
3. Sironi AM, Gastaldelli A, Mari A, Ciociaro D, Postano V, Buzzigoli E, Ghione S, Turchi S, Lombardi M, Ferrannini E (2004). Visceral Fat in Hypertension: Influence on

Insulin Resistance and â-Cell Function. *Hypertension* **44**: 127.

4. Salomaa VV, Strandberg TE, Vanhanen H, Naukkarinen V, Sarna S, Miettinen TA (1991). Glucose tolerance and blood pressure : long term follow up in middle aged men. *BMJ* **302**: 493-496.

5. Nishina M, Kikuchi T, Yamazaki H, Kameda K, Hiura M, Uchiyama M (2003). Relationship among systolic blood pressure, serum insulin and leptin, and visceral fat accumulation in obese children. *Hypertens Res* **26**: 281-288.

6. Faria AN, Ribeiro Filho FF, Gouveia Ferreira SR, Zanella MT (2002). Impact of visceral fat on blood pressure and insulin sensitivity in hypertensive obese women. *Obes Res* **10**: 1203-1206.

7. Reaven GM, Chen YD, Jeppesen J, Maheux P, Krauss RM (1993). Insulin resistance and hyperinsulinemia in individuals with small, dense low density lipoprotein particles. *J Clin Invest* **92**: 141-146.

8. Laakso M, Edelman SV, Brechtel G, Baron AD (1990). Decreased effect of insulin to stimulate skeletal muscle blood flow in obese men. *J Clin Invest* **85**:1844-1852.

9. Kashyap SR, Roman LJ, Lamont J, Masters BSS, Bajaj M, *et al* (2005). Insulin Resistance is Associated with Impaired Nitric Oxide Synthase (NOS). *J Clin Endo & Metab.* **90**:1100-1105.

10. Baron AD, Brechtel G (1993). Insulin differentially regulates systemic and skeletal muscle vascular resistance. *Am J Physiol* **265**:E61-E67.

11. Gans RO, Bilo HJ, von Maarschalkerweerd WW, Heine RJ, Nauta JJ, Donker AJ (1991). Exogenous insulin augments in healthy volunteers the cardiovascular reactivity to noradrenaline but not to angiotensin II. *J Clin Invest* **88**:512-518.

12. Laakso M, et al (1992). Impaired insulin-mediated skeletal muscle blood flow in patients with NIDDM. *Diabetes* **41**:1076-1083.

13. King GL, Davidheiser S, Banskoto N, Oliver FJ, Inoguchi T (1991). Insulin receptors and actions on vascular cells. In: *Hypertension as an Insulin-Resistant Disorder. Genetic Factors and cellular Mechanisms.* Smith U, Bruun Ne, Hedner T, Hokfelt B, eds. Elsevier

Science Publishers, Amsterdam. pp. 183-197.

14. Naruse K, King GL (2001). Effect of Diabetes on Endothelial Function. In: *Diabetes and Cardiovascular Disease*. Johnstone MT, Veves A, eds. Humana Press, Totowa, New Jersey. 45-64.

15. Bajaj JS, Bajaj M (2008). Metabolic Syndrome and Vascular Disease. In: Clinical Endocrinology and Diabetes Mellitus. Y. Sachdev, ed. Vol. II p. 772-783.

16. Duplain H, Burcelin R, Sartori C, Cook S, *et al* (2001). Insulin resistance, hyperlipidemia, and hypertension in mice lacking endothelial nitric oxide synthase. *Circulation* **104**:342-345.

17. Perreault M, Marette A (2001). Targeted disruption of inducible nitric oxide synthase protects against obesity-linked insulin resistance in muscle. *Nature* **7**:1138-1143.

18. Qasim A, Mehta NN, Tadesse MG, Wolfe ML, Rhodes T, Girman C, Reilly MP (2008). Adipokines, insulin resistance, and coronary artery calcification. *J Am Coll Cardiol* **52**:231-236.

19. Elbatarny HS, Netherton SJ, Ovens JD, Ferguson AV, Maurice DH (2007). Adiponectin, ghrelin, and leptin differentially influence human platelet and human vascular endothelial cell functions: implication in obesity-associated cardiovascular diseases. *Eur J Pharmacol* **558**:7-13.

20. Shetty GK, Economides PA, Horton ES, Mantzoros CS, Veves A (2004). Circulating Adiponectin and Resistin Levels in Relation to Metabolic Factors, Inflammatory Markers, and Vascular Reactivity in Diabetic Patients and Subjects at Risk for Diabetes. *Diabetes Care* **27**: 2450-2457.

21. Winzer C, Wagner O, Festa A, Schneider B, Roden M, *et al* (2004). Plasma Adiponectin, Insulin Sensitivity, and Subclinical Inflammation in Women with prior Gestational Diabetes Mellitus. *Diabetes Care* **27**: 1721-1727.

22. Wannamethee SG, Tchernova J, Whincup P, Lowe GD, Rumley A, *et al* (2007). Association of adiponectin with metabolic and vascular risk parameters in the British Regional Heart Study reveal stronger links to insulin resistance-related than to coronary heart disease risk-related parameters. *Int J Obes (Lond)* **31**:1089-1098.

23. Hansson L, Lindholm LH, Niskanen L, *et al* (1999). Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomized trial. *Lancet* **353**: 611-616.

24. Yusuf S, Gerstein H, Hoogwerf B, *et al* (2001). Ramipril and the development of diabetes. *JAMA* **286**: 1882-1885.

25. Lindholm LH, Ibsen H, Dahlof B, *et al* (2002). Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE) : a randomised trial against atenolol. *Lancet* **359**: 1004-1010.

26. Andraws R, Brown DL (2007). Effect of inhibition of the renin-angiotensin system on development of type 2 diabetes mellitus (meta-analysis of randomized trials). *Am J Cardiol* **99**: 1006-1012.

27. Furuhashi M, Ura N, Takizawa H, *et al* (2004). Blockade of the renin-angiotensin system decreases adipocyte size with improvement in insulin sensitivity. *J Hypertens* **22**: 1977-1982.

28. Henriksen EJ, Jacob S (2003). Angiotensin converting enzyme inhibitors and modulation of skeletal muscle insulin resistance. *Diabetes Obes Metab* **5**: 214-222.

29. Natali A, Quinones Galvan A, Santoro D, *et al* (1993). Relationship between insulin release, antinatriuresis and hypokalaemia after glucose ingestion in normal and hypertensive man. *Clin Sci (Lond)* **85**: 327-335.

30. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE (2004). Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes* **53**: 693-700.

31. Scheen AJ (2004). Prevention of type 2 diabetes mellitus through inhibition of the renin-angiotensin system. *Drugs* **64**: 2537-2565.

32. Tsikouris JP, Cox CD (2003). Pharmacologic blockage of the renin-angiotensin system : vascular benefits beyond commonly understood pharmacologic actions. *Pharmacotherapy* **23**: 1141-1152.