

# The Association of Aldosterone With Obesity-Related Hypertension and the Metabolic Syndrome

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**Summary:** Overweight and obesity are associated with arterial hypertension. Given the large increase in the obesity prevalence worldwide, the number of obese patients with hypertension is likely to increase substantially in the near future. Overweight and obese patients are exposed to an important metabolic and cardiovascular risk. The understanding of the mechanisms linking obesity to hypertension is important for specific prevention and therapy in this population. There is some evidence that obesity is associated with an increased aldosterone level. To date, 2 mechanisms may explain the interaction of fat tissue with the renin-angiotensin-aldosterone system, and therefore explain, in part, obesity-related hypertension. First, human adipose tissue produces several components of the renin-angiotensin-aldosterone system, mainly adipose tissue-derived angiotensinogen. Second, increased fatty acid production in the obese patient, especially nonesterified fatty acids, might stimulate aldosterone production, independent of renin. A better understanding of these mechanisms might have implications for the management of hypertension in overweight and obese patients. Because aldosterone also is associated with blood glucose and blood lipids, selective aldosterone blockade may represent a particularly attractive therapeutic strategy in obese patients with a clustering of cardiovascular risk factors.

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The view of the adipose tissue is changing from that of an energy-storing organ and esthetic problem to that of a highly specialized endocrine organ. This endocrine view of the adipose tissue is growing in importance with the increasing prevalence of overweight, obesity, and metabolic syndrome (MS) around the world, all associated with arterial hypertension. The MS, which is a cluster of cardiovascular risk factors (high blood pressure, dyslipidemia, overweight, and glu-

cose intolerance), is associated with a greater risk of cardiovascular morbidity and mortality than the sum of the risks attributable to each component. The underlying mechanisms responsible for this further risk increment only partially are understood (Fig. 1).<sup>1</sup> It may be because in addition to its association with hypertension and hyperinsulinemia and insulin resistance, the MS also is linked to sleep apnea and stimulations of the renin-angiotensin-aldosterone system (RAAS) and of the sympathetic nervous systems (Table 1).

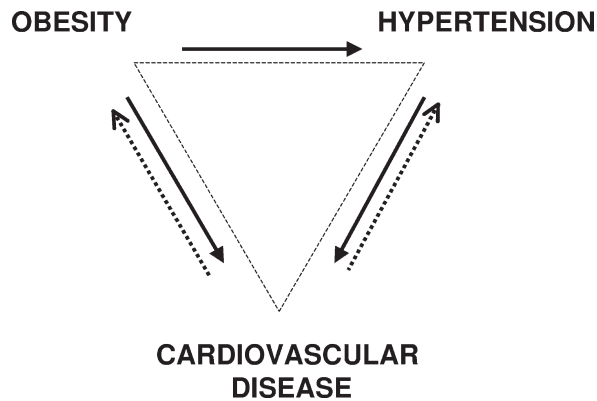
Different definitions of the MS have been proposed recently, such as the definitions proposed by the National Cholesterol Education Program Adult Treatment Panel III, the International Diabetes Federation, and the National Heart, Lung and Blood Institute/American Heart Association.<sup>2-4</sup> The different definitions have raised concerns regarding whether they can identify high-risk populations for cardiovascular

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**Figure 1.** Obesity and the vicious triangle with hypertension and cardiovascular diseases. Modified with permission from Montani et al.<sup>1</sup>

disease who should benefit from intensive behavioral and/or pharmacologic treatment. Besides these concerns reflected in the different definitions, central obesity is part of all definitions for MS, and hypertension or treated hypertension are part of the diagnostic criteria.<sup>2-4</sup>

Obesity causes hypertension—there is no doubt.<sup>5,6</sup> Several pieces of evidence support this causal relationship. First, weight gain in experimental animal studies increases blood pressure.<sup>7</sup> Second, weight loss in obese patients reduces high blood pressure.<sup>8-11</sup> Third, in prospective population-based studies, obesity is a very strong predictor of hypertension incidence in both men and women.<sup>12,13</sup> Different possible mechanisms might link excess weight to increased blood pressure and might offer therapeutic possibilities in these patients (Table 1, Fig. 1). In obese patients, the sympathetic nervous system activity is increased when compared with the nonobese control patients.<sup>14</sup> The mechanism of this activation is not clear and might involve the leptin pathway and/or might be a consequence of obstructive sleep apnea frequently observed in these patients.<sup>15</sup> Sleep apnea is associated with obesity as shown in the Wisconsin Sleep Cohort study, and obesity is associated with sleep apnea.<sup>16-18</sup> Furthermore, patients suffering from obesity may have a reduced ability to excrete a given sodium load, which can contribute to increased blood pressure.<sup>19</sup> Besides renal function impairment in obese patients there is now good evidence that the RAAS and their regulators are involved

in abnormal renal salt balance in the obese patient.<sup>20</sup>

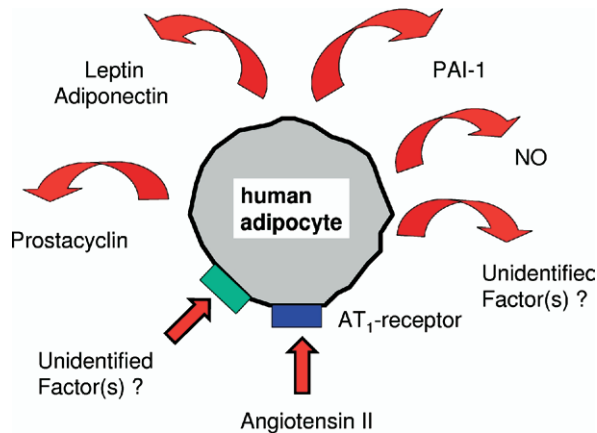
In this review, we focus on the findings and potential mechanisms that link aldosterone to obesity-induced hypertension and to other components of the MS. Other pathophysiologic mechanisms involved in obesity-induced hypertension have been reviewed elsewhere.<sup>21-24</sup>

### ALDOSTERONE, ANGIOTENSIN, AND THEIR PLASMA REGULATORS IN FAT TISSUE

An interaction between fat tissue and the aldosterone-sensitive organs might account for the numerous effects observed in obese patients such as hypertension and renal impairment.<sup>25</sup> In 1994, Egan et al<sup>26</sup> observed higher renin and aldosterone levels and a hyperinsulinemic effect of salt restriction in subjects with cardiovascular risk factor clustering. Patients with cardiovascular risk factor clustering including abdominal obesity had significantly greater values for renin and aldosterone independently of dietary salt intake. Recently, Bochud et al<sup>27</sup> showed that plasma aldosterone is associated independently with the MS in subjects of African descent. These 2 observations in human beings provide the rationale for studies on the interaction between fat tissue and the adrenal gland with respect to hypertension and the MS. The cross-talk between adipose tissue and aldosterone-sensitive organs seems to follow 2 main pathways: first, human adipose tissue produces several components of the RAAS, mainly adipose tissue-derived angiotensinogen, and second, increased fatty acid production in the obese patient, especially nonesterified fatty acids, stimulates aldosterone production in adre-

**TABLE 1. Obesity-Associated Observations**

Hyperactivity of the sympathetic nervous system
Stimulation of the RAAS
Impairment of renal function, renal histology changes
Obesity-associated sleep apnea
Hyperinsulinemia and insulin resistance



**Figure 2.** Effect of angiotensin II on human adipocytes or pre-adipocytes in culture. PAI-1, plasminogen activator inhibitor-1; NO, nitric oxide; AT<sub>1</sub>, angiotensin type 1-receptor. Modified with permission from Engeli et al.<sup>86</sup>

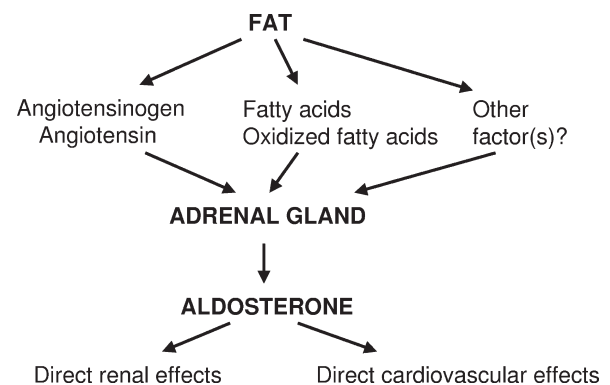
nal cells under specific conditions (Figs. 2 and 3).

Aldosterone production *in vivo* and *in vitro* can be affected by more than 20 hormones and substances. However, for the majority of these mechanisms the clinical relevance is more speculative than has been shown yet. For both pathways, adipose tissue-dependent components of the RAAS and of fatty acids, there is now some evidence that these mechanisms affecting aldosterone production play a role in the interaction between adipocytes and the adrenal gland.

Several components of the RAAS are present in human adipose tissue. Angiotensinogen has been detected in rat adipocytes and also in specific mice adipocytes.<sup>28,29</sup> Gorzelniak et al<sup>30</sup> studied the expression of RAAS genes in subcutaneous abdominal adipocytes in 10 hypertensive obese women. Renin, angiotensin converting enzyme, and angiotensin II type 1-receptor genes were up-regulated significantly in the subcutaneous adipocytes of the obese patients. The importance of this observation is underlined by further studies of the same investigators who have shown that angiotensin II type 1-receptor antagonists induce human *in vitro* adipogenesis through peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) activation.<sup>31</sup> In a very carefully conducted study in adipocytes obtained from aspiration of human subcutaneous fat, Harte et al<sup>32</sup> concluded that the human

subcutaneous adipose tissue is also an important source of angiotensin II. Indeed, insulin may stimulate the RAAS system by a potential tumor necrosis factor- $\alpha$ -mediated mechanism and thereby may contribute to explain obesity-associated hypertension. Rosiglitazone, an inhibitor of PPAR- $\gamma$  activation, down-regulates the RAAS in subcutaneous tissue, which may contribute to the long-term effect of rosiglitazone on blood pressure.<sup>32,33</sup> Janke et al<sup>34</sup> showed that certain angiotensin-receptor blockers activate the PPAR- $\gamma$  target gene expression and adipogenesis. One might speculate that this mechanism in the subcutaneous tissue is more pronounced in obese than in nonobese subjects so that a PPAR- $\gamma$  inhibitor may have a more pronounced effect in obese patients. However, this concept has not been shown yet.

Hypertension is a heterogeneous condition that is associated with obesity. One therefore expects the mechanisms linking hypertension to obesity to be heterogeneous as well. The identification of part of the RAAS system in human adipocytes offers a potential link between obesity and hypertension. Another potential link is the production of an adipocyte-derived factor that under specific conditions influences the adrenal gland and hence stimulates the production of aldosterone (Fig. 2).<sup>25</sup> Adipose tissue is turning out to be a highly sophisticated and very precisely regulated en-



**Figure 3.** Obesity and the adrenal gland. The relative importance of the angiotensinogen and the fatty acid pathways is not yet defined. Other factor(s) may be involved in this regulatory pathway, for example, glucocorticoids and their regulatory mechanisms such as 11 $\beta$ -hydroxysteroid dehydrogenase-controlled mechanisms.

doctrine tissue. This gives room for speculation that other factors might well be implicated in the complex interplay of fat, hypertension, and cardiovascular disease. For example,  $11\beta$ -hydroxysteroid dehydrogenase interconverting cortisol and cortisone are involved in the hormonal regulation of fat tissue.<sup>35,36</sup>

### **FAT TISSUE-DERIVED SUBSTANCES STIMULATE ALDOSTERONE INDEPENDENT OF RENIN**

Obesity is associated with increased plasma levels of free fatty acids (FFAs).<sup>37,38</sup> The infusion of FFA increases blood pressure in animals<sup>39</sup> as well as in nonobese<sup>40</sup> and obese<sup>41</sup> subjects. Goodfriend et al<sup>8</sup> conducted a series of elegant studies leading to the identification of a new mechanistic link between visceral obesity and hypertension that involves aldosterone stimulation independent of renin. Goodfriend et al<sup>8</sup> observed that nonesterified fatty acids (eg, linoleic acid) from visceral human adipocytes were able, in the presence of rat hepatocytes and oxygen, to stimulate aldosterone production by rat adrenal cells. They concluded that FFA liberated by fat tissue in the circulation can induce the liver to produce a substance that stimulates aldosterone secretion by the adrenal gland. Later, Goodfriend et al<sup>42</sup> isolated a compound resulting from the oxidation of linoleic acid, 12,13 epoxy-9-keo-10-trans-octadecenoic acid (EKODE), that was able to stimulate aldosterone secretion by the adrenal gland, when present in low concentrations, and was inhibitory when present in high concentration. In plasma, EKODE can be measured by liquid chromatography/mass spectrometry. In a sample of 12 Caucasian and 12 African American subjects, including both lean and obese subjects, EKODE was associated positively with plasma aldosterone levels and its effect was inhibited by atrial natriuretic peptide but not by angiotensin-receptor antagonists.<sup>43</sup> These results suggest that oxidized FFA may influence adrenal steroid production in human beings and thereby provide a possible mechanism explaining obesity-induced hypertension. These results are consistent with the observation that adipocytes secrete a substance that stimulates aldosterone production by the adrenal gland in human beings<sup>44</sup> and in rats.<sup>45</sup>

### **THE EXPERIENCE WITH PRIMARY ALDOSTERONISM, RESISTANT HYPERTENSION, AND OBSTRUCTIVE SLEEP APNEA**

Multiple observations have described tight interconnections between increased plasma aldosterone levels, resistant hypertension, and obstructive sleep apnea,<sup>20</sup> which is not surprising considering that these conditions all are associated with obesity.<sup>46-48</sup>

The prevalence of primary aldosteronism is higher than previously suspected and may affect about 8% to 15% of hypertensive patients.<sup>49-52</sup> The prevalence of primary aldosteronism increases with the severity of hypertension<sup>53</sup> and, analogously, patients with resistant hypertension have a high prevalence (10%-20%) of primary aldosteronism.<sup>54,55</sup> Primary aldosteronism has been associated with MS<sup>56</sup> and with obstructive sleep apnea.<sup>57</sup> These findings are consistent with the observation that patients with resistant hypertension have a high risk of obstructive sleep apnea<sup>57,58</sup> and increased plasma aldosterone levels.<sup>54,59,60</sup>

Several observations suggest that mineralocorticoid-receptor blockade significantly decreases blood pressure in various conditions associated with increased aldosterone production, other than classic primary aldosteronism. An increased aldosterone to renin ratio predicts a good blood pressure response to spironolactone, an aldosterone antagonist.<sup>50,51</sup> Furthermore, spironolactone is particularly effective in the management of patients with resistant hypertension.<sup>61,62</sup>

Altogether, these observations add further evidence to the association between aldosterone and obesity-related disorders.

### **THE ASSOCIATION OF ALDOSTERONE WITH ALTERATIONS IN LIPID AND GLUCOSE METABOLISM**

In mice, aldosterone induces blood glucose level increases by increasing the expression of genes involved in gluconeogenesis.<sup>63</sup> Physiologic doses of aldosterone decrease insulin receptor messenger RNA and insulin binding in human promonocytes,<sup>64</sup> which suggests that aldosterone may induce insulin resistance. The association between primary aldosteronism and

glucose intolerance and insulin resistance has been reported in some studies,<sup>65,66</sup> but not in others.<sup>67,68</sup> In human beings, plasma aldosterone is correlated positively with insulin, both in normotensive and in hypertensive subjects,<sup>69,70</sup> and also with insulin resistance measured with the homeostasis model assessment in subjects with primary aldosteronism.<sup>65,71</sup> Fallo et al<sup>56</sup> found a higher prevalence of hyperglycemia in patients with primary aldosteronism (27%) than in patients with essential hypertension (15%,  $P < .05$ ), even when restricting the analysis to MS patients (54.2% versus 34.5%, respectively,  $P < .05$ ). Giacchetti et al<sup>65</sup> examined 25 patients with aldosterone-producing adenoma after surgery and 36 patients with idiopathic hyperaldosteronism on pharmacologic treatment. The removal of aldosterone excess in these patients, either surgically or by drug therapy, induced regression not only of cardiac but also of metabolic complications such as glucose intolerance. A smaller-sized study also observed a decrease in insulin resistance after surgical removal of aldosterone-producing adenomas.<sup>72</sup> Recently, Liu et al<sup>73</sup> observed that the mineralocorticoid receptor in the human liver is associated with hepatic glucose production. This important result suggests that aldosterone may be involved in hepatic glucose metabolism.

Bochud et al<sup>27</sup> found that plasma aldosterone was associated negatively with high-density lipoprotein (HDL) cholesterol, independently of all other MS components, which confirmed previous reports.<sup>70,74,75</sup> This also is consistent with the observation that drospirenone, an oral contraceptive with antimineralocorticoid properties, which is related chemically to spironolactone, significantly increased HDL cholesterol in young healthy women.<sup>76</sup> By contrast, drospirenone was found to decrease significantly, in a dose-dependent manner, HDL cholesterol in postmenopausal women.<sup>77,78</sup> The discrepancy between the 3 latter studies may result from the fact that drospirenone treatment was accompanied by a 7-fold increase in plasma aldosterone levels in postmenopausal women<sup>77</sup> but only a 2-fold increase in premenopausal women,<sup>76</sup> and/or from the fact that drospirenone was combined with different estrogen derivatives in these studies. Giacchetti et al<sup>65</sup> ob-

served an increase in HDL cholesterol in patients with idiopathic hyperaldosteronism after pharmacologic treatment. Similarly, Gaudio et al<sup>79</sup> found HDL cholesterol to increase in response to a combination therapy of an angiotensin converting enzyme inhibitor and an angiotensin receptor blocker. The 2 latter experimental studies suggested that the RAAS, and more specifically aldosterone, interacts with lipid metabolism in human beings. In monkeys, eplerenone prevents early atherosclerosis owing to a high-cholesterol diet, without affecting the levels of blood pressure, total cholesterol, and HDL cholesterol levels.<sup>80</sup> Among the possible mechanisms explaining this protective effect are a reduction in malondialdehyde low-density lipoprotein (ie, a proxy for oxidized low-density lipoprotein) and monocyte-chemoattractant protein-1 and endothelial dysfunction.<sup>80</sup>

Situations with increased aldosterone levels, including but not restricted to primary aldosteronism, are characterized not only by hypertension-related complications but also by metabolic alterations in lipid and glucose metabolisms. The significant reduction in all-cause and cardiovascular mortality in patients with heart failure observed with spironolactone and eplerenone (2 aldosterone-receptor blockers) treatment compared with placebo when added to standard therapy in the Randomized Aldactone Evaluation Study (RALES)<sup>81</sup> and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)<sup>82</sup> trials therefore in part may be owing to the amelioration of aldosterone-related metabolic disturbances.

## PLASMA ALDOSTERONE IS ASSOCIATED INDEPENDENTLY WITH THE MS

To date, 3 studies have reported increased aldosterone levels in patients with several cardiovascular risk factors including obesity. Egan et al<sup>26</sup> studied 29 volunteers with cardiovascular risk factor clustering and found higher renin and aldosterone levels when compared with appropriate control subjects. Bochud et al<sup>27</sup> analyzed the association of plasma aldosterone and plasma renin activity with the MS in 69 families from the Seychelles made up of 356 participants (160 men and 196 women) of Af-

rican descent. Plasma aldosterone, but not plasma renin activity, was associated with the MS. This result was confirmed later by Kidambi et al<sup>71</sup> in a sample of 397 African American subjects. These observations strengthen the view of aldosterone as a contributing factor to cardiovascular disease in subjects of African descent with the MS. The association of plasma aldosterone with the MS in Caucasians is not yet clear. Egan et al (in a recent substudy of the Trial of Preventing Hypertension study), found no evidence for increased aldosterone in subjects with MS when compared with controls without MS.<sup>83</sup> However, Russo et al<sup>84</sup> found an association between the <344C/T polymorphism of the CYP11B2 gene, which encodes for aldosterone, and MS in Caucasian men, but not in women. This observation is consistent with the findings by Egan et al<sup>26</sup> and Bochud et al,<sup>27</sup> and the sex-specific nature of this genetic association in Caucasians may explain why no association between aldosterone and the MS was detected in the Trial of Preventing Hypertension substudy.<sup>83</sup>

## CONCLUSIONS

Adipose tissue plays a substantial role in the development of hypertension in the obese patient mainly by 2 aldosterone-related mechanisms: (1) increased production of compounds of the RAAS, and (2) increased production of FFAs (eg, EKODE) that directly stimulate adrenal cells. Animal studies have suggested that selective blockade of the mineralocorticoid receptor is effective in obesity-induced hypertension.<sup>85</sup> This raises an important question: can increased blood pressure in the obese patient be decreased effectively by blocking the mineralocorticoid receptor (ie, the aldosterone receptor)? If the answer is positive, this would reinforce the importance of aldosterone in obesity-related hypertension and, more generally, the endocrine view of the adipose tissue. Benefits beyond blood pressure reduction also may occur if aldosterone-related metabolic disturbances also are modified favorably. To date, we do not have clinical evidence to support these hypotheses and additional studies are needed to clarify these points definitively.

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