Aldosterone status associates with insulin resistance in patients with heart failure-data from the ALOFT study

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ABSTRACT

Background: Aldosterone plays a key role in the pathophysiology of heart failure. In around 50% of such patients, aldosterone 'escapes' from inhibition by drugs that interrupt the renin-angiotensin axis; such patients have a worse clinical outcome. Insulin resistance is a risk factor in heart failure and cardiovascular disease. The relationship between aldosterone status and insulin sensitivity was investigated in a cohort of heart failure patients.

Methods: 302 patients with New York Heart Association (NYHA) class II-IV heart failure on conventional therapy were randomized in ALiskiren Observation of heart Failure Treatment study (ALOFT), designed to test the safety of a directly acting renin inhibitor. Plasma aldosterone and 24-hour urinary aldosterone excretion as well as fasting insulin and Homeostasis model assessment of insulin resistance (HOMA-IR) were measured. Subjects with aldosterone escape and high urinary aldosterone were identified according to previously accepted definitions.

Results: Twenty per-cent of subjects demonstrated aldosterone escape and 34% had high urinary aldosterone levels. At baseline, there was a positive correlation between fasting insulin and plasma($r=0.22$ $p<0.01$) and urinary aldosterone($r=0.19$ $p<0.03$). Aldosterone escape and high urinary aldosterone subjects both demonstrated higher levels of fasting insulin ($p<0.008$, $p<0.03$), HOMA-IR ($p<0.06$, $p<0.03$) and insulin-glucose ratios ($p<0.006$, $p<0.06$) when compared to low aldosterone counterparts. All associations remained significant when adjusted for potential confounders.

Conclusions: This study demonstrates a novel direct relationship between aldosterone status and insulin resistance in heart failure. This observation merits further study and may identify an additional mechanism that contributes to the adverse clinical outcome associated with aldosterone escape.

INTRODUCTION

The mineralocorticoid hormone, aldosterone, plays an important role in development and outcome of cardiovascular disease. Relative excess of aldosterone, as defined by a raised ratio of aldosterone to renin (ARR), is found in approximately 10% of subjects with hypertension and up to 20% of cases of resistant hypertension(1). Patients with Primary Aldosteronism (PA) also have worse cardiovascular outcomes than those with essential hypertension(2) while aldosterone levels after myocardial infarction are good predictors of a range of adverse outcomes. Finally, whilst it is well recognised that aldosterone plays a key role in the aetiology and progression of heart failure, more recent evidence suggests a role in the development of left ventricular fibrosis (independent of blood pressure effects)(3) as well as its contribution to cardiac remodelling after myocardial infarction(4).

In patients treated for heart failure using conventional therapy, the concept of 'aldosterone escape' (or breakthrough) is well recognised. This describes the failure of suppression of plasma aldosterone levels despite treatment with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), both of which should inhibit aldosterone production(5). The incidence of this phenomenon in heart failure is variable, with estimates ranging from 10-51%, mainly due to a lack of consensus in the definition of aldosterone escape(6). However, it is accepted that aldosterone escape is associated with poor clinical outcome; studies have shown that heart failure patients with aldosterone escape tend to demonstrate higher LV mass, decreased arterial compliance, reduced exercise capacity and a more rapid decline in renal function than patients in whom aldosterone levels remain suppressed with treatment(6). The mechanism of aldosterone escape in heart failure is likely to be multifactorial, and may reflect the importance of trophins other than angiotensin II, including plasma potassium, in the regulation of aldosterone production.

While much of the focus on the adverse cardiovascular consequences of aldosterone has been on vascular structure and function, it is clear that the hormone has important metabolic effects that may also influence cardiovascular risk(7). In particular, there is evidence of an association between aldosterone and insulin resistance and risk of diabetes. For example, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus recently named PA as a potential cause of diabetes *per se*(8). Overall, the majority of clinical studies report that PA patients have higher rates of impaired glucose tolerance than essential hypertensives, but it is unclear whether this is due to insulin resistance or impaired insulin release; nonetheless, insulin resistance is reversed by amelioration of aldosterone excess(9;10).

Insulin resistance occurs in up to 50% of hypertensive subjects and is associated with a 2-5 fold increased risk of CV mortality(11). Insulin resistance is also common in patients with heart failure; the prevalence of type 2 diabetes mellitus in heart failure patients is 6-25% and higher if symptomatic heart failure(12). Diabetes mellitus increases the risk of

hospitalisation in heart failure and is an independent predictor of mortality in population studies (12).
Thus, while aldosterone and insulin resistance both contribute to the pathophysiology and adverse outcome associated with heart failure, the relationship between these biochemical parameters in heart failure remains unclear. This was explored within a stable heart failure population from the ALiskiren Observation of heart Failure Treatment (ALOFT) study, designed to assess the safety and tolerability of the new direct renin inhibitor, Aliskiren. In particular, as heart failure patients with aldosterone escape have a less good prognosis, we wished to determine whether these subjects also have a greater degree of insulin resistance.

METHODS

Recruitment details and procedures have been described elsewhere (13). Briefly, the ALOFT study randomised 302 patients with New York Heart Association (NYHA) class II-IV heart failure treated with either ACE inhibitor or ARB and beta-blocker (in 95%) to either treatment with aliskiren or placebo. For the purposes of this report, subjects taking mineralocorticoid receptor blockers (n=101) were excluded from further analysis.
At the initial baseline visit, 186 subjects underwent 24 hour urine collection for measurement of aldosterone, total protein and sodium excretion. Additionally, early morning fasting plasma samples were taken from subjects (supine) for plasma glucose, glycosylated haemoglobin (HbA1c), HOMA-IR (fasting insulin (mU/ml) x fasting plasma glucose (mmol/l)/22.5 as previously described(14)) as well as aldosterone, plasma renin activity (PRA) and plasma renin concentration (PRC).
As all patients had been on a stable dose of ACE inhibitor or ARB for at least 4 weeks prior to analysis, we used a plasma aldosterone cut-off level of > 144pg/ml to define plasma aldosterone escape in keeping with previous studies(15). Twenty four hour urinary aldosterone level of >12micrograms/24 hours was used to define ‘high’ urinary aldosterone again in agreement with previous studies and with well recognised criteria for the diagnosis of Primary Aldosteronism (PA)(16).
As not all biochemical data were normally distributed, non-parametric methods of analysis were used to directly compare markers of insulin sensitivity according to aldosterone status (Mann-Whitney test using Minitab, state college PA, version 14). Adjustment for potential confounders (age, sex, body mass index, diabetes status and blood pressure) was performed using binary logistic regression. A p-value <0.05 was deemed significant.

RESULTS

General

Summary statistics of the subjects subdivided according to plasma and urinary aldosterone levels are demonstrated in Table I. Of the patients studied, 20% (37) demonstrated aldosterone escape and 34% (63) had high urinary aldosterone excretion. There was some overlap between these two groups with 26 subjects demonstrating aldosterone escape in both urine and plasma.

Aldosterone levels positively correlated with fasting plasma insulin at baseline. This was seen with both plasma aldosterone ($r=0.216$, $p<0.01$; Figure 1) and urinary aldosterone excretion rates ($r=0.188$, $p<0.03$).

(a)

	Aldosterone escape (n=37)	No aldosterone escape (n=150)	p value
Sex	**5 female**	**28 female**	
Age (y)	**67 (61-75)**	**72 (65-77.2)**	**0.155**
SBP (mm/Hg)	**125.3 (119.3-132)**	**130 (121.1-132)**	**0.023**
DBP(mm/Hg)	**77.3 (70-80.3)**	**78.2 (72.8-81.4)**	**0.481**
BMI	**26.6 (24.4-28.5)**	**27 (24.9-29.6)**	**0.51**
Plasma aldosterone (pg/ml)	**202 (163.3-232.2)**	**55.4 (12.4-85)**	**<0.00001**
Urinary aldosterone (mcg/24h)	**17.37 (11.9-23.8)**	**6.82 (3.1-12)**	**<0.0001**
LVEF (%)	**31.9 (26-34.7)**	**30.9 (28.1-34.5)**	**0.5519**
Number (%) with diabetes	**18 (49)**	**51 (34)**	**0.09**

(b)

	High UAldo (n=63)	Low UAldo (n=123)	p value
Sex	**11 female**	**22 female**	
Age (y)	**69 (63-76)**	**72 (64-76)**	**0.561**
SBP(mm/Hg)	**125.33 (120-134.7)**	**130.67 (120-145)**	**0.01**
DBP(mm/Hg)	**77.33 (73-80)**	**78.33 (71.7-82.3)**	**0.7823**
BMI	**27.1 (25.1-29)**	**26.9 (24.5-29.7)**	**0.999**
Plasma aldosterone (pg/ml)	**112.86 (60.1-209.3)**	**56.88 (15.5-89.7)**	**<0.00001**
Urinary aldosterone (mcg/24h)	**19.19 (15.8-39)**	**5.8 (2.63-8.14)**	**<0.0001**
LVEF (%)	**32.2 (28.2-34.9)**	**30.6 (27.2-33.9)**	**0.498**
Number (%) with diabetes	**29 (46)**	**41 (33)**	**0.09**

Table I. Summary characteristics (medians (+inter-quartile range)) of ALOFT subjects subdivided according to (a) plasma and (b) urinary aldosterone levels.
Data were compared by Mann-Whitney testing.
SBP:systolic blood pressure, DBP:diastolic blood pressure, BMI: body mass index, LVEF: left ventricular ejection fraction

Insulin sensitivity and aldosterone status

Subjects on insulin (n=23) were excluded from this analysis. Early morning fasting insulin was significantly higher in aldosterone escape and high urinary aldosterone groups in comparison to subjects without aldosterone escape and lower levels of urinary aldosterone excretion (Figure 2). This relationship was

consistent using other markers of insulin sensitivity; HOMA-IR levels and insulin-glucose ratios (IGR) were higher in aldosterone escape and high urinary aldosterone cohorts (Figure 2). Patients who demonstrated both high plasma and urinary aldosterone levels were most insulin resistant ($p<0.01$, data not shown). All relationships remained significant when adjusted for potential confounders known to influence insulin resistance (age/sex/blood pressure/BMI).
When plasma and urinary aldosterone levels were divided into tertiles, it was found that, as plasma levels of aldosterone increased, fasting insulin also increased (Figure 3) as well as HOMA-IR ($p<0.007$) and IGR ($p<0.0001$).

Diabetes Status
Patients with non-insulin treated diabetes were not excluded from this study. This was because exclusion of diabetics resulted in a substantial reduction in subject numbers particularly in the aldosterone excess groups and a loss of study power meaning that although there was still a tendency to increased insulin resistance in the aldosterone excess groups, this did not always reach statistical significance. Additionally, there was a trend to higher prevalence of both diabetes and insulin use in subjects with biochemical evidence of aldosterone excess although again this did not reach statistical significance (Table II). However, the presence of diabetes were incorporated into binary logistic regression analysis and the relationships between insulin resistance and biochemical aldosterone excess remained significant ($p<0.008$ aldosterone escape and insulin, $p<0.03$ high urinary aldosterone and insulin).

Cohort	**Diabetes**	**p value**	**Insulin**
Aldosterone escape	**18 (49%)**	**<0.09**	**4 (11%)**
No aldosterone escape	51 (34%)		9 (6%)
High urinary aldosterone	**29 (46%)**	**<0.09**	**6 (9.5%)**
Low urinary aldosterone	41 (33%)		5 (4%)

Table II. Prevalence of diabetes status and insulin use in cohort stratified according to plasma and urinary aldosterone status.

DISCUSSION

These data demonstrate in a stable heart failure population that subjects with relative aldosterone excess have evidence of increased insulin resistance, a

relationship which persists after correction for diabetes status. In addition, there is a trend to an increased prevalence of diabetes in the high aldosterone subjects although this does not reach statistical significance.

High aldosterone levels and insulin resistance are both associated, independently, with greater risk of cardiovascular disease and heart failure. Subjects with hypertension and aldosterone excess have an excess of adverse vascular events (particularly stroke) when compared to subjects with equivalent essential hypertension(2). It is noteworthy that that serum levels of aldosterone (and the glucocorticoid hormone, cortisol) have recently been shown to be independent predictors of increased mortality risk in patients with chronic heart failure (17) while the role of aldosterone in heart failure has been highlighted by large scale clinical trials demonstrating additional benefit of mineralocorticoid blockade in conjunction with conventional therapy(5).

Aldosterone levels are positively correlated with poor outcome after myocardial infarction, including increased risk of death, cardiac arrest, dysryhthmia. An association between essential hypertension and insulin resistance is also supported by a large body of evidence and is consistent with the notion that insulin resistant subjects have greater long term cardiovascular risk(18-20).

Insulin resistance is associated with vascular endothelial dysfunction and, in particular, with reduced availability of endothelial nitric oxide(21); it is possible that this contributes to the associated increased risk of cardiovascular events in patients with hypertension and insulin resistance. Insulin resistance is independently associated with risk of heart failure and adverse outcome in that circumstance(12). However, despite the associations between aldosterone and insulin resistance in cardiovascular disease, the nature and potential mechanism of the relationship between the two remains unclear. In a large prospective study, Catena et al. demonstrated that patients with PA were more insulin resistant that normotensive controls and that medical or surgical treatment of the aldosterone excess improved insulin sensitivity(9). Nevertheless, PA subjects were less insulin resistant than those with essential hypertension. The same group subsequently demonstrated that plasma aldosterone levels correlated with markers of insulin resistance and hyperinsulinaemia in hypertensive patients(22). Indeed, the majority of clinical evidence supports an association between aldosterone excess and increased insulin resistance in hypertension although there are conflicting reports as to whether this is a stronger(23) or weaker (9) association than in essential hypertension.

Our data suggest a positive correlation between aldosterone and insulin resistance in heart failure. This finding is consistent with other observational findings. Thus, chronic heart failure and diabetes often co-exist, an association noted in the Framingham Study where 19% of patients with chronic heart failure had diabetes; the risk of heart failure increased 2-8 fold in the presence of diabetes(24). This relationship between chronic heart failure and diabetes may also extend to insulin resistance. In one large prospective study of 1187 elderly men there was a clear inverse relationship between the risk of heart failure and insulin sensitivity and there are other groups who have confirmed such an observation(25). This notion is further supported by recent evidence from the CHARM study illustrating that, in heart failure patients,

glycosylated haemoglobin A1c (HbA1c) is an independent predictor of morbidity and mortality(26).

The mechanism of the link between aldosterone and insulin resistance remains unclear. It is, of course, possible that the association is not causal; subjects with more severe heart failure (who may be more likely to be insulin resistant) may have greater activation of the neuroendocrine system and, consequently, higher aldosterone levels. Alternatively, it is possible that insulin resistance, which in its early stages is associated with hyperinsulinaemia, might directly lead to increased aldosterone production. This seems plausible as we observed a positive correlation between plasma insulin and aldosterone and so a possible explanation is that activation of the RAAS contributes directly to insulin resistance. An association between insulin resistance and the renin-angiotensin-aldosterone system has recently been strengthened by several large scale clinical trials which demonstrate that blockade of the RAAS with ACE inhibitors or angiotensin receptor blockers results in a reduction in new cases of diabetes mellitus(27). However, this link remains controversial with a recent robust clinical trial failing to show a significant effect of ramipril on the subsequent development of diabetes in subjects with impaired glucose tolerance or impaired fasting glucose(28).

A simple haemodynamic explanation linking the RAAS to the development of insulin resistance is possible, where increased angiotensin II and aldosterone levels may be associated with reduced blood flow to skeletal muscle and, as a result, diminished tissue glucose uptake(29). However, there is controversy about the contribution of flow to the efficiency of glucose extraction and more direct effects on insulin release and action seem more likely. This is supported by work by Mosso *et al* who demonstrated that impaired glucose metabolism in PA patients was associated with decreased markers of pancreatic beta cell function (C-peptide and HOMA-βF) which improved in response to spironolactone treatment(30). Another potential mechanism is aldosterone-induced electrolyte abnormalities-hypokalaemia is known to alter insulin secretion and modulate insulin receptor function(31) and recent in vitro experiments on isolated pancreatic islets suggest that extracellular potassium stimulates insulin secretion(32).In addition, magnesium deficiency can also reduce insulin production and magnesium supplementation prevents diabetes in rat models(33). Finally, mineralocorticoid receptors are present on adipoctyes and their activation affects insulin signalling and adipocytokine release(34). Subsequent experiments have demonstrated that adipocytokines can stimulate production of adrenal corticosteroids *in vitro*(35). These effects may directly alter tissue insulin sensitivity, and offer a plausible direct association between aldosterone, insulin resistance and obesity(36).

Limitations of this study are mainly those imposed as a result of *post-hoc* analysis of data where the primary outcome was not to examine the relationship between aldosterone and insulin status. In addition, diabetic subjects would, ideally, not have been included in this study but were included to provide sufficient study power. However diabetes status and insulin use were incorporated into a binary logistic regression model of aldosterone and insulin resistance and did not alter these relationships. The final limitation is our use of simple indirect measurements of insulin sensitivity which, although robust and in common clinical use, are less sensitive than the gold standard measure of insulin sensitivity, the euglycaemic-hyperinsulinaemic glucose

clamp. Strengths of the study include the fact that this was a large, well phenotyped heart failure cohort with reliable biochemical measurements of both insulin and aldosterone in both plasma and urine, allowing accurate determination of mineralocorticoid production.

CONCLUSIONS

We have shown that increased aldosterone levels associate with biochemical features of insulin resistance in a heart failure population. This raises the possibility that increased insulin resistance could contribute to the adverse clinical outcome associated with aldosterone escape in heart failure. This hypothesis justifies further investigation in a focussed prospective clinical study using gold standard measurements of insulin sensitivity.

FIGURE LEGENDS

Figure 1. Correlation between early morning fasting insulin and plasma aldosterone levels

Figure 2. Relationship between (a) fasting insulin (b) HOMA-IR and (c) insulin/glucose ratio and plasma and urinary aldosterone
(Data compared by Mann-Whitney non-parametric testing)

Figure 3. Relationship between plasma and urinary aldosterone tertiles and fasting plasma insulin.
Data analysed by one-way ANOVA.
Plasma aldosterone (pg/ml): tertile 1 34.5-116, tertile 2 119-266. tertile 3 269-1795
Urinary aldosterone (mcg/24h); tertile 1 2.65-16.2, tertile 2 16.2-38.2, tertile 3 38.2-255.2

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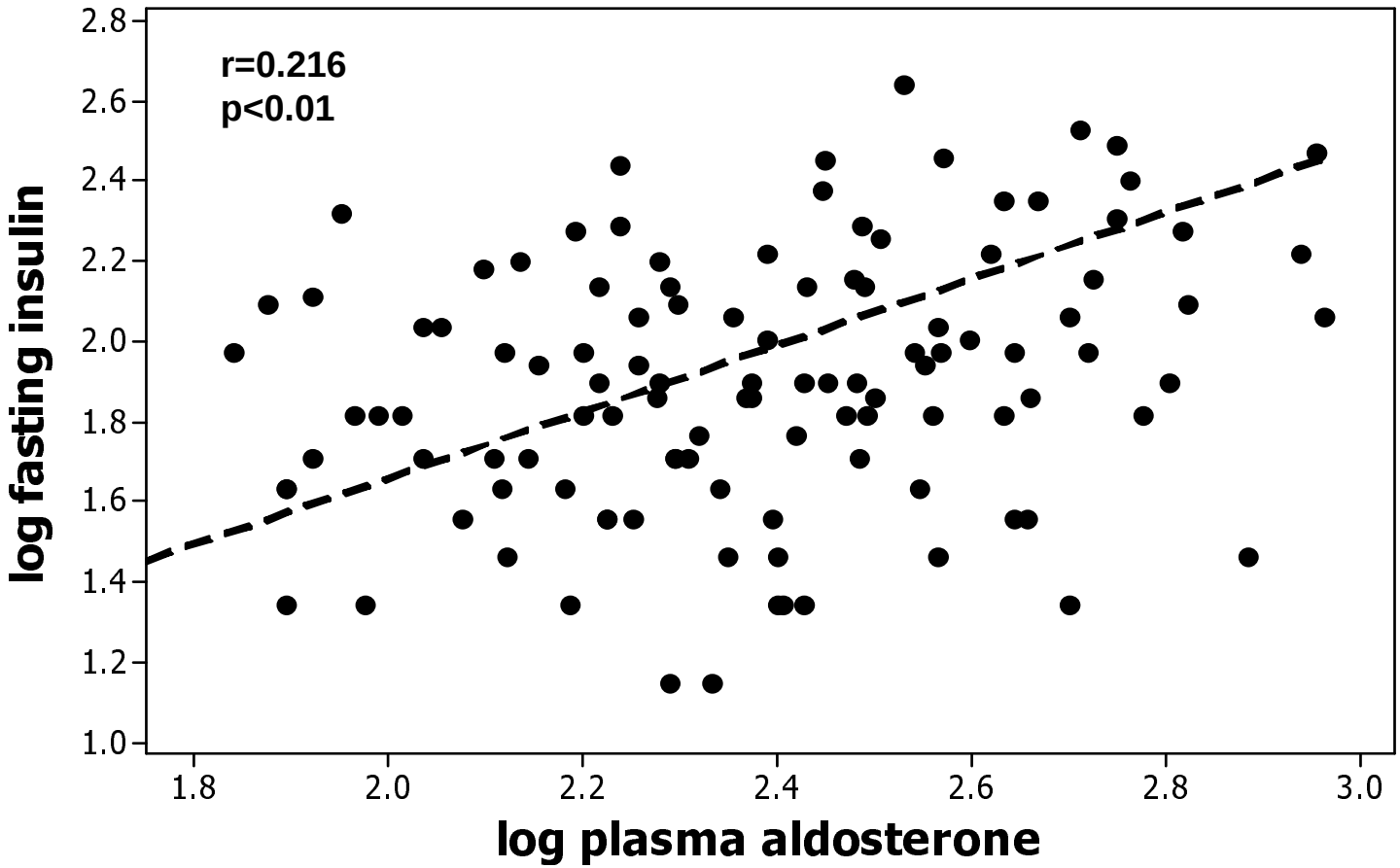
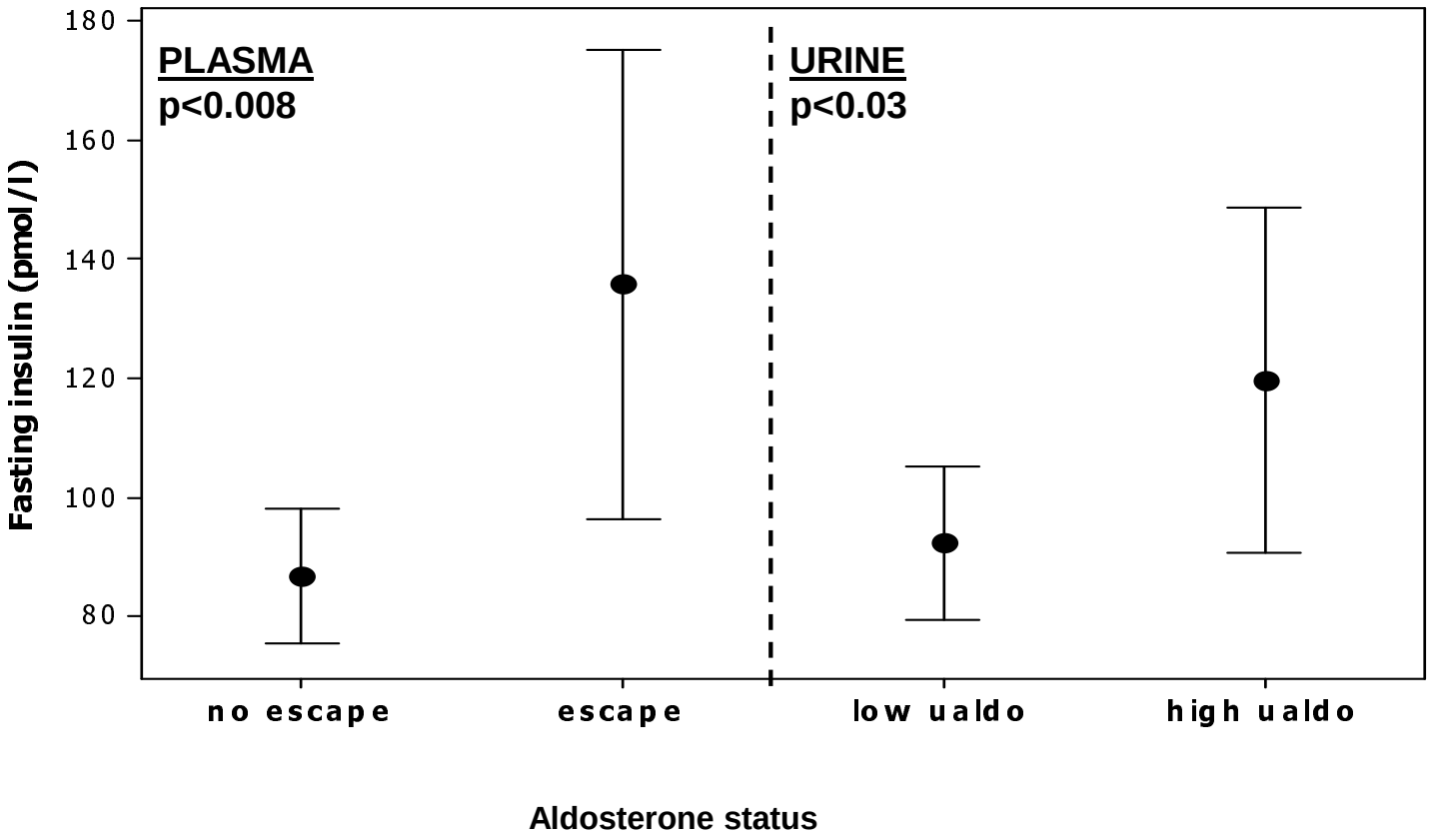


Figure 1



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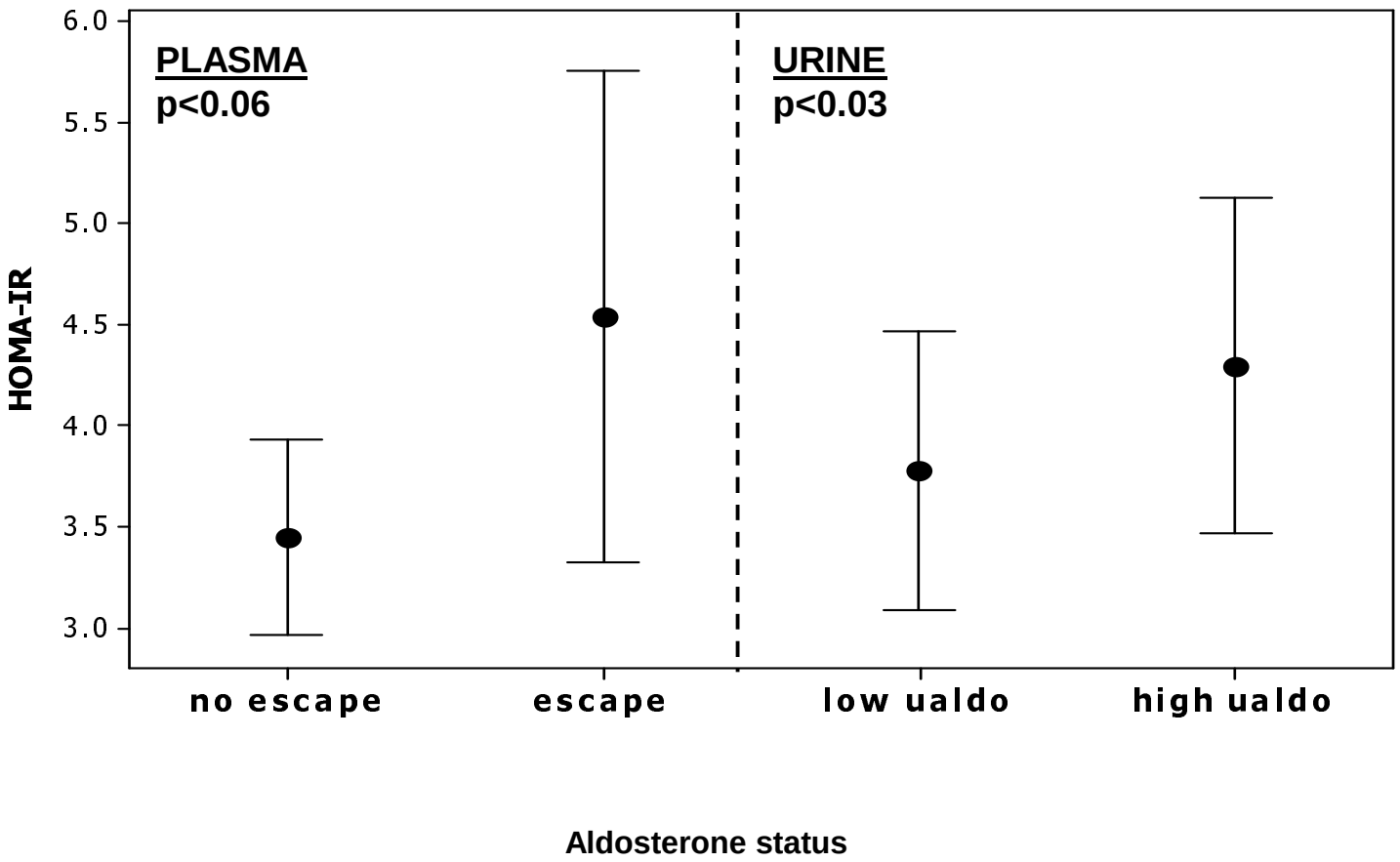

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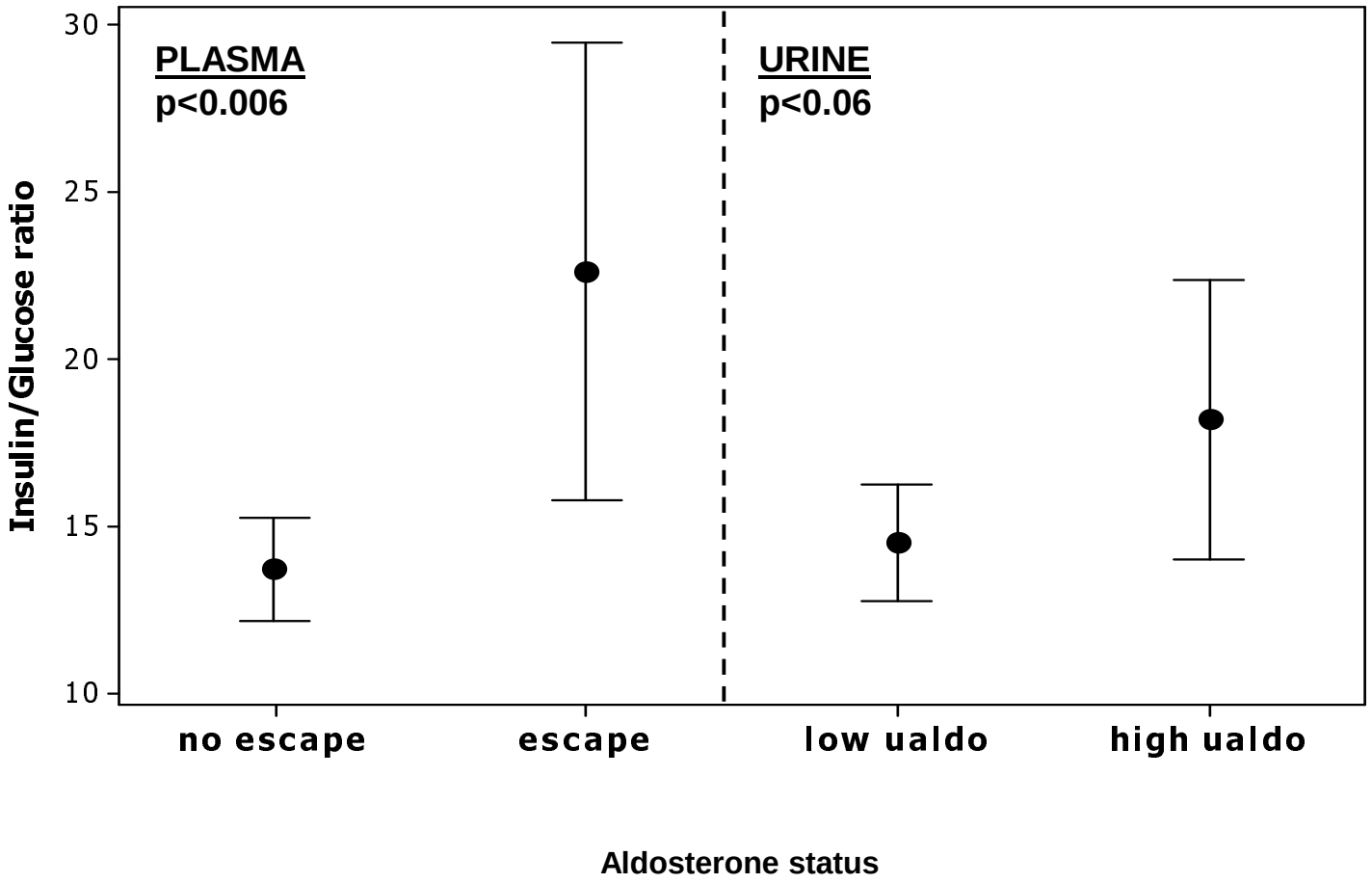

Figure 2c

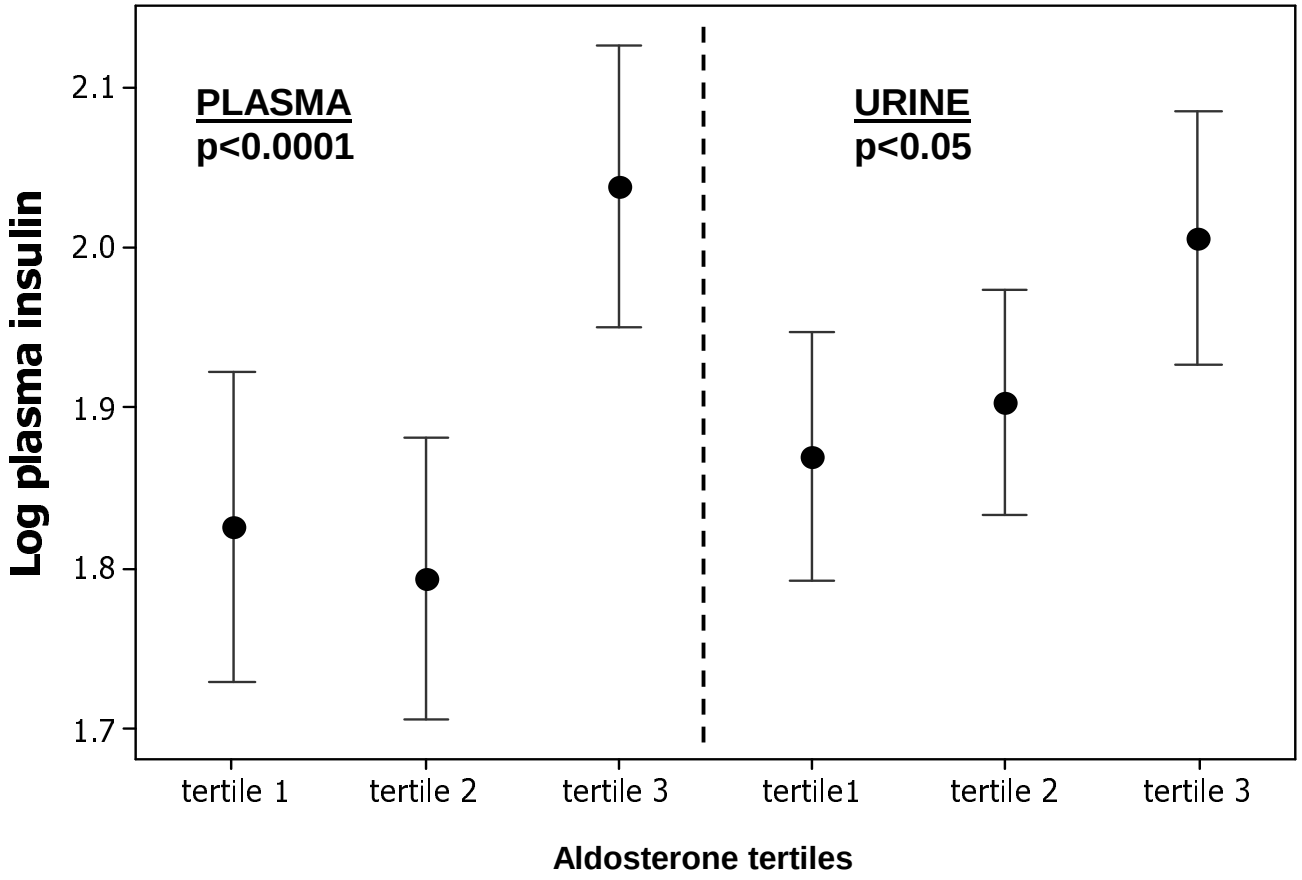

Figure 3