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Ischemic Heart Disease, Diabetes and Mineralocorticoid Receptors

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1. Introduction

Ischemic heart disease continues to be a leading cause of death in most countries, with the death rate in men almost twice as high as that of women. Following an ischemic event, the primary clinical strategy is to quickly restore blood flow to the heart muscle, myocardial reperfusion, using drug therapy (thrombolytics) or percutaneous coronary intervention. The damage that follows ischemia-reperfusion is triggered by increased production of oxygen free radicals at the time of reperfusion when blood flow is restored (Ambrosio et al. 1993; Marczin et al. 2003) and impaired myocardial antioxidant defences, leading to cardiomyocyte apoptosis and increased infarct size.

Hyperglycaemia and high plasma levels of aldosterone are two critical factors that produce poor outcomes following an ischemic event and reperfusion strategies. Diabetes is now the fastest growing disease worldwide, and a public health concern globally given the aging population -currently affecting more than 240 million people worldwide, and the number is predicted to rise to more than 360 million by 2030, according to the World Health Organization. Global health expenditure on diabetes is estimated to rise to USD 490 billion (Zhang et al. 2010) and cardiovascular disease is the major cause of death. In adults with type 2 diabetes, cardiovascular disease is responsible for 65-75% of deaths due to myocardial infarction and end stage renal disease; and the age-adjusted relative risk for cardiovascular complications in type 1 diabetes may exceed that of type 2 (Nadeua et al. 2010). Although first line treatment for diabetes is anti-hyperglycaemic agents, additional therapeutic strategies are needed. In addition, during hypoglycaemia there is an increase in aldosterone production (Adler et al. 2010) and there is emerging evidence of a relationship between aldosterone and insulin resistance.

High plasma aldosterone levels during percutaneous coronary intervention double the risk of mortality and are an independent risk factor for mortality (Beygui et al. 2006). Inappropriately elevated aldosterone levels produce cardiac and vascular inflammation and fibrosis, leading to remodelling and disease via activation of mineralocorticoid receptors (MR) (Brilla et al. 1990; Young et al. 1995). Recent experimental studies (Mihailidou et al. 2009) show that during myocardial ischemia-reperfusion, cardiac damage is aggravated by activation of mineralocorticoid receptors by both aldosterone (Fig.1) and cortisol (Fig. 2).

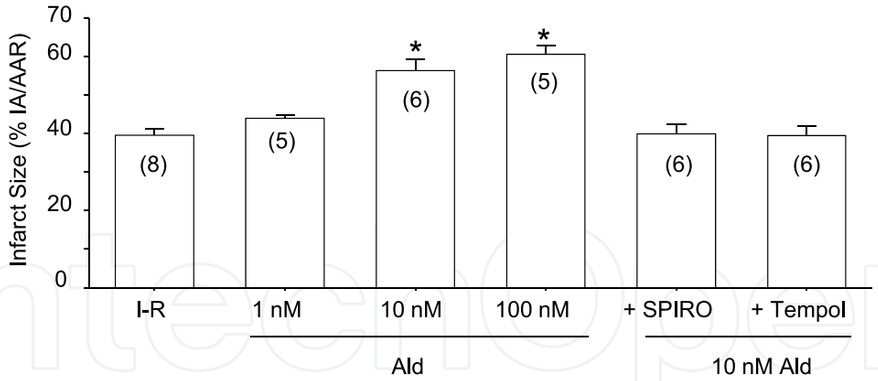

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Fig. 1.

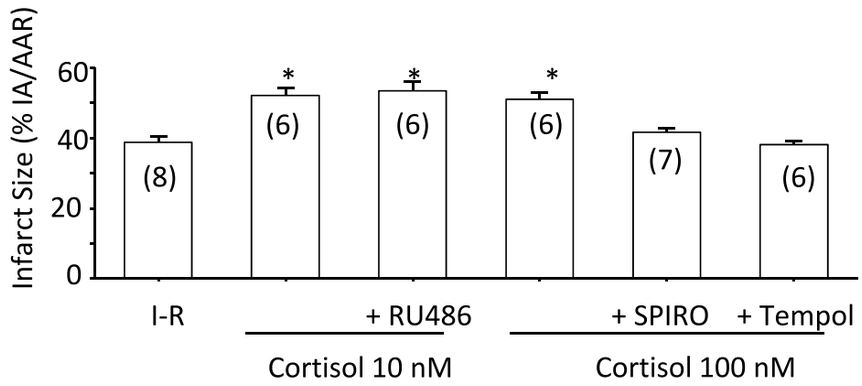

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Fig. 2.

Current therapies, such as antagonism of the renin-angiotensin-system, mitigate the cardiorenal complications of diabetes but do not suppress aldosterone production. Aldosterone levels increase ("aldosterone breakthrough") in 10-53% patients and recent studies suggest an association between aldosterone production and insulin resistance in normotensive subjects (Balkau et al. 1998), indicating aldosterone is an independent risk factor for myocardial damage. The results from RALES (Randomised ALdactone Evaluation Study, Pitt et al. 1999), EPHESUS (Eplerenone Post acute Myocardial Infarction HEart Failure SUrvival and efficacy Study, Pitt et al. 2003), and recently EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure, Zannad et al. 2011) provide strong evidence that preventing MR activation increases survival and decreases hospitalization in patients with heart failure and acute myocardial infarction. In these trials 32% of patients were diabetic.

Since patients with diabetes have a 2-3 fold increased risk of ischemic heart disease, any new drug therapy for lowering glucose levels in this population must be evaluated in terms of its safety for use in patients with cardiovascular disease. It would be advantageous if this medication is shown to have cardio-protective effects, and to ensure there isn't aggravated cardiac damage following a heart attack. Glucagon-Like Peptide-1 (GLP-1) agonists are a relatively new class of anti-hyperglycaemic medications for the management of patients

with diabetes. These agents also elicit a cytoprotective effect on beta cells leading to preservation and survival of beta-cell mass (Tschen et al. 2009; 2011; Brubaker & Drucker 2004). The impact of these new therapeutic agents on cardiovascular disease remains unclear. Controlled large clinical studies of GLP-1 agonists on cardiovascular outcomes following ischemic heart disease for patients with diabetes are currently in progress. Whether there is added benefit of combining GLP-1 agonists with a mineralocorticoid receptor antagonist has not been examined.

Given the increasing aging populations globally, increased incidence of both type 1 and type 2 diabetes and elevated mortality in patients with high plasma aldosterone levels, this chapter will provide a review of our current understanding of the incidence of ischemic heart disease in both type 1 and type 2 diabetes; mechanisms involved and new treatment strategies. These include the GLP-1 agonists and mineralocorticoid receptor antagonists as potential additional therapeutic strategies to reduce cardiovascular complications of diabetes.

2. Ischemic heart disease and diabetes

Cardiovascular disease is the major cause of disease burden and death globally and along with diabetes and cancer make up two-thirds of all deaths globally, according to the World Health Organization's report for 2011 World Health Statistics. The impact of hyperglycemia in patients with acute myocardial infarction (AMI) varies with age, with higher risk for in-hospital mortality among younger patients (Nicolau et al. 2011). Hyperglycemia was associated with 7.6-fold increased odds for in-hospital death in patients younger than 50 years, compared with a 3.5-fold increased risk in those aged 50-60 years. Worldwide, there is a higher risk of diabetes or cardiovascular disease in rural areas than in urban areas (Wan et al. 2007). The prevalence of type 2 diabetes is increasing dramatically due to the aging population, obesity and physical inactivity. Although Type 1 diabetes is less common and usually has onset in younger subjects, age-adjusted relative risk for cardiovascular complications in type 1 may exceed type 2 diabetes (Nadeau et al. 2010).

Patients with either type 1 or type 2 diabetes have significantly higher mortality and morbidity following acute myocardial infarction than do the rest of the population, with increasing focus on hyperglycemia contributing directly to the excessive cardiovascular risk in patients with diabetes. The hazard ratio for major cardiovascular disease (CVD) was reported to be 3.6 (95% CI 2.9–4.5) in men with type 1 diabetes compared with those without diabetes (Soedamah-Muthu et al. 2006), while men with type 2 diabetes, the hazard ratio was 3.3 (95% CI 2.5– 4.5) and 10.1 (6.7–17.4) in women. (Juutilainen et al. 2008). Clinically, elevated but non-diabetic blood glucose levels increase cardiovascular mortality risk (Balkau et al. 1998). During myocardial reperfusion injury, hyperglycaemia increases cardiomyocyte apoptosis in both human (Frustaci et al.2000) and animal models (Fiordaliso et al. 2000; Sheu et al. 2007) of diabetes. Restoring blood flow to the ischemic myocardium is accompanied be increased oxygen free radicals (Ambrosio et al. 1993; Brown et al. 1988) and impaired myocardial antioxidant defence capacity leading to tissue injury (Leichtweis et al 2001), and therefore additional therapeutic strategies are needed to complement glycemic control.

Inflammation also promotes reperfusion injury (Kawaguchi et al. 2011), and both type 1 and type 2 diabetes include inflammatory components: type 1 diabetes is an auto-immune

disease (Atkinson and Eisenbarth, 2001), and more recently type 2 diabetes has also been considered an auto-inflammatory condition (Donath and Shoelson, 2011) leading to an increase production of pro-inflammatory mediators including pro-inflammatory cytokines IL-6 and TNF-α. Activation of TNF-α, activates apoptosis, and amplifies the innate immune response. The innate immune response has been identified to interact with danger associated molecular patterns (DAMPs) found on proteins released by necrotic cells following ischemia-reperfusion that include HMGB1 and heat shock proteins via toll like receptors (TLRs). This interaction activates NF–κβ signalling promoting innate immune cell infiltration into the myocardium, increased cytokine production and increased pro-apoptotic activity through caspase 3/7 and hence further aggravating reperfusion injury (Arslan et al., 2010). Additionally $CD4^+$ T-cells have been identified to infiltrate the myocardium during reperfusion and through the release of cytokine IFN-γ promote infiltration of innate immune cells, in particular macrophages and neutrophils, the effector cells of the immune response to reperfusion injury (Yang et al., 2006). This increase in adaptive and innate immune responses in diabetes promotes activity of the complement system, which also further aggravates reperfusion injury (van der Pals et al., 2010).

3. Mechanisms involved in hyperglycaemia-aggravated ischemic heart disease

During prolonged ischemia ATP levels decrease leading to reduced Na^+/K^+ ATPase and sarcoplasmic reticulum (SR) Ca^{2+} pump activity and cystolic Na^+ and Ca^{2+} retention. Additionally the decreasing oxygen supply during ischemia leads to an increased reliance on anaerobic glycolysis evident in the increased production of anaerobic-glycolysis by-products and hydrogen ions (H^+), thus decreasing cellular pH and lactate in the ischemic myocardium (van der Vusse et al. 1987). The increase in H^+ in the myocardium promotes the activity of the sodium (Na^+)/H^+ exchanger leading to further increase in sodium retention, This is followed by calcium entry through the activity of the Na^+/Ca^{2+} exchanger; increased Ca^{2+} opens the ryanodine receptor further increasing cytosolic Ca^{2+} referred to as Ca^{2+} overload (Cannell et al. 1995) triggering cell death. ROS production also promotes Ca^{2+} overload through its interaction with various Ca^{2+}-related ion channels, including increasing the open probability of the ryanodine receptor found on the sarcoplasmic reticulum via oxidation of key thiol groups within the protein (Boraso & Williams, 1994), Ca^{2+} leakage through lipid perioxidation of phospholipid membranes (Burton et al.1990) and stimulation of the Na^+-Ca^{2+} exchanger (Shi et al. 1989) through both lipid perioxidation and oxidation of thiol groups within the exchanger protein.

Increased production of reactive oxygen species (ROS) (Arroyo et al., 1987; Steenbergen et al., 1987) during reperfusion triggers increased uncoupling of mitochondria complex I (Rolo and Palmeira, 2006, Tanaka et al., 2000). Additionally diabetes is associated with decreased antioxidant capacity measured by both direct enzyme activity by total plasma anti-oxidant capacity (TRAP) assay and indirectly by measures of lipid peroxidation such as lipid hydroperoxides and conjugate dienes (Likidlilid et al., 2007, Marra et al., 2002, Santini et al., 1997; Santos et al., 2011) and calcium overload (Steenbergen et al., 1987), leading to cell death and cardiac damage (Chen et al., 2002). Clinically, the Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) trial found that diabetic patients had increased incidence of mortality and myocardial infarction 9 months after percutaneous coronary

intervention (Mathew et al., 2004). Diabetic patients with hypertension were at a greater risk of adverse outcomes following percutaneous coronary intervention (Lingman et al., 2011)

Hyperglycaemia that is not controlled can lead to abnormal cardiac contractile dysfunction, with decreased Ca^{2+} sensitivity of contractile proteins. Animal studies show that there is increased post-translational modification of contractile proteins with phosphorylation of myofilament proteins troponin I and troponin T resulting in decreased Ca^{2+} sensitivity (Akella et al., 1995). Myocardial tissue collected from diabetic and non-diabetic patients undergoing coronary artery bypass surgery showed that the presence of diabetes decreased Ca^{2+} sensitivity (Jweied et al. 2005). Diabetic patients also have a higher risk of developing hypertension than normoglycaemic individuals. Sodium (Na^{+}) retention has been identified as a possible cause of this increased risk of hypertension due to increased Na^{+} -glucose co-transporter activity found in the renal tubules of diabetic patients (Nosadini et al., 1993). Hyperglycaemia and hypertension have an additive effect on long-term cardiovascular risk, and when both are present there is greater risk of microvascular complications, including nephropathy and retinopathy, and macrovascular complications such as atherosclerosis.

During ischemia-reperfusion (refer Fig. 3), there is programmed loss of cardiomyocytes, apoptosis, with rates of 2–12% reported in the border zone of human myocardial infarcts (Ottaviani et al., 1999; Olivetti et al., 1996). This loss of viable tissue leads to structural remodelling of the heart and deteriorating cardiac function. Both acute stress hyperglycaemia (Suleiman et al., 2005) and diabetes (Mathew et al., 2004; Muhlestein et al., 2003) aggravate injury following reperfusion of the ischemic myocardium. Hyperglycaemia increases cardiomyocyte apoptosis, both acutely as shown by recent studies (Wong et al. 2011) as well as after prolonged exposure in diabetic animals (Fiordaliso et al. 2000; Sheu et al. 2007) and human tissue (Frustaci et al. 2000). Aggravated reperfusion injury correlates with increased apoptosis in the area at risk (Crow et al. 2004). Clinically, elevated but non-diabetic blood glucose levels also increase cardiovascular mortality risk (Balkau et al. 1998).

Apoptosis is up-regulated in hyperglycaemic cellular models of ischemia, where cardiac myocytes are deprived of serum and placed in hypoxic conditions (Bonavita, 2003, Aki et al., 2010). Bonavita et al 2003 identified activation of pro-apoptotic mediators of Bid and Bax and down-regulation of anti-apoptotic mediator Bcl-xl in H9c2 rat cardiomyoblast cell line. Further support is provided by Aki et al. (2010) using H9c2 cells in hypoxic hyperglycaemic conditions that showed AIF release through ATP depletion promoting chromatin condensation and DNA fragmentation. Receptor for Advanced Glycation End products (RAGE) expression has been identified to be crucial to the promotion of apoptosis and reperfusion injury via increased c-Jun N-terminal Kinases (JNK) signalling promoting pro-apoptotic caspase-3 activation and cytochrome-c release (Aleshin et al., 2008).

As well as apoptosis, when cells have been exposed to sustained damage, there is necrosis of myocardial tissue, which is aggravated by hyperglycaemia. Hyperglycaemia-activated ROS promote the production of methylgloxal a side product of many metabolic pathways; increase in methygloxal promotes the NF-κβ to bind to the promoter region of RAGE (Yao and Brownlee, 2010). Increased RAGE expression and increased induced nitric oxide synthase (iNOS) expression, increase nitric oxide production (NO) (Bucciarelli et al., 2006). NO and ROS species combine to form peroxynitrate, increasing high mobility group box 1 (HMGB1) release, a marker of necrotic cell death, although mechanisms has not been defined (Loukili et al., 2011).

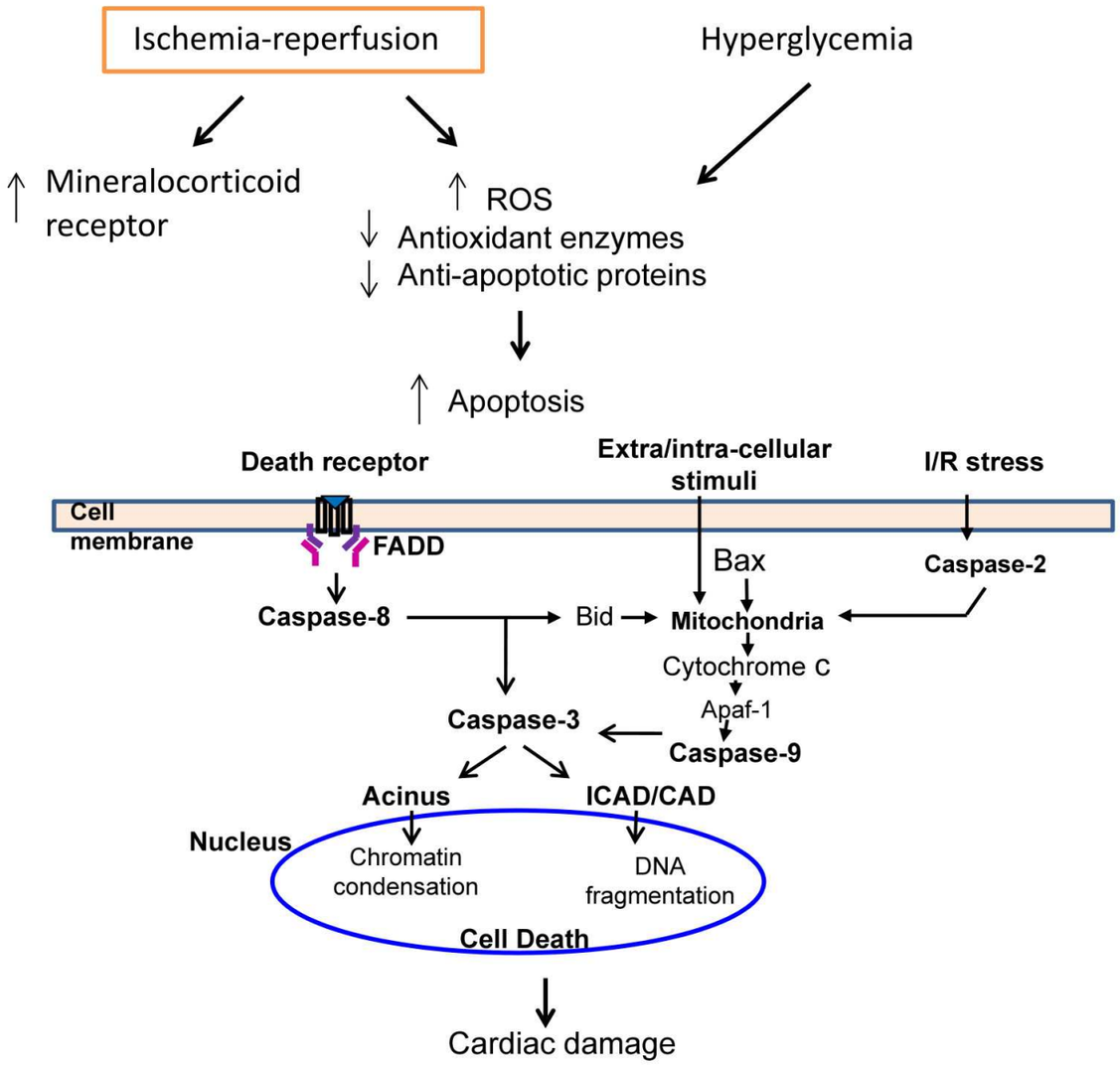

Fig. 3. Ischemia-reperfusion induced signal transduction pathway leading to apoptosis in cardiac myocytes.

4. New treatment strategies during ischemic heart disease

First line treatment for diabetes is anti-hyperglycaemic agents, with insulin the anti-hyperglycaemic agent for type 1 diabetes and in some type 2 diabetes cases. Intensive glycaemic control clinically delayed development of microvascular complications in type 2 diabetic patients in the United Kingdom Prospective Diabetes Study (UKPDS, 1998a), but did not lead to a reduction in cardiovascular events; a subgroup of patients treated with metformin had a 39% reduction in myocardial infarction, although there were only a small number of events. Patients with Type 1 diabetes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study only showed a reduction in risk of any cardiovascular complications by 42% only years after recruitment (The Diabetes Control and Complications Trial/Epidemiology of Diabetes

Interventions and Complications Research Group, 2003). In the large randomised clinical trials, ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) and ACCORD (Action to Control Cardiovascular Risk in Diabetes), intensive glycemic control compared to standard glucose-lowering targets in type 2 diabetes led to a reduction in risk for microvascular complications, although the optimum treatment for minimising the risk of cardiovascular complications was not defined. Metformin is routinely used in type 2 diabetes and has some cardiovascular benefits in obese type 2 diabetic patients (UKPDS, 1998b). In a pre-clinical study, acute stress hyperglycaemia aggravated infarct area and apoptosis following ischemia-reperfusion whereas perfusion with insulin decreased apoptosis and reduced reperfusion injury (Wong et al., 2011).

4.1 GLP-1 agonists

Glucagon-like peptide 1 (GLP-1) agonists are an exciting new class of anti-hyperglycaemic medication that not only lower glucose levels, but also reduce weight and have protective effects on pancreatic islets. Since the insulinotropic and insulinomimetic effects of GLP-1 are mitigated at plasma glucose concentrations of 3.9 mmol/L, this minimizes the risks of hypoglycemia and the need for glucose infusion. Therefore, the pharmacological properties of GLP-1 are attractive as a means to stimulate myocardial glucose uptake during post-ischemic contractile dysfunction. Currently, there are limited clinical studies to confirm the impact of GLP-1 agonists on cardiovascular events in subjects with type 2 diabetes. Glucagon like peptide-1 (GLP-1) agonists, mimic the action of the incretin GLP-1 upon its binding to the GLP-1 receptor, which has been shown to be expressed in cardiomyocytes (Ban et al., 2008). GLP-1 also promotes the release of insulin, whilst inhibiting the release of glucagon, both these effects occur postprandial.

Several animal studies involving murine and canine models have examined the effects of GLP-1 agonists on the ischaemic myocardium (Timmers et al. 2009; Noyan-Ashraf et al. 2009; Kristensen et al. 2009; Ban et al. 2010). Most, but not all of these studies suggest that GLP-1 agonists may have beneficial effects on the myocardium following an ischemic insult. These benefits ranged from reduction in infarct size to improvement in left ventricular function, although the mechanisms for the cardio-protective action are not well understood. In addition, most studies used non-diabetic animal models, where the hearts were subjected to normal glucose levels and transient administration of GLP-1 agonists. In a recent study (Noyan-Ashraf et al. 2009), Liraglutide conferred cardio-protection over Metformin despite equivalent degrees of glycaemic control. In this study, diabetes was induced in mice by using streptozotocin, and therefore a model of Type I diabetes. The cardioprotective properties of GLP-1 agonist are independent of its glycaemic control properties and inactivate a key pro-apoptotic protein BAD mediated via PKB/AKT signalling, thus decreasing apoptosis and reperfusion injury (Timmers et al. 2009). The effects of GLP-1 on outcomes following acute coronary occlusion for subjects with Type 2 diabetes have yet to be defined.

4.2 Mineralocorticoid receptor antagonists

High plasma aldosterone levels during percutaneous coronary intervention double the risk of mortality and are an independent risk factor for mortality (Beygui et al. 2006). Pre-

clinically the administration of aldosterone increased reperfusion injury by promoting apoptosis (Mihailidou et al., 2009). Aldosterone at inappropriate levels promotes inflammation and cardiovascular remodelling via activation of mineralocorticoid receptors (MR). Aldosterone has also been reported to trigger oxidative stress, inflammation, thrombosis and sudden cardiac death (Rajagopalan et al. 2002; Struthers 2001). ACE inhibitors or angiotensin receptor antagonists mitigate the cardiorenal complications of diabetes but do not suppress aldosterone production. Aldosterone levels increase ("aldosterone breakthrough") in 10-53% patients, indicating aldosterone is an independent risk factor for myocardial damage.

Recent studies show aldosterone interferes with insulin signalling pathways and reduces expression of insulin-sensitizing factors adiponectin and peroxisome proliferator activated receptor–γ (Wada et al. 2009; Guo et al. 2008). Blockade of the mineralocorticoid receptor increased adiponectin and peroxisome proliferator-activated receptor-γ in adipose tissue leading to improved insulin sensitivity in obese, diabetic ob/ob and db/db mice (Guo et al. 2008; Hirata et al. 2009). Further confirmation of cross talk between aldosterone and insulin signalling pathways is that insulin resistance improved with treatment in patients with primary hyperaldosteronism (Catena et al. 2006). Spironolactone has also been shown to be effective in decreasing albuminuria in patients with type 2 diabetes with proteinuria who were being treated with ACE inhibitors. (Davidson et al. 2008). Although the mechanism was not defined, an anti-inflammatory action was proposed.

The relationship between aldosterone, glucose metabolism and insulin resistance is poorly explored. The results from RALES (Randomised ALdactone Evaluation Study), EPHESUS (Eplerenone Post acute Myocardial Infarction HEart Failure SUrvival and efficacy Study) [Pitt et al. 2003], and recently EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) provide strong evidence that preventing mineralocorticoid receptor activation increases survival and decreases hospitalization in patients with heart failure and acute myocardial infarction. In these trials 32% of patients were diabetic, highlighting a potential benefit of MR antagonist use to minimise cardiovascular complications in diabetic patients in addition to anti-hyperglycaemic treatment. Subgroup analysis of EPHESUS showed the beneficial effects of eplerenone were also found in patients with diabetes (O'Keefe et al. 2008). Diabetic patients treated with eplerenone had a higher rate of absolute risk reduction, compared with patients without diabetes, for both end-point of death from cardiovascular causes or hospitalization for cardiovascular events (5.1 vs. 3.5%).

5. Conclusion

There is an enormous public health problem emerging given the increasing aging population who are at highest risk of having an acute ischemic event and with diabetes the fastest growing disease, the proportion of people at risk of cardiovascular disease is therefore increasing dramatically. Globally health expenditure on diabetes is estimated to rise, with the health burden growing - currently 300 million people with diabetes worldwide, despite preventative strategies. Additional therapies are required and the results from clinical trials to determine the cardiovascular effects of the new anti-hyperglycemic agents, GLP-1 agonists are eagerly anticipated. Mineralocorticoid receptor antagonists, spironolactone and eplerenone have demonstrated specific actions at low doses,

preventing end-organ damage. In particular, diabetic patients showed greater absolute cardiovascular risk reduction. Provided there is monitoring of plasma K^+, there is potential for use of MR antagonists in diabetes.

6. References

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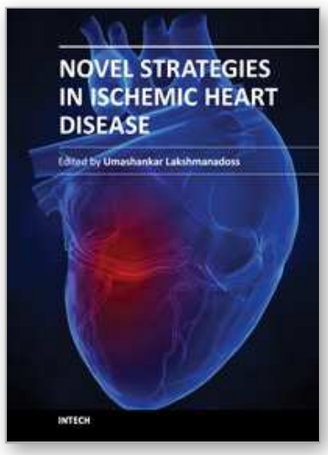

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