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Mineralocorticoids and Cardiovascular Disease in Females with Insulin Resistance and Obesity

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Abstract

Purpose of the Review—In the present review, we will discuss the evidence and the mechanisms underlying the complex interplay between obesity, mineralocorticoid receptor activation, and cardiovascular dysfunction with special emphasis on the pathogenesis of cardiovascular disease (CVD) in obese and insulin-resistant females.

Recent Findings—Since the initial isolation of aldosterone in 1953 and the cloning of the mineralocorticoid receptor (MR) decades later, our understanding has expanded tremendously regarding their involvement in the pathogenesis of CVD. Recent results from both pre-clinical and clinical studies support a close correlation between increase adiposity and enhanced aldosterone production (MR activation).

Summary—Importantly, insulin resistance and obese females are more prone to the deleterious cardiovascular effects of MR activation, and enhanced MR activation in females has emerged as an important causative event in the genesis of a more severe CVD in diabetic women. Different clinical trials have been completed examining the effect of MR blockade in subjects with CVD. Despite its important beneficial mortality impact, side effects are frequent and a newer MR antagonist, finerenone, with less risk of hyperkalemia is currently being tested in large clinical trials.

Keywords

Obesity; Females; Cardiovascular disease; Aldosterone; Mineralocorticoid receptor

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Compliance with Ethics Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

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Introduction

Individuals with type 2 diabetes (DM2) and/or features of the metabolic syndrome are at significantly higher risk of cardiovascular disease (CVD) when compared to non-diabetic and non-obese subjects [1–4]. A nationwide survey in 2014 revealed a prevalence of obesity in the USA of 35.0% in men and 40.4% in women [5]. Parallel with the increase in the frequency of obesity, the prevalence of DM2 continues to growth. Alarmingly, for adults in the USA in their 20s, the likelihood of developing diabetes is 40.2% for men and 39.6% for women [6]. Importantly, CVD is one of the main complications of DM2 [6, 7] accounting for 75% of the hospital admissions and over 50% of deaths in diabetic patients [8, 9].

It has been established that excess body weight is associated with inappropriate activation of the Renin Angiotensin Aldosterone System, reflected by significant elevations in both plasma and urine concentrations of aldosterone [10, 11]. These abnormalities are in turn associated with increased risk of CVD and chronic kidney disease (CKD) [12]. Several clinical studies have demonstrated that high circulating levels of aldosterone associated with obesity have deleterious effects in the heart and the vasculature [13–15]. Further, it has been shown that elevated aldosterone levels are associated with insulin resistance in humans exposed to a standardized high-sodium diet [16]. Also, primary hyperaldosteronism is associated with worsening insulin resistance that is reversed after treatment of excess aldosterone secretion [17].

Importantly, the relationship between insulin resistance, obesity, and CVD exhibits sexual dimorphism and is affected by insulin sensitivity [18–20]. Whereas non-obese and insulin sensitive pre-menopausal women are at significant lower risk of CVD relative to post-menopausal women and men, obese and insulin-resistant women lose the protection provided by estrogen and have higher and more severe frequency of CVD relative to men. Over 30 years ago, Barret-Connor et al. reported a higher age-adjusted risk of death from ischemic heart disease in diabetic women when compared with diabetic men [21]. Similarly, Kannel et al. described in the Framingham study cohort that a diagnosis of diabetes mellitus blunts the beneficial CVD risk profile classically associated with females [22]. Further, in a cohort study of 73,783 subjects in Newfoundland and Labrador, Roche et al. compared retrospectively the risk of cardiovascular mortality in males and females with and without DM2 [23]. Females with DM2 had an increased risk of CVD mortality (hazard ratio 6.54 [4.80–8.91]) and CVD hospitalizations (hazard ratio 5.22 [4.31–6.3]) [24] compared with both non-diabetic females and diabetic men. A prospective analysis of Nurses' Health Study cohort (121,049 women 30 to 55 years of age with type 2 diabetes were followed for over 20 years) examined the impact of DM2 on all-cause mortality and mortality specifically attributed to coronary heart disease (CHD). When compared with women without DM2, the age-adjusted relative risk of all-cause mortality was 3.39 (CI 2.50–3.60) for diabetic women without history of CHD and 6.84 (CI 4.71–9.95) for diabetic women with history of CHD. Further, in women with long duration of DM2 (> 15 years) and prior CHD, there was a 30-fold increase in the risk of fatal CHD [25].

In this review, we discuss the evidence and the mechanisms underlying the complex interplay between obesity, mineralocorticoid receptor activation, and cardiovascular

dysfunction with special emphasis on the pathogenesis of CVD in obese and insulin-resistant females.

Aldosterone and the Vasculature

Aldosterone, a mineralocorticoid, was originally isolated by Drs. Sylvia A. Simpson and James F. Tait in 1953 [26]. Our knowledge about the mechanisms that regulate the actions of aldosterone and other mineralocorticoids in general has been steadily increasing over the ensuing several decades. These hormones are critical for blood pressure control, as well as for the homeostasis of fluids and electrolytes via regulation of sodium retention in the kidneys, and directly affect the vasculature as well by acting on endothelial cells and vascular smooth cells (VSMC) [27, 28]. Classically, the effects of aldosterone have been attributed by binding, activation, and signaling through the mineralocorticoid receptor (MR) [29], which was initially cloned in 1987 by Arriza et al. [30].

MR can be activated by glucocorticoids as well as by aldosterone [31]. Expression of the 11-betahydroxysteroid dehydrogenase type 2 (11βHSD2), which inactivates cortisol to cortisone, modulates tissue-specific sensitivity to mineralocorticoids over cortisol. 11βHSD2 is present in endothelial cells and VSMC [31]. In addition to aldosterone, several other ligands and pathways have been shown to trigger signaling through MR, including Angiotensin II (Ang II) [32] and rac-1 (Rho family small GTPase) [24]. Signaling through MR results in genomic actions mediated by activation of specific DNA hormone response elements. This in turns leads to transcriptional regulation of genes critical for sodium transport, including the epithelial sodium channel ENaC, serum and glucocorticoid-induced kinase 1 (SGK-1), and sodium/potassium channels. Importantly, in VSMC, MR also activates numerous genes that promote vascular fibrosis and remodeling such as interleukin-16, collagen types I and II, and bone morphometric protein 2 [32, 33, 34••]. Furthermore, recent studies have also suggested a role for micro-RNAs (small non-coding RNA molecules) as post-transcriptional regulators of genes involved in MR signaling-induced remodeling of the vasculature [35]. Additional mechanisms implicated in regulation of vascular damage by MR are actively being elucidated and include: interactions with inflammatory transcription factors (NF-kB and AP-1, basic fibroblastic growth factor) that promote hypertrophy, cardiac remodeling, and fibrosis independently of blood pressure [36].

Sex steroids modulate certain acute non-genomic actions of aldosterone. In addition to actions mediated by classic cytoplasmic estrogen receptors □ and □, there is mounting evidence that estrogen activates the membrane-bound G-protein couple receptor (GPER). GPER is expressed in both endothelial cells and VSMCs [37], and its activation results in acute blood pressure drop [38], enhanced response to prostanoids [39], and inhibition of endothelin-1-induced vasoconstriction [40]. Remarkably, in rodent aortic tissue, aldosterone activates GPER, regulates aldosterone-mediated apoptosis, and leads to activation of the extracellular signal-regulated kinase (ERK) ½ activation and myosin light chain (MLC) phosphorylation in VSMC [41]. In this same study, ERK phosphorylation was used as a surrogate to evaluate aldosterone sensitivity, and MLC phosphorylation was utilized as a marker for downstream aldosterone signaling specific to VSMC. Additional studies have

confirmed the importance of GPER as a mediator of rapid actions of aldosterone in vascular tissue [42].

Evidence from Human Studies

According to CDC data, approximately 5.7 million people suffer from heart failure in the USA, which carries an estimated 50% mortality risk at 5 years after initial diagnosis [43]. Extensive clinical evidence regarding the deleterious effects of MR activation has accumulated over the last several years, in particular regarding fibrosis and remodeling in the cardiovascular system. This prompted the design of various clinical trials aimed at examining the impact of MR blockade on CVD outcomes.

A preliminary study done in 1960 by Hans Selye on salt and fludrocortisone-treated mice suggested a protective effect of the MR blocker spironolactone in preventing cardiac necrosis and renal calcification and leading to reduced mortality [44]. These initial observations were translated into humans later on, and a protective effect of MR antagonism using spironolactone was demonstrated in the Randomized Aldactone Evaluation Study (RALES). In this large clinical trial (27% women), MR blockade with spironolactone in addition to standard therapy substantially reduced the risk significantly frequency of hospitalization (35%), improvement in heart failure symptoms, and death rate (30%) among patients with severe heart failure (New York Heart Association class-NYHA-IV). The trial was discontinued early (24 months) as an interim analysis determined that spironolactone was efficacious [45]. Nevertheless, increased clinical use of spironolactone after the RALES trial led to augmented recognition of adverse effects of the medication, in particular hyperkalemia [46, 47] and gynecomastia [48, 49], which led to development and later approval of eplerenone by FDA in September 2002.

Eplerenone is a selective MR antagonist that does not bind to glucocorticoids, progesterone, or androgen receptors and, therefore, is not linked to increased frequency of gynecomastia [50]. The efficacy of eplerenone was studied during the EPHESUS trial in 2003 [51]. This major clinical trial reported a 15% reduction in the relative risk of death, as well as a reduced risk of hospitalization for heart failure. Serious hyperkalemia occurred in 5.5% of the patients compared to 3.9% of the patients in the placebo group [51]. Following RALES and EPHESUS results, a focused update was introduced in 2009 to the ACC/AHA 2005 guidelines pertaining to the Heart Failure [52] recommending usage of MR antagonist in heart failure patients.

A more recent trial, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) was published in 2011 and reported that eplerenone reduced the rate of death from cardiovascular causes or hospitalization from heart failure compared to placebo by 37%, in patients with NYHA class II. This was a randomized, double-blinded trial which assigned 2737 patients (> 55 years of age, NYHA class II HF and Ejection Fraction < 35%) to receive either eplerenone or placebo. There was increased incidence of hyperkalemia in the eplerenone group compared to placebo, which prompted the recommendation that serial potassium levels should be measured regularly and dosage be adjusted accordingly. After all these clinical trials, MR antagonists have become a definite

part of the medication regimen for individuals with heart failure [53], with the clause to monitor closely potassium levels.

Cooper et al. recently published a retrospective analysis using a clinical registry data linked to Medicare claims of patients admitted to the hospital with heart failure during an 8-year period with history of diabetes mellitus of CKD [54]. Of 16,848 patients analyzed, 12.3% received MR antagonists at discharge. MR antagonist treatment was associated with higher risk for readmission secondary to hyperkalemia and acute renal failure if they had borderline or preserved ejection fraction, while patients with reduced ejection fraction did not exhibit this increased risk [54].

Finerenone: a New MR Antagonist

As discussed above, clinical use of MR blockers, spironolactone, and eplerenone is limited by the risk of side effects, in particular gynecomastia and hyperkalemia. A new non-steroid dihydropyridine-based MR antagonist, finerenone, is currently in phase III clinical trials. Finerenone (previous nomenclature BAY 94–8862) is a potent selective MR antagonist that exhibits no transactivation activity toward any other steroid hormone receptor, thus being associated with lower frequency of side effect [55]. In a rat model of heart failure (DOCA + salt and ischemia), finerenone improved parameters of myocardial injury more effectively than eplerenone [56]. In a model of pressure-overload heart failure (aortic constriction) in C57Bl6/J male mice, finerenone resulted in significant reduction of cardiac hypertrophy when compared with eplerenone. In addition, the authors also found a differential expression of the brain natriuretic peptide and troponin T type 2 gene [57]. Finerenone also has been shown to abrogate cardiac fibrosis induced by short-term isoproterenol in 129/sv mice [58•]. Interestingly, in this model, finerenone treatment significantly reduced fibrosis and macrophage infiltration, whereas eplerenone did not. Further, finerenone decreased inhibition of tenascin-X (TNX), a glycoprotein involved in pro-fibrotic pathways by regulating the bridging of collagen fibrils, which induces collagen deposition, and extracellular matrix degradation.

All these data about the efficacy and safety of finerenone led to a multicenter, randomized, double-blinded phase II study which was conducted in patients with heart failure with reduced left ventricle ejection fraction (< 40%) and mild or moderate CKD [59]. The Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS) was designed to evaluate the safety and tolerability of finerenone and showed that finerenone is as effective as spironolactone in decreasing biomarkers of hemodynamic stress and is associated with lower incidence of hyperkalemia and worsening renal function [60]. This evidence later led to a randomized, double-blind, phase IIb multicenter dose-finding study Mineralocorticoid Receptor Antagonist Tolerability Study-Heart Failure (ARTS-HF) which compared the efficacy and safety of different treatment regimens of finerenone with eplerenone in patients with DM2 and/or CKD. The trial showed that finerenone was similar in tolerability and efficacy to eplerenone in reducing the N-terminal pro-brain natriuretic peptide (NT-proBNP) by more than 30% [61].

Further studies are currently ongoing which are aimed at better delineating the beneficial effects of MR antagonists as well the right dosages. The MiREnDa (Mineralocorticoid Receptor Antagonist in End Stage Renal Disease) is trying to determine the effect of spironolactone on the left ventricular mass index in end-stage renal disease [62]. Another randomized clinical trial currently ongoing (FIGARO-DKD) will evaluate the efficacy and safety of Finerenone on the reduction of cardiovascular morbidity and mortality in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease in addition to standard of care (https://clinicaltrials.gov/ct2/show/NCT02545049).

These clinical trials will continue to elucidate the potential benefits of MR blockade in preventing CVD in obese and insulin-resistant patients that are already at heightened risk.

Increased Adiposity, Aldosterone, and CVD in Females

The hallmark of obesity in humans is expansion of adipose tissue [63]. The relationship between obesity and activation of the MR receptor has been extensively demonstrated in both clinical and pre-clinical studies. In an analysis of 2891 participants of the Framingham offspring cohort, Kathiresan et al. reported that female sex was correlated with elevated aldosterone levels [64]. However, post-menopausal women who were not using hormone replacement therapy had lower aldosterone levels [64], which might point toward an effect of sex-steroids in the higher levels. A different study found, in a group of normotensive adults, that overweight subjects had higher urinary aldosterone and serum aldosterone responses to Ang II infusion when compared with adults with a body mass index (BMI) < 25 [10]. This group also examined the aldosterone response to acute Ang II infusion after 2 weeks of a high-salt diet in 84 healthy subjects (mean age 40 ± 10.8 years). There was significant negative correlation between insulin sensitivity, BMI, diastolic blood pressure, and Ang II-stimulated aldosterone levels [16]. Conversely, weight loss results in lower serum plasma aldosterone, in concert with significant reductions in blood pressure in post-menopausal obese women [65].

A recent study by Romero et al. showed, in 1592 subjects of the HyperPATH cohort, that women when compared to men have 30% greater salt sensitivity of blood pressure (regardless of menopausal status). In addition, upon an acute infusion of Ang II, the elevation of aldosterone production was greater in premenopausal females compared to men. Authors found an interaction between sex and aldosterone on blood pressure responses to Ang II. In a rat model of Ang II infusion, female rats also exhibited higher aldosterone levels. Importantly, cardiac injury and renal injury (documented by proteinuria) were greater in female rats too [66].

Bender et al. showed that MR blockade ameliorates diastolic dysfunction related to obesity independently of changes in blood pressure. In obese Zucker rats, MR blockade resulted in improved diastolic relaxation, fibrosis, and oxidative stress [67]. Briones and collaborators have shown that adipocytes express aldosterone synthase, and via the angiotensin II receptor type 1(AT1′0 receptor secrete aldosterone under both basal conditions and in response to Ang II stimulation [68]. In addition, the adipocyte-derived cytokine, leptin, has been also been shown to be a direct regulator of aldosterone synthase [69••, 70•]. Specifically to

females, Huby et al. showed that in mice, leptin infusion resulted in elevation of aldosterone levels and increased adrenal expression of aldosterone synthase. In the ob/ob leptin deficient model, infusion of leptin caused an increase in aldosterone levels. The authors also noted that rodent models of leptin deficiency or insensitivity do not exhibit aldosterone elevations or enhanced adrenal aldosterone synthase expression despite being obese. Moreover, cultured human adrenocortical cells express leptin receptors and produce increasing amount of aldosterone in response to increasing concentrations of leptin. In addition, leptin-induced endothelial dysfunction and cardiac fibrosis were abrogated by the MR receptor blockade with spironolactone [69••]. This group has also reported using two different female rodent models (the protein tyrosine phosphatase 1b knockout that exhibits leptin hypersensitivity and the agouti yellow-obese hyperleptinemic mice) that elevated levels of aldosterone were parallel with increases in blood pressure and endothelial dysfunction. Furthermore, both leptin antagonism and mineralocorticoid receptor blockade improved blood pressure and endothelial function in female mice [70•].

Other preclinical models have explored the role of MR in the genesis of CVD in females. DeMarco et al. showed in insulin-resistant and obese C57Bl6/J female mice that treatment with the MR antagonist, spironolactone, resulted in amelioration of aortic stiffening as well as aortic remodeling [71]. Further work by Jia et al. showed that endothelial-specific knockout of the MR receptor protects female fed a diet high in fructose and high in fat against arterial stiffening and endothelial dysfunction via reduction in vascular inflammation and oxidative stress [72]. In parallel, we have demonstrated that females develop diastolic dysfunction when insulin resistance and obese earlier than males [73], and MR antagonism prevents the development of diastolic dysfunction [74].

More recently, a study by Jaffe et al. showed that female mice have higher susceptibility to microvascular dysfunction when obese and hyperlipidemic in comparison to males. Authors also noted that females have lower endothelial potassium channel IK1 and SK3 expression, loss of H2 O2-mediated vasodilation, and increased superoxide production. Relevant to MR activation, deletion of the endothelial MR receptor in females resulted in enhanced nitric oxide and prevention of hyperlipidemia-induced oxidative stress [75••].

Conclusions

Collectively, there is abundant evidence both from clinical and pre-clinical studies demonstrating that aldosterone exerts a critical role as a mediator of vascular dysfunction and CVD in the setting of obesity and insulin resistance. The mechanisms implicated in aldosterone action in cardiovascular tissues are multifactorial and involve enhanced MR activation and signaling involving both genomic and rapid non-genomic mechanisms. In addition, aldosterone effects on vasculature involve complex cross talk with other hormones, factors, and pathways that contribute to tissue injury. In particular, there is mounting evidence of a critical influence of estrogen as a contributor to MR activation. The fact that obese and insulin-resistant women have increased levels of aldosterone in concert with evidence of more aggressive CVD relative to men [76] has prompted additional research that demonstrate clear sex differences in the pathogenesis of CVD. The progress in our knowledge in these areas has raised our awareness about the importance of considering sex

differences when utilizing current and newer strategies as well as medications to curb the impact of excessive aldosterone in the cardiovascular system.

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AUTHOR QUERIES

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Q1. Please check if the affiliation are presented correctly.

Q2. The abstract section must contain the following subheadings: Purpose of Review, Recent Finding, and Summary. Please check if the modification is fine.

Q3. Please supply the missing words/data in this occurrence “classic cytoplasmic estrogen receptors α and β.”