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ORIGINAL ARTICLE

Effect of eplerenone on insulin action in essential hypertension: a randomised, controlled, crossover study

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An association exists between hyperaldosteronism, hypertension and impaired insulin action. Eplerenone is a selective mineralocorticoid receptor antagonist; however, little is known about its effects on insulin action. The aim of this study was to determine the effect of eplerenone on insulin action in hypertensive adults, using the hyperinsulinaemic euglycaemic clamp. A randomised, controlled, double-blind, crossover design was employed. After a 6-week washout period, hypertensive, non-diabetic patients were treated with either eplerenone 25 mg twice daily or doxazosin 2 mg twice daily for 12 weeks. After each treatment period, insulin action was assessed by a hyperinsulinaemic euglycaemic clamp, with isotope dilution methodology. After washout, treatment groups were crossed over. Fifteen patients completed the study. There were no differences in fasting glucose, or fasting insulin between treatment with eplerenone or doxazosin. The measure of overall insulin sensitivity, exogenous glucose infusion rates during the last 30 min of the clamp, was similar with both treatments; 23.4 (3.9) $\mu mol\,kg^{-1}\,min^{-1}$ after eplerenone and 23.3 (3.6) $\mu mol\,kg^{-1}\,min^{-1}$ after doxazosin ($P = 0.83$). Isotopically determined fasting endogenous glucose production rates were similar after both treatments (eplerenone 9.4 (0.6) $\mu mol\,kg^{-1}\,min^{-1}$ vs doxazosin 10.6 (0.7) $\mu mol\,kg^{-1}\,min^{-1}$). There was a trend for lower endogenous glucose production rates during hyperinsulinaemia following eplerenone compared with doxazosin (2.0 (0.8) $\mu mol\,kg^{-1}\,min^{-1}$ vs 4.1 (0.9) $\mu mol\,kg^{-1}\,min^{-1}$). There was no difference in insulin stimulated peripheral glucose utilisation rates after treatment with eplerenone or doxazosin (25.4 (3.6) $\mu mol\,kg^{-1}\,min^{-1}$ vs 27.0 (3.9) $\mu mol\,kg^{-1}\,min^{-1}$). This study gives reassuring evidence of the neutral effect of eplerenone on insulin action in hypertensive, non-diabetic patients.

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INTRODUCTION

The association between hypertension and insulin resistance is well established. It is also well known that antihypertensive medications have important effects on glucose metabolism. Beta blockers and thiazide diuretics cause impaired insulin sensitivity, whereas there is conflicting evidence on the effect of angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). ACE inhibitors have been shown to be neutral in their effects on glucose metabolism in patients with essential hypertension,[1] obesity[2] and type 2 diabetes mellitus,[3,4] whereas others report that treatment with ACE inhibitors[5] or ARBs[6] attenuates insulin resistance.

Insulin resistance is also associated with hyperaldosteronism,[7] with estimates of the prevalence of impaired glucose tolerance in primary aldosteronism between 15 and 25%.[8] The relationship between aldosterone and insulin sensitivity appears to be independent of blood pressure, body mass index and age.[9–11]

Eplerenone is a well-tolerated selective mineralocorticoid receptor antagonist. A reduction in mortality has been demonstrated following treatment with eplerenone in post-myocardial infarction left ventricular dysfunction[12] and in mild systolic heart failure.[13] Animal data suggest that eplerenone may have a beneficial effect on insulin action;[14] however, there is limited data on its effect in man. The aim of this study was to describe the effect of selective mineralocorticoid receptor antagonism on insulin action in hypertensive adults.

MATERIALS AND METHODS

Subjects

Adult patients aged <70 years with essential hypertension were studied. Patients were recruited from local general practices and in response to a poster advertisement. Individuals with a history of secondary hypertension or who required more than three antihypertensive agents to control blood pressure were excluded. Diabetes, significant hepatic or renal disease and body mass index $> 35\,kg\,m^{-2}$ were also exclusion criteria.

All subjects gave written informed consent and the protocol was approval by the Regional Ethics Committee and the Administration of Radioactive Substances Advisory Committee. An International Standard Randomised Controlled trial Number was issued for the study (ISRCTN21269614). A grant was received from the Research and Development Office, Northern Ireland Health and Social Care Agency.

Study design

At the start of the study, participants' antihypertensive medication was stopped and placebo lactose tablets substituted for 6 weeks. Blood pressure was monitored every 2 weeks during this washout period, and every 4 weeks during active treatment periods. Blood pressure was measured using an automated blood pressure machine (Omron Electronics Ltd, Milton Keynes, UK) taken as the mean of the second and third readings after 10 min seated.

Participants were assigned to a randomised crossover trial consisting of a 12-week period of either eplerenone 25 mg twice daily (Inspra; Pfizer Inc., New York, NY, USA) or doxazosin mesilate followed by a 12-week period taking the complementary medication separated by a 6-week placebo

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washout. The clinical trials pharmacist in the Royal Victoria Hospital, Belfast undertook the blinded block randomisation procedure, and dispensed the overencapsulated medication in identical containers. The investigators were unblinded after the last patient completed the trial. If blood pressure was above 160/95 mm Hg on two occasions, then open-label extended release doxazosin (Cardura XL; Pfizer Inc.) was introduced and titrated to a maximum of 12 mg per day, as required. Doxazosin was used as a comparator as it has been shown to have a neutral effect on insulin action.[15]

Assessment of insulin action

Insulin action was assessed in the last week of each active treatment period by a one-step hyperinsulinaemic euglycaemic clamp, as previously described.[16,17] A cannula was placed in the left arm for all infusions and in the right arm for blood sampling. The right hand was placed in a plexiglass box maintained at 55 °C (Department of Medical Physics, Nottingham University) to arterialise the venous blood.

A primed-continuous infusion of high-performance liquid chromatography-purified [3-^{3}H]glucose was administered during a 2-h equilibration period (− 120 min to zero time). The initial tracer prime was adjusted, based on fasting plasma glucose.[18] A continuous infusion of insulin was commenced at 1 mU kg^{-1} min^{-1} (zero to + 120 min).

Plasma glucose was measured at 5 min intervals on a bedside analyser (Beckman Glucose Analyser2; Beckman, High Wycombe, UK) and maintained at the subject's fasting glucose concentration by an infusion of 20% glucose, prelabelled with [3-^{3}H]glucose to match the predicted basal plasma glucose-specific activity, with the modification that the primed continuous tracer infusion was reduced to 50% of the basal rate at + 20 min and to 25% at + 40 min to maintain tracer steady state.[16]

Analytical techniques

Arterialised venous blood was used for all analyses in the glucose clamp studies. Plasma for measurement of glucose-specific activity was deproteinised with barium hydroxide and zinc sulphate by the method of Somogyi.[19] Aliquots of tracer infusate and labelled exogenous glucose infusion were spiked into non-radioactive plasma and processed in parallel to allow calculation of [3-^{3}H]glucose infusion rates (GIR). Glucose was measured using an automated glucose oxidase method using a Beckman Glucose Analyser 2.

Insulin and C-peptide were measured using a chemiluminescent substrate. Insulin was measured on an Abbott Architect i2000SR immunoassay analyser (Abbot Diagnostics, Maidenhead, UK) and C-peptide on an Immulite 2500 immunoassay analyser (Siemens Healthcare Diagnostics Ltd, Camberly, UK). Serum aldosterone was measured using the Coat-A-Count solid phase radioimmunoassay (Siemens Medical Solution Diagnostics, Ulster Diagnostics, Moneyrea, UK).

Calculations

The non-steady state equations of Steele *et al.*[20] as modified by DeBodo *et al.*[21] were used to calculate rates of glucose turnover during the periods − 30 min to time zero and 90–120 min, assuming a pool fraction value of 0.65 and an extracellular volume of 190 ml kg^{-1}. The radioactivity of tracer and exogenous glucose infusate 'spikes', calculated as the mean of quadruplicates after subtraction of background counts, was used directly to calculate [3-^{3}H]GIRs. Infusion rates of [3-^{3}H]glucose were calculated as the sum of the tracer infused continuously and the tracer in the labelled exogenous glucose infusion. Rates of endogenous (hepatic) glucose production were then calculated by subtraction of the exogenous GIRs required to maintain euglycaemia from the isotopically determined rates of glucose appearance. Exogenous GIRs were calculated for each 10 min interval by multiplying the mean infusion pump rate (ml min^{-1}) by the measured concentration of infused glucose and expressed per kilogram body weight.

Statistical methods

Statistical analysis was by Hills and Armitage,[22] enabling comparison of the effects of treatment to be adjusted for period effects. Results are described as mean (s.e.m.). Variables that were non-normally distributed are described as median (lower quartile, upper quartile). The power of the study, calculated from previous clamp data,[18] gave a 90% chance of detecting a 10% change in insulin action at the 5% level of significance.

RESULTS

Sixteen subjects started the study, with one subject withdrawing following the loss of venous access during the assessment of insulin action. Clinical, anthropometric and biochemical data of the subjects after 6-week placebo run-in are presented in Table 1. The nine males and six females who completed the study were overweight (mean body mass index 28.9 (0.8) kg m^{-2}). Blood pressure was 137/87 (4/2) mm Hg with five patients required additional therapy with open-label doxazosin during the run-in, at a mean dose of 8.8 (1.5) mg. The subjects who required doxazosin during run-in remained on this for the duration of the study.

Subjects were not diabetic, mean fasting glucose 5.4 (0.1) mmol l^{-1}. One patient demonstrated impaired fasting glucose, with a fasting glucose of 6.7 mmol l^{-1}. There was no evidence of secondary hypertension, in particular mean aldosterone was 357 (58) pmol l^{-1}.

There were no significant differences in fasting glucose or fasting insulin between treatment with eplerenone or doxazosin. There was no difference in blood pressure or serum potassium between treatments (Table 2). Serum aldosterone was higher after treatment with eplerenone than with doxazosin (778 (130) pmol l^{-1} vs 507 (65) pmol l^{-1}), confirming adherence to the study medication, although this difference did not reach statistical significance.

During the clamp studies, plasma glucose was maintained at a constant level by exogenous glucose infusion with mean coefficients of variation of 4.5% after eplerenone therapy and 5.8% following doxazosin. The measure of overall insulin sensitivity, exogenous GIRs during the last 30 min of the clamp (Figure 1), was similar after both treatments; 23.4 (3.9) μmol kg^{-1} min^{-1} after treatment with eplerenone vs 23.3 (3.6) μmol kg^{-1} min^{-1} after doxazosin ($P = 0.83$). The insulin infusion rate of 1 mU kg^{-1} min^{-1} resulted in a small difference in insulin concentration between treatment groups in the last 30 min of the clamp (Figure 1) (78.4 (5.4) mU l^{-1} after eplerenone vs 70.9 (4.6) mU l^{-1} after doxazosin). The ratio of GIR/insulin during this time gives a measure of glucose metabolised per unit of insulin, which is an index of insulin sensitivity.[23] There was no difference in the ratio between treatments (eplerenone 0.35 (0.07) vs doxazosin 0.38 (0.08)).

Isotopically determined endogenous glucose production rates in the fasting state (9.4 (0.5) μmol kg^{-1} min^{-1} after eplerenone and 10.6 (0.7) μmol kg^{-1} min^{-1} after doxazosin) were not different and suppressed during hyperinsulinaemia to a similar extent following both treatments. Although there was a trend towards lower endogenous glucose production following treatment with eplerenone 2.0 (0.8) μmol kg^{-1} min^{-1} vs 4.1 (0.9) μmol kg^{-1} min^{-1} after doxazosin, this association did not reach statistical significance ($P = 0.085$).

Peripheral glucose utilisation rates during hyperinsulinaemia were not different after treatment with eplerenone (25.4 (3.6) μmol kg^{-1} min^{-1}) or doxazosin (27.0 (3.9) μmol kg^{-1} min^{-1}).

Table 1. Baseline characteristics

Characteristic	*Mean*	*s.e.m.*
Sex (M/F)	9/6	
Age (years)	55.3	1.8
Height (m)	1.73	0.03
Weight (kg)	86.9	3.7
Body mass index (kg m^{-2})	28.9	0.8
Blood pressure (mm Hg)	137/87	4/3
Fasting plasma glucose (mmol l^{-1})	5.4	0.1
Fasting insulin (mU l^{-1})[a]	8.3	4.3, 12.6
Aldosterone (pmol l^{-1})	357	57

[a]Median (interquartile range).

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Table 2. Blood pressure and biochemical parameters after eplerenone and doxazosin

Characteristic	*Eplerenone*	*Doxazosin*	P
Systolic blood pressure (mm Hg)	142 (4)	146 (4)	NS
Diastolic blood pressure (mm Hg)	90 (3)	90 (3)	NS
Fasting glucose (mmol l^{-1})	5.3 (0.1)	5.3 (0.1)	NS
Fasting insulin (mU l^{-1})[a]	9.1 (5.3, 13.2)	8.7 (4.4, 9.9)	NS
Sodium (mmol l^{-1})	140 (0.48)	142 (0.49)	NS
Potassium (mmol l^{-1})	4.2 (0.07)	4.2 (0.07)	NS
Creatinine (μmol l^{-1})	82 (3.82)	82 (3.32)	NS
Aldosterone (pmol l^{-1})	778 (130)	507 (65)	NS

[a]Median (interquartile range).

Non-esterified free fatty acids were significantly higher during the fasting state after treatment with eplerenone (eplerenone 1.2 (0.1) mmol l^{-1} vs doxazosin 0.9 (0.1) mmol l^{-1}, $P<0.01$); however, there was no difference in non-esterified free fatty acid concentration during hyperinsulinaemia (eplerenone 0.9 (0.1) mmol l^{-1}; doxazosin 0.7 (0.1) mmol l^{-1}).

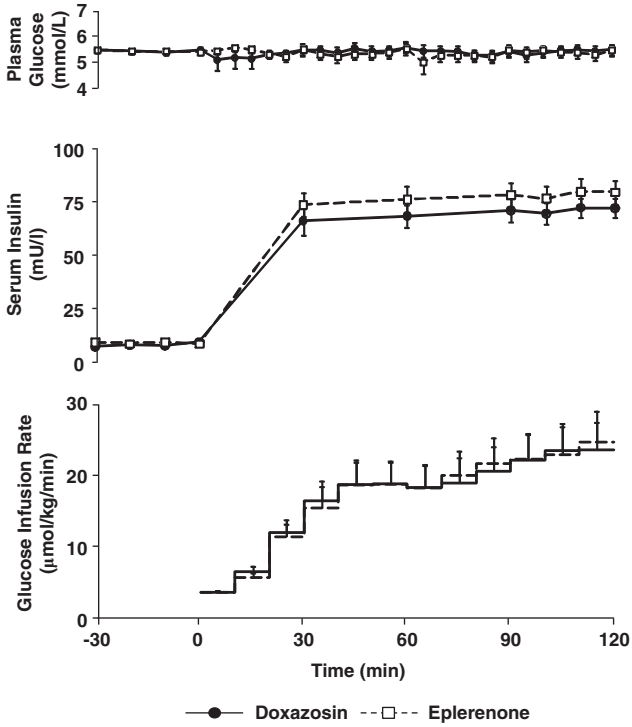

Figure 1. Plasma glucose, serum insulin and glucose infusion rates during the final 30 min of the hyperinsulinaemic euglycaemic clamp (mean ± s.e.m.). Exogenous glucose infusion rates during the final 30 min of the clamp are a measure of overall insulin sensitivity, and they were similar after both eplerenone and doxazosin.

DISCUSSION

There is increasing evidence to support the use of mineralocorticoid receptor antagonists in patients with hypertension,[24] heart failure,[13,25] post-myocardial infarction[12] and diabetic nephropathy.[26] Of the two mineralocorticoid receptor antagonists currently available, eplerenone is the more selective agent, and is better tolerated than spironolactone, particularly because of the absence of antiandrogenic side effects.

In this study, we have demonstrated for the first time that short-term treatment with the selective mineralocorticoid receptor antagonist eplerenone has a neutral effect on insulin action in non-diabetic, hypertensive adults. GIR required to maintain euglycaemia during the final 30 min of a 2-h insulin infusion were almost identical after both 12-week treatment periods. Inclusion of isotope dilution methodology in the hyperinsulinaemic euglycaemic clamp allows assessment of hepatic insulin sensitivity by calculating endogenous glucose production in both fasting state and following hyperinsulinaemia. There was no effect of treatment with eplerenone compared with doxazosin on either fasting hepatic glucose production or its suppression during hyperinsulinaemia.

It is recognised that hyperaldosteronism is associated with impaired glucose tolerance though the mechanism is less well established. In a cohort of patients with aldosterone producing adenoma, surgical treatment with normalisation of aldosterone improved insulin sensitivity as measured by a glucose clamp. Treatment with spironolactone—while normalising blood pressure but not reducing serum aldosterone concentration—did not improve insulin sensitivity. Importantly, potassium was normal during the glucose clamps in this study removing hypokalaemia as a possible confounder.[27] This study suggests that aldosterone may have direct effects on insulin action, which may not be attenuated by blocking the mineralocorticoid receptor.

Spironolactone use in patients without hyperaldosteronism suggests that it may have negative effects on insulin action. One month's treatment with spironolactone resulted in a significant increase in HbA1c in normotensive patients with type 2 diabetes mellitus.[28] Similarly, in hypertensive, obese, diabetic patients HbA1c was shown to rise following treatment with spironolactone 50 mg.[29]

In a direct comparison of 4 months treatment with eplerenone or spironolactone in mild chronic heart failure HbA1c levels increased significantly after treatment with spironolactone though HbA1c was unchanged following eplerenone. Cortisol also increased significantly following spironolactone treatment, but not after eplerenone. The negative effect of spironolactone on HbA1c may be related to this increase in cortisol, as spironolactone has a 100-fold higher affinity for the glucocorticoid receptor than eplerenone.[30] However, neither assessment of glucocorticoids by measurement of random cortisol nor use of HbA1c as a marker of insulin action is the most sensitive measure of these indices.

Rodent work with eplerenone also supports its more neutral effect on insulin sensitivity, demonstrating that mineralocorticoid receptor blockade reversed obesity-related changes in gene expression.[14] The incidence of diabetes is higher in patients with heart failure than in the general population. However, in mild chronic heart failure, treatment with eplerenone was not associated with increased rates of new-onset diabetes mellitus in this high-risk patient population.[31]

Our study showing a neutral effect of eplerenone in non-diabetic, hypertensive patients is therefore in keeping with other studies,[14,30,31] but our use of a glucose clamp technique, the gold standard assessment of insulin action, makes the results all the more compelling.

The findings of this study are timely given the renewed interest in aldosterone and its deleterious effects. Primary aldosteronism, an important cause of secondary hypertension,[32] is associated with increased cardiovascular events compared with essential hypertension of similar degree,[33] and is treated with a mineralocorticoid receptor antagonist where surgery is not appropriate and there is increasing recognition of the role of mineralocorticoid receptor antagonists in the treatment of all stages of heart failure;[12,13,25] therefore, wider use of eplerenone may be anticipated.

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CONCLUSION

Eplerenone 25 mg twice daily was shown to have a neutral effect on insulin sensitivity in hypertensive patients. While these results are reassuring, further work on eplerenone is required in diabetic and obese patients where the adverse metabolic effects of antihypertensive treatment may be greater.

What is known about this topic

- Hypertension and hyperaldosteronism are associated with impaired insulin action.
- Antihypertensive medications can have important metabolic effects, with evidence suggesting spironolactone worsens HbA1c in patients with hypertension and type 2 diabetes mellitus.

What this study adds

- In patients with essential hypertension, eplerenone has a neutral effect on insulin action, as measured by a hyperinsulinaemic, euglycaemic clamp technique, which is the gold standard for assessing insulin action.
- Using isotope dilution methodology to study whole body insulin-stimulated glucose metabolism, we also show that eplerenone has a neutral effect on endogenous glucose production and peripheral glucose uptake in patients with essential hypertension.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1 Wiggam IM, Hunter SJ, Atkinson AB, Ennis CN, Henry JS, Browne JN *et al.* Captopril does not improve insulin action in essential hypertension: a double-blind placebo controlled study. *J Hypertens* 1998; **16**: 103–109.
2 Goossens GH, Blaak EE, Schiffers PM, Saris WHM, van Baak MA. Effect of short-term ACE inhibitor treatment on peripheral insulin sensitivity in obese insulin-resistant subjects. *Diabetologia* 2006; **49**: 3009–3016.
3 Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and anti-hypertensive therapy as risk factors for type 2 diabetes mellitus. *New Engl J Med* 2000; **342**: 905–912.
4 Petrie JR, Morris AD, Ueda S, Small M, Donnell R, Connell JMC *et al.* Trandolapril does not improve insulin sensitivity in patients with hypertension and type 2 diabetes: A double-blind, placebo-controlled crossover trial. *J Clin Endocrinol Metab* 2000; **85**: 1882–1889.
5 Galletti F, Strazzullo P, Capaldo B, Fabris F, Ferrara LA, Gloriosa N *et al.* Controlled study of the effect of angiotension converting enzyme inhibiton versus calcium-entry blockade on insulin sensitivity in overweight hypertensive patients: Trandolapril Itatlian Study (TRIS). *J Hypertens* 1999; **17**: 439–445.
6 Mori Y, Tanaka T, Matsuura K, Yokoyama J, Utsunomiya K. Influence of telmisartan on insulin response after glucose loading in obese patients with hypertension: ARB trial of hypertension in obese patients with hyperinsulinemia assessed by oral glucose tolerance test (ATHLETE). *Adv Ther* 2011; **28**: 698–706.
7 Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003; **26**(Suppl 14): S5–S20.
8 Giacchetti G, Sechi LA, Rilli S, Carey R. The renin–angiotensin–aldosterone system, glucose metabolism and diabetes. *Trends Endocrin Metab* 2005; **16**: 120–126.
9 Bentley-Lewis R, Adler GK, Perlstein T, Seely EW, Hopkins PN, Williams GH *et al.* Body mass index predicts aldosterone production in normotensive adults on a high salt diet. *J Clin Endocrinol Metab* 2007; **92**(11): 4472–4475.
10 Garg R, Hurwitz S, Williams GH, Hopkins PN, Adler GK. Aldosterone production and insulin resistance in healthy adults. *J Clin Endocrinol Metab* 2010; **95**(4): 1986–1990.
11 Catena C, Lapenna R, Baroselli S, Nadalini E, Colussi G-L, Novello M *et al.* Insulin sensitivity in patients with primary aldosteronism: a follow up study. *J Clin Endocrinol Metab* 2006; **91**: 3457–3463.
12 Pitt BP, Remme W, Zannad F, Neaton J, Martinez F, Roniker B *et al.* Eplerenone, a selective aldosterone blocker in patients with left ventricular dysfunction after myocardial infarction. *New Engl J Med* 2003; **348**: 1309–1321.
13 Zanad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H *et al.* Eplerenone in patients with systolic heart failure and mild symptoms. *New Engl J Med* 2011; **364**(1): 11–21.
14 Guo C, Ricchiuti V, Lian BQ, Yao TM, Coutinho P, Romero JR *et al.* Mineralocoticoid receptor blockade reverses obesity-related changes in expressions of adiponectin, peroxisome proliferator-activated receptor-γ and pro-inflammatory adipokines. *Circulation* 2008; **117**(17): 2253–2261.
15 Harper R, Ennis CN, Heany AP, Sheridan B, Gormley M, Atkinson AB *et al.* A comparison of the effects of low and conventional dose thiazide diuretic on insulin action in hypertensive patients with NIDDM. *Diabetologia* 1995; **38**: 853–859.
16 Courtney CH, McCance DR, Atkinson AB, Bassett J, Ennis CN, Sheridan B *et al.* Effect of the alpha-adrenergic blocker, doxazosin, on endothelial function and insulin action. *Metabolism* 2003; **52**(9): 1147–1152.
17 Neely RD, Rooney DP, Atkinson AB, Sheridan B, Ennis CN, Trimble ER *et al.* Underestimation of glucose turnover determined using (6-3H) glucose tracer in non-steady state. The role of a tritiated tracer impurity. *Diabetologia* 1990; **33**: 681–687.
18 Harper R, Ennis CN, Sheridan B, Atkinson AB, Johnston GD, Bell PM. Effects of low dose versus conventional dose thiazide diuretic on insulin action in essential hypertension. *BMJ* 1994; **309**: 226–230.
19 Somogyi M. Determination of blood sugar. *J Biol Chem* 1945; **160**: 69–73.
20 Steele R, Wall JS, DeBodo RC, Atlszuler N. Measurement of size and turnover rate of body glucose pool by the dilutional method. *Am J Physiol* 1956; **1987**: 15–24.
21 DeBodo RC, Stelle R, Altszuler N, Dunn A, Bishop JS. Effects of insulin on hepatic glucose metabolism and glucose utilization by tissue. *Diabetes* 1963; **12**: 16–30.
22 Hills M, Armitage P. The two-period cross-over clinical trial. *Br J Clin Pharmacol* 1979; **8**: 7–20.
23 DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979; **237**(3): E214–E223.
24 Chapman N, Dobson J, Wilson S, Dahlof B, Sever PS, Wedel H *et al.* Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension* 2007; **49**: 839–845.
25 Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *New Engl J Med* 1999; **341**: 709–717.
26 Rossing K, Schjoedt KJ, Smidt UM, Boomsma F, Parving H-H. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy. *Diabetes Care* 2005; **28**: 2106–2112.
27 Sindelka G, Widimsky J, Haas T, Pazny M, Hilgertova J, Skrha J. Insulin action in primary hyperaldosteronsim before and after surgical or pharmacological treatment. *Exp Clin Endocrinol Diabetes* 2000; **108**(1): 21–25.
28 Davies JI, Band M, Morris A, Struthers AD. Spironolactone impairs endothelial function and heart rate variability in patients with type 2 diabetes. *Diabetologia* 2004; **47**(10): 1687–1694.
29 Swaminathan K, Davies J, George J, Rajendra NS, Morris AD, Struthers AD. Spironolactone for poorly controlled hypertension in type 2 diabetes: conflicting effects on blood pressure, endothelial function, glycaemic control and hormonal profiles. *Diabetologia* 2008; **51**(5): 762–768.
30 Yamaji M, Tsutamoto T, Kawahara C, Nishiyama K, Yamamoto T, Fujii M *et al.* Effect of eplerenone versus spironolactone on cortisol and haemoglobin A_{1c} levels in patients with chronic heart failure. *Am Heart J* 2010; **160**: 915–921.
31 Preiss D, van Veldhuisen DJ, Sattar N, Krum H, Swedberg K, Shi H *et al.* Eplerenone and new-onset diabetes in patients with mild heart failure: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Eu J Heart Fail* 2012; **14**: 909–915.
32 Young WF. Primary aldosteronism; renaissance of a syndrome. *Clin Endocrinol* 2007; **66**: 607–618.
33 Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *J Am Coll Cardiol* 2005; **45**(8): 1243–1248.

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