Microvascular effects of aldosterone and salt in health, obesity and hypertension

9.

VALORISATION ADDENDUM

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In this chapter, we outline the relevance of our findings and their implications for daily practice.

The obesity epidemic

Obesity has become a major threat to public health. In 2015, obesity affected around 600 million adults worldwide. High BMI accounted for 4 million deaths globally, nearly 40% of which occurred among individuals with a BMI between 25 and 30. Cardiovascular disease was the leading cause of death, responsible for more than two-thirds of mortality attributed to high BMI[1]. In the Netherlands, overweight has been estimated to be responsible for 20% of total annual health care costs, and obesity for 9% of these costs. Of the costs attributable to overweight, i.e. € 1,185,688,644, 48% is accounted for by diabetes, 10% by hypertension, another 10% by stroke, and 16% by coronary heart disease[2]. Thus, it is superfluous to say that prevention of obesity-related complications saves lives and money.

Weight loss strategies

The first step in the management of obesity-related complications should be focused on inducing weight loss. Indeed, weight loss interventions have been proven to be beneficial in terms of lowering blood pressure, reducing incidence of type 2 diabetes and cardiovascular disease, and decreasing cardiovascular and all-cause mortality[3-5]. This may be partially accounted for by improvement of microvascular and metabolic insulin sensitivity[6, 7], which is confirmed by our findings in **Chapter 4**. Identifying the molecular mechanisms underlying the amelioration of insulin-mediated muscle microvascular recruitment and insulin-induced whole-body glucose disposal following weight loss provides more insight in the pathophysiology of obesity-related complications. This can be helpful in the development of new pharmacological therapies, as weight loss is often difficult to achieve and sustain. In our study population, serum aldosterone concentration was comparable in lean and moderately abdominally obese individuals, but the regulation of aldosterone levels by salt intake was not entirely normal. Thus, although aldosterone does not seem to have a share in the improvement of microvascular and metabolic insulin resistance after weight loss observed in the abdominally obese male subpopulation, its role may become more

prominent if these individuals gain weight, and in individuals with advanced stages of obesity in general.

Pharmacological therapies

Currently, two mineralocorticoid receptor antagonists (MRAs) are available: Spironolactone and Eplerenone. They are widely used in the treatment of heart failure and primary aldosteronism, and as add-on therapy for (resistant) essential hypertension, but are not registered as first-choice antihypertensive regimen in the Netherlands[8]. Although Spironolactone has been demonstrated in the PATHWAY-2 study to be the most effective fourth agent for treatment of uncontrolled resistant hypertension[9], both Spironolactone and Eplerenone have been proven to effectively lower blood pressure as single antihypertensive drug as well. However, effects on long-term morbidity and mortality are not known[10,11]. During recent years it has become clear that the blood pressure lowering effects of MRAs may not only be attributable to increased sodium excretion, but potentially also to reduced vascular resistance[12]. In the light of our observations in **Chapter 3** of an inverse association between ARR and left kidney perfusion, and a direct association with blood pressure in individuals with therapy-resistant essential hypertension, addition of an MRA to the antihypertensive regimen of these patients may partially lower blood pressure by improving renal perfusion, which could also contribute to the preservation of renal function. Indeed, although evidence on the effect of MRAs on hard renal endpoints is limited, they have been shown to reduce urinary protein/albumin excretion[13]. In practice, it will be difficult to prove an effect of MRAs on individual kidney perfusion, unless measurements of differential renal blood flow can be performed in an experimental setting. Nevertheless, our results are an additional argument for clinicians to add an MRA to the existing antihypertensive regimen of individuals with resistant hypertension, naturally with regular monitoring of serum potassium levels.

Obesity is one of the strongest risk factors for uncontrolled hypertension[14]. Although we have demonstrated that aldosterone levels were similar in lean and moderately abdominally obese, predominantly normotensive, men, and not associated with blood pressure in these men (**Chapter 4**), aldosterone was directly associated with blood pressure under circumstances of higher salt intake in a larger population of both lean and abdominally obese individuals, although statistically non-significant **(Chapter 6)**. Interestingly, body mass index has been recently demonstrated to predict 24h urinary aldosterone levels in patients with resistant hypertension[15]. In this study, BMI varied from 15.5 to 73.8 kg/m^2. This once again confirms that increased aldosterone levels

may become overt and clinically relevant as body weight increases. Thus, clinicians should consider starting an MRA early in the treatment of obesity-related hypertension. In moderately abdominally obese men, aldosterone was also not associated with microvascular and metabolic insulin sensitivity, but in a larger abdominally obese study population, aldosterone displayed an inverse, but statistically non-significant relationship with metabolic insulin sensitivity (**Chapter 6**). As seems the case with blood pressure, effects of aldosterone on microvascular and metabolic insulin sensitivity may be only demonstrable in individuals with severe (abdominal) obesity. While awaiting these data, potential beneficial effects of MRAs on insulin sensitivity, as demonstrated in patients with primary hyperaldosteronism[16], can be detected easily by measuring blood glucose levels or HbA1c. Of course, more subtle effects on metabolic insulin signalling, not directly translating in changes in glucose concentration, and on insulin's microvascular actions, cannot be demonstrated in this manner, and should be investigated in controlled experiments.

In terms of cost-effectiveness, the daily costs of Spironolactone are corresponding to those of ACE-inhibitors or AT2-receptor antagonists, but Eplerenone is more expensive[8]. Although Eplerenone has a higher affinity for the mineralocorticoid receptor compared to Spironolactone, resulting in less side effects, it is advisable to prescribe Spironolactone first, and only switch to Eplerenone if these side effects become manifest.

Salt: less or more?

In **Chapter 5**, we have demonstrated that on a low, compared to a high salt diet, blood pressure decreases and insulin-mediated muscle microvascular recruitment improves, but insulin-induced whole-body glucose disposal decreases as well. Moreover, aldosterone was directly associated with blood pressure when salt intake was higher than 8.6 g per day (**Chapter 6**). This immediately raises the question whether we should decrease or increase our salt intake. Over the years, this answer has become less straightforward. It has been demonstrated recently that high intake of sodium is a major dietary risk factor for morbidity and mortality worldwide[17]. Conversely, a salt reduction from 11.7 to 3.9 g per day has been shown to reduce blood pressure, more in hypertensive than normotensive individuals[18], with maximum efficacy after one week already[19]. In terms of cardiovascular disease and (all-cause) mortality, however, there does not seem to be a beneficial effect of low, compared to usual salt intake, and mortality even appears to be increased with low salt intake. High, compared to usual salt intake, on the other hand, has been shown to raise both the risk for cardiovascular

disease and all-cause mortality[20]. Thus, our findings of impaired insulin-mediated glucose uptake on a low salt diet may provide an underlying explanation for the lack of effect of salt restriction on the occurrence of cardiovascular events, and increased mortality, although the consequences of long-term salt restriction for whole-body glucose disposal are not known. Until then, the question remains how to adjust salt intake. Because there is no evidence for beneficial health effects of a salt reduction below 5.8 g per day[21], it is advisable to maintain this as target value. In the Netherlands, median salt intake is still higher than recommended, i.e. 9.7 g per day for men and 7.4 g per day for women[22]. Thus, in practice, it is an ongoing challenge to decrease salt intake to ~6 g per day, not to speak of larger reductions. This starts with motivating every individual patient, especially those with risk factors for cardiovascular disease, and referral to a dietician may be of great benefit. Compliance to the adjusted diet can be verified by measuring 24h urinary sodium excretion, and potential adverse effects on glucose metabolism through determination of blood glucose levels or HbA1c. However, changes in insulin sensitivity in such a way that glucose levels increase are not to be expected, as the absolute decrease in insulin-mediated whole-body glucose disposal induced by 11.7 g reduction in salt intake was relatively subtle.

The responsibility to reduce salt intake lies not only with the individual, but also with governments. Even if a person is extremely motivated to change his or her diet, it is difficult to reach a salt intake as low as 6 g per day, due to the high salt content of bread, meat and processed foods. In the Netherlands, several initiatives focus on the reduction of salt levels in these food products. Although reductions as large as 21% (bread) have been achieved already, a 30-40% salt reduction in major salt contributing foods is necessary to approach the recommended 6 g per day[22]. This naturally requires the formulation of sharper regulations concerning the composition of food products by authorities, and cooperation of the food industry, but increasing public awareness of the adverse health effects of high salt ingestion, and which food products to avoid, is still a fundamental part of the challenge to reduce dietary salt intake.

Conclusion

In this thesis, we investigated microvascular effects of aldosterone and salt in several study populations, i.e. normotensive lean, therapy-resistant essential hypertensive, and abdominally obese individuals. Our data are in support of weight loss as important remedy to ameliorate obesity-related microvascular and metabolic insulin resistance, and hypertension, and of MRAs as (add-on) therapy in therapy-resistant hypertension, preferentially in obese individuals. However, studies demonstrating a role of

aldosterone in the pathophysiology of microvascular, and thereby metabolic, insulin resistance in severe abdominal obesity are still awaited. It is equally important to gain knowledge on the effects of MRAs on morbidity and mortality, and on insulin's microvascular and metabolic actions. Our findings may also provide an explanation for the increased mortality observed with salt restriction below 6 g per day, and an additional mechanism for the blood pressure lowering effects of reducing salt intake, at least in healthy individuals. How a decrease in salt ingestion affects the incidence of cardiovascular disease and mortality in this population remains to be established.

Nevertheless, our results contribute to the understanding of pathophysiological mechanisms of obesity-related complications, which may guide clinicians in decisions regarding their treatment.

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