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Sodium restriction and insulin resistance: A review of 23 clinical trials

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Background: Many clinicians recommend low-salt diets for lowering blood pressure but there may be unintended consequences such as worsening insulin resistance.

Aim: This paper aimed to find human clinical studies looking at low-salt diets on markers of glucose and insulin.

Methods: We reviewed PubMed using the search terms 'sodium', 'insulin' and 'insulin resistance' and found 23 human clinical studies testing low-salt diets showing negative harms on insulin or glucose.

Results: Twenty-three human clinical trials have shown that low-salt diets lead to systemic or vascular insulin resistance, glucose intolerance, elevated fasting insulin and/or elevations in glucose and/or insulin levels after an oral glucose tolerance test.

Conclusion: We discovered 23 human clinical studies showing that low-salt diets worsen markers of insulin and glucose. Caution is advised when recommending salt restriction for blood pressure control as this may lead to worsening insulin resistance.

Contribution: This review has revealed that low salt diets can induce insulin resistance.

Keywords: salt; sodium; insulin resistance; insulin; hyperinsulinaemia; glucose.

Introduction

Many clinicians recommend low-salt diets for lowering blood pressure but there may be unintended consequences such as worsening insulin resistance. Indeed, a lack of sodium has been shown to increase insulin levels, which may be a compensatory mechanism to help the kidneys retain sodium. Additionally, low-salt diets elevate stress hormones, such as noradrenaline, aldosterone, renin and angiotensin-II, which contribute to vascular stiffening and vascular and systemic insulin resistance.[1,2,3] Several lines of evidence suggest that salt restriction may increase mortality and cardiovascular events.[4,5,6] This review will discuss 23 human clinical studies that have shown negative effects with sodium restriction on glucose and insulin. There is also a brief discussion at the end regarding trials that have shown no effect, or even worsening insulin sensitivity, on a high-salt diet.

Study 1

Feldman and Schmidt randomised eight male participants (25–40 years old) with normal and high blood pressure to moderate salt restriction (1725 mg of sodium per day) versus a normal-salt intake (5405 mg of sodium per day) for 1 week in a crossover, double-blind design.[1] The authors concluded that moderate salt restriction aggravated both systemic and vascular insulin resistance. They also noted that there was no reduction in blood pressure with the low-salt diet due to the impairment of insulin, '… impairment of the vasodilating effect of insulin could be a factor attenuating the blood pressure lowering effect of a low sodium diet'.[1] Resistance to the vasodilating effects of insulin has been noted to occur in hypertension.[7,8] Insulin enhances its own ability to promote glucose uptake by its action to increase skeletal muscle blood flow.[8] Low-salt diets can reduce blood flow to skeletal muscle via increased peripheral resistance.[9] This can then reduce insulin and glucose delivery to skeletal muscle, worsening systemic and vascular insulin resistance, which could lead to hypertension, cardiovascular disease and early death.[4,10,11,12,13] Thus, caution is advised when recommending salt restriction for blood pressure control. Furthermore, salt restriction increases norepinephrine and plasma insulin. Indeed, the fasting plasma insulin more than doubled in this study, going from 4.4 mIU/L to 9.9 mIU/L after the low-sodium intake.[1] Thus, in young men with normal and high blood pressure, a moderate salt

restriction induces systemic and vascular insulin resistance without lowering blood pressure.

Study 2

Iwaoka and colleagues investigated whether a change in salt intake would alter the glycaemic response to an oral glucose load. They randomised 31 middle-aged patients with essential hypertension for 1 week to a low-salt (782 mg of sodium/day) and a high-salt (7866 mg of sodium/day) diet in a cross-over design. The area under the curve (AUC) for glucose and insulin after an oral glucose tolerance test significantly decreased after the high-salt diet compared to the low-salt diet. The authors of the study concluded, 'These results suggest that extreme salt restriction may deteriorate glucose metabolism in hypertensive patients, especially those with diabetes mellitus or impaired glucose tolerance'.[14] The authors also noted that, 'The deterioration of glucose tolerance and lipid profile with salt restriction in hypertensives is very similar to the changes noted with thiazide treatment'.[14] Thiazide diuretics have well known side effects, such as worsening insulin resistance and blood lipid profiles, which may be due to sodium depletion. The authors speculated that a low-sodium intake may increase glucose levels after an oral glucose tolerance test because they (1) lower intracellular sodium concentrations, which may increase glucose absorption at the intestine due to the dependence on the gradient of sodium between the intestinal lumen and epithelial cells and (2) the catecholamine increase would decrease tissue glucose uptake and stimulate hepatic glucose production.[14]

Study 3

Meland and colleagues randomised 34 patients with essential hypertension (mean age 53 years) to a parallel group designed trial of 12 weeks of a moderate salt restricted diet (24 h urine sodium excretion went from 3680 mg/day to 2737 mg/day).[15] Moderate sodium restriction caused a significant 40% increase in insulin C-peptide, 5.6% increase in glucose and an 11% decrease in high-density lipoprotein (HDL). The authors wrote:

> A moderate salt restricted diet seems to increase insulin C-peptide concentration substantially. A minor increase of fasting glucose may also follow dietary salt restriction … It is concluded that salt restriction may increase insulin resistance in hypertensive patients.[15]

One of the most powerful independent predictors of developing type 2 diabetes is an elevation in fasting C-peptide.[16] Thus, low-salt diets may increase the risk for prediabetes and type 2 diabetes by worsening insulin resistance and elevating insulin levels.

Study 4

Iwaoka and colleagues looked at the effects of a low and high-salt diet on plasma glucose and insulin responses to an oral glucose tolerance test.[17] Fifteen untreated hypertensive patients (>160/95 mmHg) were randomised to a low-salt (800 mg of sodium/day) or high-salt (8000 mg of sodium/day) diet for 8 days. Participants were then given an oral glucose tolerance test (75-gram glucose load). Patients were then crossed over to the other level of salt intake. The daily amounts of calories, carbohydrates, protein, fats and potassium were not significantly different between the low and high-salt diets. The individuals started with an average blood pressure of 173.3/104 mmHg. Interestingly, 40% of the group did not have a significant reduction in blood pressure on the low-sodium intake (800 mg/day) versus the high-sodium intake (8000 mg/day) despite the potassium intake in both groups being low (2.3 g/day and 2.4 g/day, respectively). Mean plasma glucose and insulin concentrations and mean incremental areas under the 2-h plasma glucose and insulin curves were significantly lower after glucose ingestion during the high-salt diet compared to the low-salt diet. In other words, low-salt diets significantly worsen insulin and glucose (AUC and mean concentrations) after an oral glucose tolerance test.

The authors speculated that a lower intracellular sodium content on a low-salt diet may have caused higher glucose and insulin levels after an oral glucose load. They noted that red blood cell sodium concentrations were higher in 11 out of 14 patients on the high-salt diet. Although the difference was not considered statistically significant, this may have played a role in reducing glucose absorption from the intestine in those on the high-salt diet. Dietary glucose is accompanied by sodium when it is absorbed from the intestine. Thus, acutely, sodium can increase the absorption of glucose and lead to elevations in the glycaemic response.[18,19] However, over several days, a low-salt diet can lower small intestinal cell sodium concentrations, which would increase the driving force for sodium and glucose absorption (as sodium follows a gradient between the intestinal lumen and the interior of the intestinal epithelium). Stated differently, a high-salt intake over a prolonged period of time increases sodium concentrations inside the intestinal epithelial cells, reducing the efficiency of glucose absorption that is coupled with sodium. This may explain the lower glucose and insulin spikes after an oral glucose tolerance test on a high-salt intake. Thus, after a few days of a normal or high-salt intake, there may be a reduction in glucose absorption from the diet.

Study 5

Del Río and colleagues performed a double-blind randomised trial in 30 non-diabetic mildly hypertensive participants (diastolic blood pressure 90 mmHg – 104 mmHg) with normal kidney function.[20] After a wash-out period, patients were maintained on a low-salt intake (2.8 grams of salt/day) and placebo for 2 weeks, and then the same diet but with added salt supplements (11.7 grams of salt/day) for another 2 weeks, separated by a second wash-out period. At the end of each dietary period, blood measurements were drawn. During the salt restriction period plasma renin activity, creatinine, uric acid, insulin, total cholesterol and apoB increased, whereas HDL and apo A-1 decreased. The authors

concluded, '… these observations seem to indicate that strict salt restriction may cause, at least in the short-term, adverse metabolic changes in hypertensive patients'.[20] Based on urinary sodium excretion, the low-sodium group was consuming ~1095 mg of sodium/day and the high-sodium group ~4575 mg of sodium/day. Importantly, there was no significant reduction in blood pressure on the low-sodium diet. However, there was a significant drop in body weight, likely reflecting extracellular volume depletion due to negative sodium balance. Thus, in patients with stage 1 hypertension, a low-salt diet induces numerous harmful metabolic changes including a rise in insulin and blood volume depletion with no significant reduction in blood pressure. The rise in creatinine and uric acid with salt restriction is thought to be due to a drop in blood volume and decreased blood flow to the kidneys, which has been noted in several salt restriction studies.[20,21,22,23] Additionally, the elevated insulin on a low-salt diet may cause hypertension, as hyperinsulinaemia is found in 41% of hypertensive patients.[24] The activation of the renin angiotensin aldosterone system (RAAS) on a low-salt diet may induce insulin resistance and hyperinsulinaemia. Indeed, medications that block the RAAS improve insulin sensitivity and counteract the dyslipidaemia induced by sodium-depleting diuretic medications.[25,26] As discussed previously, low-salt diets induce volume depletion and increased peripheral vascular resistance, which can cause a reduction in blood flow to skeletal muscle increasing insulin resistance via reduced insulin and glucose delivery to skeletal muscle.

Study 6

Garg and colleagues placed 152 healthy men and women on a low-salt diet (urine sodium <460 mg/day) and a high-salt diet (urine sodium 3450 mg/day) for 7 days each in random order.[27] Insulin resistance (measured via the homeostatic model assessment of insulin resistance) was significantly higher on the low-salt intake compared to the high-salt intake. Serum aldosterone (21 ng/dL vs 3.4 ng/dL), 24-h urine aldosterone (63 ug/day vs 9.5 ug/day), plasma renin activity (3.1 ng/mL per hour vs 0.39 ng/mL per hour), angiotensin-II (43.9 pg/mL vs 28.1 pg/mL) and 24-h urine norepinephrine excretion (78 ug/day vs 67.9 ug/day) were also significantly higher on a low-salt diet compared with the high-salt diet. Thus, low-salt diets worsen insulin resistance and increase aldosterone, renin, angiotensin-II and urine norepinephrine levels.

Study 7

Egan and colleagues placed 29 volunteers on 1 week of an isocaloric low-salt (460 mg/day of sodium) or normal-salt diet (4600 mg/day of sodium).[28] In the high-risk participants who had risk factors associated with abdominal obesity and hyperinsulinaemia, fasting insulin and triglycerides, the insulin response to oral glucose, and plasma aldosterone all rose significantly more with salt restriction versus the normal-salt diet. Total cholesterol in the low, medium and high-risk individuals was all significantly greater during the low compared to the normal-salt diet. In the high-risk participants, mean ambulatory blood pressure was significantly higher on the low-salt versus the normal-salt diet (103 mmHg vs 98 mmHg). In these same individuals, fasting insulin was 15.9 uU/mL on the normal-salt but 26.3 uU/mL on the low-salt diet with triglyceride levels being 164 mg/dL and 197 mg/dL, respectively. Thus, low-salt diets raise insulin and triglyceride levels compared to a normal-salt intake. Even in the low-risk group, insulin AUC was significantly higher on the low-salt diet versus the normal-salt diet, whereas fasting insulin only had a trend for being higher. Thus, in obese individuals with elevated blood pressure, a low-salt diet significantly worsens insulin resistance and elevates fasting insulin levels and insulin AUC. In individuals who are low-risk for obesity and hyperinsulinaemia, low-salt diets significantly increased insulin AUC after a glucose load. The larger rise in non-esterified fatty acids and activation of the RAAS with salt restriction in the high-risk individuals were thought to have contributed to the elevations in insulin. Additionally, in the high-risk individuals, the very large increase in the RAAS was thought to contribute to the higher blood pressure on the low-salt diet versus the normal-salt diet.

Study 8

Egan and colleagues performed a double-blind study on 27 Caucasian men (ages 23–55) with normal to mildly elevated blood pressure comparing a low-salt diet (460 mg of sodium) to a normal-salt diet (4600 mg of sodium) for 7 days.[23] The mean arterial blood pressure was not significantly different between the 10-fold difference in dietary salt intake. However, fasting insulin values were significantly higher during the low-salt period. Total cholesterol and calculated low-density lipoprotein cholesterol (LDL-C) tended to be higher on the low versus high-salt diet. Norepinephrine, plasma renin activity, serum creatinine and serum uric acid were significantly higher on the low-salt versus the normal-salt diet. Twelve individuals were salt sensitive (mean arterial pressure on the high-salt diet ≥5% vs the low-salt diet) and 11 were salt resistant (mean arterial pressure on low-salt ≥5% vs the high-salt diet). In other words, 44% of the men were salt sensitive but 41% were reverse responders, who had higher blood pressure on the low-salt diet. The authors went on to note, '… a study of hypertensive patients by Longworth et al., 37% (30/82) of outpatients manifested increases of mean blood pressure ranging from 1 [*mm Hg*] to 25 mm Hg when dietary NaCI [*salt*] was mildly restricted from 197 mEq/day [*4531 mg of sodium*] to 70 mEq/day [*1610 mg of sodium*].[29] … Weinberger et al., observed that roughly 58% (219/375) of normotensive [*participants*] and 33% (64/192) of hypertensive [*participants*] were SR [*salt resistant*] [*a decrease of blood pressure of 5 mmHg or less with salt restriction, our insertion*] ...[30] In a study of predominantly young white men, Sullivan and Ratts observed SR (< 5% increase of mean blood pressure on high *v* [*versus*] low NaCI) in approximately 84% (77/92) of normotensive and 71% (46/65) of hypertensive [*participants*].[31] Kotchen and colleagues reported significantly greater supine and seated diastolic blood pressure in 12

normotensive men during a low [*230 mg/day*] *v* a high [*5750 mg*] sodium diet.[32] Another report confirms the observation of higher seated diastolic blood pressure during a low *v* high-salt diet and extends these observations to both black and white hypertensive and normotensive [*participants*][33′].[22] All of these studies indicate that a large percentage of the population does not have a clinically meaningful drop in blood pressure with salt restriction and that in many cases there can even be an increase in blood pressure.

Study 9

Weder and colleagues tested salt restriction in 27 hypertensive and normotensive participants in a randomised, placebo-controlled, double blind comparison of 1-week periods of salt restriction (460 mg of sodium/day) versus a normal-salt intake (4784 mg of sodium/day).[34] Salt restriction had no significant effect on blood pressure but, as noted by the authors, 'a generally adverse impact on risk factors for cardiovascular disease'.[34] The authors noted that salt restriction caused increases in total and LDL-C that were borderline significant ($P = 0.07$). Plasma norepinephrine and fasting plasma insulin all significantly increased with salt restriction. The authors concluded:

> … [*I*]n the present study, the net cardiovascular risk benefit of an average blood pressure reduction of only 1.1 mmHg could well be more than offset by the rises in cholesterol, insulin, norepinephrine and hematocrit resulting from salt restriction.[34]

Importantly, 10 out of the 27 patients (37%) had lower blood pressure on the high-salt intake versus the low-salt intake, with five individuals having a mean arterial blood pressure >5 mmHg lower. Thus, a low-salt intake did not decrease blood pressure but rather increased blood viscosity, insulin and norepinephrine levels.

Study 10

Garg and colleagues evaluated 389 salt-sensitive and salt-resistant hypertensive participants on 1 week of salt restriction (230 mg of sodium/day) versus a normal-salt intake (4600 mg of sodium/day).[35] Fasting plasma glucose, insulin and homeostasis model assessment of insulin resistance were higher on the low-salt diet as compared with the high-salt diet. This study demonstrated that 1 week of a low-salt diet increased insulin resistance equally in both salt sensitive and salt resistant hypertensive individuals and that salt sensitivity of blood pressure does not modify the relationship between salt restriction and insulin resistance. Interestingly, an activation of RAAS in this study did not correlate with an increase in insulin resistance.

Study 11

Ruppert and colleagues studied 147 non-obese normotensive participants aged 19–78 years in a randomised single-blind crossover trial. Patients were randomly assigned to a low-salt diet (460 mg of sodium/day) or a high-salt diet (6900 mg of sodium/day) for 7 days each.[36] Sodium restriction lowered mean arterial blood pressure by 7.5 mmHg in 17% (salt sensitive), no drop in blood pressure in 67% (salt-resistant) and raised blood pressure by 6 mmHg in 16% of participants (reverse reactors). Salt restriction increased total and LDL cholesterol in all three groups but the largest increase occurred in reverse reactors, which was thought to be due to an increase in noradrenaline and suppression of LDL receptor activity.[37,38] Salt restriction also increased serum insulin, uric acid, creatinine, renin activity, aldosterone and noradrenaline. Thus, salt restriction has an adverse impact on blood lipids, insulin, and stress hormones with approximately the same percentage of normotensive individuals having an increase in blood pressure (16%) as compared to decrease in blood pressure (17%) with salt restriction. Serum triglycerides significantly increased in the salt sensitive group with salt restriction. Lastly, haematocrit increased by a mean of 2% in all groups, indicating an increase in blood viscosity due to volume depletion. Thus, this study provides further support for caution when advocating sodium restriction, particularly in normotensive individuals.

Study 12

Gomi and colleagues assessed the effects of sodium restriction in 12 participants with primary hypertension in a controlled 1-week study.[39] Participants took a normal-sodium diet followed by a randomised crossover study in which the participants were placed on either moderate or strict reduced sodium diets for 1 week. There was a significant decrease in systolic and diastolic blood pressure when sodium was reduced from 4600 mg/day to 2300 mg/day. However, further reduction in sodium intake to 690 mg/day resulted in no additional decrease in blood pressure but increased plasma insulin by 40.6% without changing plasma glucose. Insulin sensitivity was not changed with moderate dietary sodium reduction. However, strict sodium reduction significantly decreased glucose infusion rate by 19.8% and insulin sensitivity index by 20.5% with a paralleled increase in plasma norepinephrine of 90.0%. These results suggest that severe sodium restriction leads to deterioration of insulin sensitivity when plasma norepinephrine levels increase and suggest that a more moderate sodium restriction may lower blood pressure without adversely affecting glucose metabolism. Sympathetic hyperactivity can lead to constriction of peripheral blood vessels reducing skeletal muscle blood flow and inducing insulin resistance.[8,40] Thus, activation of the sympathetic nervous system with sodium restriction may be the dominant regulator of insulin sensitivity.

Study 13

Perry and colleagues tested 5 days of modest sodium restriction (<1840 mg of sodium/day) on insulin sensitivity in 15 healthy males in a double-blind, placebo-controlled, randomised, cross-over euglycaemic hyperinsulinaemic clamp study.[41] One phase was given sodium tablets and the other a matched placebo. Insulin sensitivity was reduced by 15% using the gold standard euglycaemic hyperinsulinaemic clamp during moderate dietary sodium restriction (mean

urinary sodium was 1610 mg/day). There was no evidence from the study that angiotensin-II had an influence on insulin-stimulated glucose uptake or suppression of lipolysis. This suggests that angiotensin-II may not be involved in worsening insulin sensitivity with salt restriction. Indeed, this effect may have more to do with norepinephrine and perhaps aldosterone.[42] Thus, as compared to the previous study, a moderate sodium restriction can reduce insulin sensitivity when using the gold standard euglycaemic hyperinsulinaemic clamp.

Study 14

Petrie and colleagues assessed the effect of dietary sodium restriction on insulin sensitivity and endogenous glucose production in eight normotensive patents with diet-controlled type 2 diabetes.[43] This study used a hyperinsulinaemic clamp in a randomised, double-blind, placebo-controlled, cross-over protocol after two 4-day periods on a sodium replete (average 24-h urine sodium was 4531 mg) and sodium deplete (average 24-h urine sodium was 1541 mg) diet. Insulin sensitivity was significantly reduced by 12% during the sodium deplete diet as measured by the insulin suppression test. There were also trends for an increase in fasting insulin and endogenous glucose production during steady-state hyperinsulinaemia with the sodium deplete diet. Thus, in normotensive individuals with type 2 diabetes, sodium restriction worsens insulin sensitivity.

Study 15

Fliser and colleagues assessed insulin sensitivity using the euglycaemic clamp technique in 14 healthy males on a high (4600 mg/day) and low (460 mg/day) sodium intake.[44] Half the group ($n = 7$) received high- and low-salt diets in random order each for 7 days. The other half ($n = 7$) received the respective diet in random order for 3 days. Insulin sensitivity was significantly lower during the low-salt intake compared to the high-salt intake in the group receiving the diets for 3 days but not 7 days. However, mean serum insulin was significantly higher on the low-salt intake as compared with high-salt intake for all groups (3 and 7 days). It was hypothesised that the elevation in fasting insulin on a low-salt intake may be important for maintaining high muscle blood flow and insulin-mediated glucose uptake. Mean plasma renin activity, angiotensin II and noradrenaline levels were also higher after low salt than after high-salt intake in both groups. The authors concluded that a low-sodium intake raises fasting insulin levels in healthy men but that the reduction in insulin sensitivity with salt restriction of 3 days goes away after 7 days. However, other studies have shown that these effects last even to 28 days.[45]

Study 16

Ames and colleagues placed 21 patients with primary hypertension on consecutive 4-week periods of placebo and salt supplementation (2 g four times a day) in a single-blind crossover study.[45] A 75-gram oral glucose tolerance test with simultaneous insulin levels was performed at the end of each intervention period. The urinary sodium excretion was 3105 mg/day in the placebo phase and 6141 mg/day during the salt supplementation. Blood pressure did not significantly increase during sodium supplementation. Total glycaemic response to the oral glucose tolerance test (area under the glucose curve) was 8.0% lower during salt supplementation ($P < 0.001$). The total insulinaemic response to the oral glucose tolerance test was also significantly lowered by sodium loading among participants with diabetes. The authors concluded, 'Thus, an abundant sodium intake may improve glucose tolerance and insulin resistance, especially in diabetic, salt-sensitive, and or medicated essential hypertensive subjects'.[45] The authors went on to note, '… it would appear that sodium loading improves glucose utilization only when some degree of insulin resistance is present'.[45] The improvement in glucose tolerance and insulin curves with sodium loading may be due to better blood volume. Indeed, there was no improvement in glucose or insulin parameters when diastolic blood pressure did not increase with sodium feeding. In other words, when there was an increase in diastolic blood pressure with sodium loading (indicating an increase in blood volume) there were improvements in glucose/insulin responses to the oral glucose tolerance test. Enhanced blood volume/flow and insulin delivery to skeletal muscle has been one of the leading theories for why increased sodium intakes improve insulin sensitivity. The authors' final note went on to state:

> First, in hypertensive subjects who are insulin resistant sodium supplementation moderates the insulin resistance, decreasing glucose excursions after oral glucose while maintaining or decreasing insulin concentrations. In these subjects, the lower sodium intake was associated with larger glucose and insulin excursions in the oral glucose tolerance test, indicating an aggravated insulin resistant state. Second, the ameliorative effects of salt supplementation are seen predominately among salt-sensitive hypertensive patients, among those with glucose intolerance and frank diabetes mellitus, and among those receiving anti-hypertensive therapy with diuretic and beta-blocking drugs.[45]

Considering population-wide sodium restriction messaging, particularly as a means to lower blood pressure, this data questions this advice.

Study 17

Townsend and colleagues selected 21 healthy normotensive lean volunteers who underwent a euglycaemic clamp following 6 days of a low-salt diet (460 mg of sodium per day) and, subsequently, 6 days of a high-salt diet (4600 mg of sodium/day).[46] Compared to the low-salt diet, the high-salt diet significantly increased insulin-mediated glucose disposal by 21% during euglycaemic clamp conditions. The authors noted that the low-salt diet significantly increased renin, aldosterone and noradrenaline compared to the high-salt diet. Interestingly, there was no change in calf blood flow before and during insulin infusion on the varying salt intakes. However, a previous study by Foo et al. did find an increase

in calf blood flow during the high-salt intervention, which did not translate into greater glucose uptake.[47] However, Foo et al. assessed insulin sensitivity using two doses of insulin for 120 min each, whereas Townsend et al. studied a single insulin dose for 180 min. It was noted by Townsend and colleagues that when they re-analysed their data at 120 min, the difference in salt interventions lost statistical significance (P = 0.10). Thus, if the effects of varying salt intakes on insulin-mediated glucose disposal are not measured out to at least 180 min, findings may be null. Furthermore, aldosterone levels only increased 2-fold in the study by Foo and colleagues on the low-salt diet, whereas it increased 4–5-fold in this study. The authors of this study concluded:

> We propose the 4–5-fold increase in serum aldosterone and the greater increase in plasma noradrenaline concentration following the low-salt intervention compared with the high-salt period may have contributed to the differences in insulin sensitivity following the adjustment in dietary sodium.[46]

Indeed, the average heart rate in participants on day 6 of the high-salt diet (66 beats/min) tended to be lower than on the low-salt diet (72 beats/min), consistent with an increased sympathetic activity on the low-salt intake. Additionally, there was also a strong correlation between increases in plasma renin activity and serum aldosterone concentrations and decreased insulin sensitivity in a study by Melander and colleagues, which corroborates these findings.[48]

Study 18

Fliser and colleagues studied 16 normotensive healthy volunteers during 7 days of high (4600 mg sodium/day) and 7 days of low (460 mg sodium/day) salt intake.[49] The individuals were examined on either placebo or on an α1-adrenergic blocker doxazosin (2 mg/day). The study was a single blind parallel group random order design with two arms of treatment. Total cholesterol and LDL-cholesterol were significantly higher during the low-salt intake. The rise in total and LDL-cholesterol on low-salt intake was blunted after α1-adrenergic blockade with doxazosin, which reflects the literature showing that α1-receptor stimulation increases LDL and very low-density lipoprotein (VLDL) triglyceride.[38] Additionally, C-peptide levels were higher on the low-salt intake compared to the high-salt intake. Importantly, α1-adrenergic blockade with doxazosin attenuated the rise of C-peptide levels on the low-salt diet. Thus, based on this study, the adverse effects of low-salt diets on blood lipids and insulin sensitivity are driven by the activation of α1-adrenergic receptors by noradrenaline.

Study 19

Raji and colleagues studied 426 essential hypertensive and normotensive participants and placed them on a low (230 mg sodium per day) or high (4600 mg sodium/day) salt diet for 7 days.[50] After completion of 7 days on one diet (high or low salt), the participants were then placed on the other diet. The authors noted that in those who had the most insulin resistance, salt restriction caused a significant increase in insulin resistance, which was not seen in low-renin participants. This may explain the variability of the effect of sodium intake on insulin sensitivity in different studies. In this study, insulin sensitivity was measured by Homeostatic Model Assessment (HOMA)-index. This index has been shown to correlate well with the gold-standard euglycaemic hyperinsulinaemic clamp and the minimal model method, in both diabetic and normal participants. Thus, in insulin resistant normal/high renin hypertensive individuals, sodium restriction worsens insulin sensitivity.

Study 20

Melander and colleagues studied 28 healthy participants (13 men and 15 women) with a family history of hypertension and placed them on 1 week of salt restriction (230 mg of sodium/day) and 1 week of salt loading (5520 mg sodium/day).[48] Insulin sensitivity was measured with the gold standard hyperinsulinaemic euglycaemic clamp after the low- and high-salt diets. Fasting serum insulin and glucose were significantly higher on the low-salt diet compared to the high-salt diet. Glucose disposal also tended to be higher on the high-salt diet compared to the low-salt diet (P = 0.10). The authors noted:

> … [*I*]ncreased salt sensitivity and decreased activity of the renin-angiotensin-aldosterone system predict improved insulin sensitivity with high-salt intake compared with low-salt intake in men … This suggests that a high-salt intake may have beneficial effects on insulin sensitivity in salt-sensitive men …[48]

Study 21

Sharma and colleagues studied 23 healthy, lean, male volunteers on 460 mg or 5980 mg sodium/day for 6 days each in a single-blind randomised crossover study.[51] Glucose tolerance deteriorated with salt restriction in the salt-resistant group but improved in the salt-sensitive group. Fasting insulin was also higher on the low-salt diet versus the high-salt diet in those who were salt resistant (11.4 vs 10.4, respectively) but lower in those who were salt sensitive (10.8 vs 11.6, respectively, although differences were not significant in either case). Those who were salt-sensitive were noted to have a higher glucose and insulin level following an oral glucose intake of 75 g, suggesting that insulin resistance may drive salt-sensitivity.

The response to varying salt intakes regarding insulin sensitivity may be determined by baseline insulin resistance but also changes in sympathetic activity. For example, there was a higher heart rate on the high-salt intake compared to the low-salt intake in all groups. However, glucose tolerance deteriorated with salt restriction in the salt resistant group. Thus, impaired insulin sensitivity would not explain the elevated heart rate in the salt resistant group with a high-salt intake. Furthermore, there was likely an increase in blood volume on the high-salt diet versus the low-salt diet (as body weight increased by 1.4 kg in just 6 days). This would typically result in a reduction in heart rate with a high-salt intake, as volume depletion on a low-salt intake generally

leads to a significant increase in heart rate. Thus, there is no reasonable explanation as to why heart rate was higher on the high-salt diet compared to the low-salt diet in the salt resistant group of this study. As previously stated, and shown in several aforementioned studies, activation of the sympathetic nervous system is thought to be a main driver of insulin resistance caused by salt restriction, and this does not seem to have occurred in this study, which is highly unusual.

Study 22 and 23

Several other studies show that salt restriction raises fasting insulin or insulin levels after an oral glucose load but does not worsen insulin sensitivity.[52,53] However, some studies show that a high-salt intake may impair insulin sensitivity.[54,55] Thus, while the majority of studies suggest that low-salt diets worsen insulin sensitivity the results are not entirely consistent. This is not uncommon, however, as many factors can lead to discordant findings, such as different patient populations, background diet, duration of study, level of sodium intake, measurements of insulin resistance, among others. Additional studies should be performed to further evaluate the effects of varying sodium intakes on insulin sensitivity.

Mechanisms for how low-salt diets induce insulin resistance[1,20,27,28]

- Activation of the sympathetic nervous system.
  - Blocking sympathetic nervous system signalling improves insulin sensitivity.[56]
  - Catecholamines contribute to decreased insulin sensitivity[57] - catecholamines decrease tissue glucose uptake and stimulate hepatic glucose production.[14]
  - Sympathetic hyperactivity can lead to constriction of peripheral blood vessels reducing skeletal muscle blood flow and inducing insulin resistance.[8,40]
- Activation of the RAAS.[28]
- Elevation of non-esterified fatty acids.[28]
- Lower intracellular sodium concentrations, which can increase glucose absorption at the intestine.[14]
- Volume depletion.
  - Reduced blood flow and insulin or glucose delivery to skeletal muscle.

Despite certain groups of individuals having a significant reduction in blood pressure with sodium restriction, an equally substantial subgroup (younger individuals with normotension or prehypertension) can have significant increases in blood pressure with salt restriction.[23,28,29,32,33,34,36,58,59] Additionally, low-salt intakes consistently increase the RAAS and elevate heart rate, which may outweigh any blood pressure lowering benefit.[2,3,5] Considering that at least 23 studies have shown that low-salt diets worsen insulin resistance, fasting insulin and/or glucose/insulin responses to an oral glucose tolerance test, sodium restriction should be used cautiously. Furthermore, a meta-analysis found that 19≈of 20 randomised, crossover trials showed that sodium restriction significantly increases fasting insulin levels.[60] Additionally, a low-sodium intake is associated with an increase in all-cause mortality, cardiovascular mortality and cardiovascular events.[4,5,6,10,61,62,63] Based on the overall evidence, sodium restriction (especially <2300 mg/day) should be used cautiously as a recommendation to lower blood pressure as it may worsen insulin resistance, activate the sympathetic nervous system and RAAS, and worsen blood lipids, blood viscosity, creatinine, uric acid and kidney function. Eating a diet mainly consisting of whole foods, while maintaining a normal-sodium intake (3000 mg – 5000 mg) per day, may be a better option for improving overall metabolic health and blood pressure. More studies should be performed to further ascertain whether low-salt diets worsen markers of glucose and insulin in humans beyond several weeks.

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Competing interests

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Authors' contributions

J.J.D. performed the literature search and wrote the initial draft manuscript. J.H.O. provided edits.

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References

1. Feldman RD, Schmidt ND. Moderate dietary salt restriction increases vascular and systemic insulin resistance. Am J Hypertens. 1999;12(6):643–647. https://doi.org/10.1016/S0895-7061(99)00016-3
2. Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. Cochrane Database Syst Rev. 2017;4:Cd004022. https://doi.org/10.1002/14651858.CD004022.pub4
3. Graudal NA, Galloe AM, Garred P. Effects of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride: A meta-analysis. JAMA. 1998;279(17):1383–1391. https://doi.org/10.1001/jama.279.17.1383

4. Graudal N, Jurgens G, Baslund B, et al. Compared with usual sodium intake, low- and excessive-sodium diets are associated with increased mortality: A meta-analysis. Am J Hypertens. 2014;27(9):1129–1137. https://doi.org/10.1093/ajh/hpu028
5. Graudal NA, Hubeck-Graudal T, Jurgens G. Reduced dietary sodium intake increases heart rate. A meta-analysis of 63 randomized controlled trials including 72 study populations. Front Physiol. 2016;7:111. https://doi.org/10.3389/fphys.2016.00111
6. O'Donnell M, Mente A, Rangarajan S, et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. N Engl J Med. 2014;371:612–623. https://doi.org/10.1056/NEJMoa1311889
7. Feldman RD, Bierbrier GS. Insulin-mediated vasodilation: Impairment with increased blood pressure and body mass. Lancet. 1993;342(8873):707–709. https://doi.org/10.1016/0140-6736(93)91708-T
8. Baron AD, Brechtel-Hook G, Johnson A, et al. Skeletal muscle blood flow. A possible link between insulin resistance and blood pressure. Hypertension. 1993;21:129–135. https://doi.org/10.1161/01.HYP.21.2.129
9. Omvik P, Lund-Johansen P. Is sodium restriction effective treatment of borderline and mild essential hypertension? A long-term haemodynamic study at rest and during exercise. J Hypertens. 1986;4(5):535–541. https://doi.org/10.1097/00004872-198610000-00004
10. Alderman MH, Madhavan S, Cohen H, et al. Low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men. Hypertension. 1995;25:1144–1152. https://doi.org/10.1161/01.HYP.25.6.1144
11. Alderman MH, Cohen H, Madhavan S. Dietary sodium intake and mortality: The National Health and Nutrition Examination Survey (NHANES I). Lancet. 1998;351(9105):781–785. https://doi.org/10.1016/S0140-6736(97)09092-2
12. Cohen HW, Hailpern SM, Fang J, et al. Sodium intake and mortality in the NHANES II follow-up study. Am J Med. 2006;119(3):275.e7–e14. https://doi.org/10.1016/j.amjmed.2005.10.042
13. Cohen HW, Hailpern SM, Alderman MH. Sodium intake and mortality follow-up in the Third National Health and Nutrition Examination Survey (NHANES III). J Gen Intern Med. 2008;23:1297–1302. https://doi.org/10.1007/s11606-008-0645-6
14. Iwaoka T, Umeda T, Inoue J, et al. Dietary NaCl restriction deteriorates oral glucose tolerance in hypertensive patients with impairment of glucose tolerance. Am J Hypertens. 1994;7(5):460–463. https://doi.org/10.1093/ajh/7.5.460
15. Meland E, Laerum E, Aakvaag A, et al. Salt restriction and increased insulin production in hypertensive patients. Scand J Clin Lab Investig. 1994;54(5):405–409. https://doi.org/10.3109/00365519409088441
16. Cruickshank JK, Cooper J, Burnett M, et al. Ethnic differences in fasting plasma C-peptide and insulin in relation to glucose tolerance and blood pressure. Lancet. 1991;338(8771):842–847. https://doi.org/10.1016/0140-6736(91)91501-K
17. Iwaoka T, Umeda T, Ohno M, et al. The effect of low and high NaCl diets on oral glucose tolerance. Klin Wochenschr. 1988;66:724–728. https://doi.org/10.1007/BF01726415
18. Ferrannini E, Barrett E, Bevilacqua S, et al. Sodium elevates the plasma glucose response to glucose ingestion in man. J Clin Endocrinol Metab. 1982;54(2):455–458. https://doi.org/10.1210/jcem-54-2-455
19. Thorburn AW, Brand JC, Truswell AS. Salt and the glycaemic response. Br Med J. 1986;292:1697–1699. https://doi.org/10.1136/bmj.292.6537.1697
20. Del Río A, Rodríguez-Villamil JL. Metabolic effects of strict salt restriction in essential hypertensive patients. J Intern Med. 1993;233(5):409–414. https://doi.org/10.1111/j.1365-2796.1993.tb00692.x
21. Masugi F, Ogihara T, Hashizume K, et al. Changes in plasma lipids and uric acid with sodium loading and sodium depletion in patients with essential hypertension. J Hum Hypertens. 1988;1:293–298.
22. Juraschek SP, Gelber AC, Choi HK, et al. Effects of the Dietary Approaches to Stop Hypertension (DASH) diet and sodium intake on serum uric acid. Arthritis Rheumatol. 2016;68(12):3002–3009. https://doi.org/10.1002/art.39813
23. Egan BM, Weder AB, Petrin J, et al. Neurohumoral and metabolic effects of short-term dietary NaCl restriction in men. Relationship to salt-sensitivity status. Am J Hypertens. 1991;4(5_Pt_1):416–421. https://doi.org/10.1093/ajh/4.5.416
24. Zavaroni I, Mazza S, Dall'Aglio E, et al. Prevalence of hyperinsulinaemia in patients with high blood pressure. J Intern Med. 1992;231(3):235–240. https://doi.org/10.1111/j.1365-2796.1992.tb00529.x
25. Pollare T, Lithell H, Berne C. A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. N Engl J Med. 1989;321:868–873. https://doi.org/10.1056/NEJM198909283211305
26. Weinberger MH. Influence of an angiotensin converting-enzyme inhibitor on diuretic-induced metabolic effects in hypertension. Hypertension. 1983;5:Iii132-8. https://doi.org/10.1161/01.HYP.5.5_Pt_2.III132
27. Garg R, Williams GH, Hurwitz S, et al. Low-salt diet increases insulin resistance in healthy subjects. Metabolism. 2011;60:965–968. https://doi.org/10.1016/j.metabol.2010.09.005
28. Egan BM, Stepniakowski K, Goodfriend TL. Renin and aldosterone are higher and the hyperinsulinemic effect of salt restriction greater in subjects with risk factors clustering. Am J Hypertens. 1994;7(10_Pt_1):886–893. https://doi.org/10.1093/ajh/7.10.886
29. Longworth DL, Drayer JI, Weber MA, et al. Divergent blood pressure responses during short-term sodium restriction in hypertension. Clin Pharmacol Ther. 1980;27(4):544–546. https://doi.org/10.1038/clpt.1980.76
30. Weinberger MH, Miller JZ, Luft FC, et al. Definitions and characteristics of sodium sensitivity and blood pressure resistance. Hypertension. 1986;8:Ii127-34. https://doi.org/10.1161/01.HYP.8.6_Pt_2.II127
31. Sullivan JM, Ratts TE. Sodium sensitivity in human subjects. Hemodynamic and hormonal correlates. Hypertension. 1988;11(10_Pt_1):717–723. https://doi.org/10.1161/01.HYP.11.6.717
32. Kotchen TA, Kotchen JM, Guthrie Jr, GP, et al. Baroreceptor sensitivity in prehypertensive young adults. Hypertension. 1989;13(6_pt_2):878–883. https://doi.org/10.1161/01.HYP.13.6.878
33. Dimsdale JE, Ziegler M, Mills P, et al. Prediction of salt sensitivity. Am J Hypertens. 1990;3(6_Pt_1):429–435. https://doi.org/10.1093/ajh/3.6.429
34. Weder AB, Egan BM. Potential deleterious impact of dietary salt restriction on cardiovascular risk factors. Klin Wochenschr. 1991;69(Suppl 25):45–50.
35. Garg R, Sun B, Williams J. Effect of low salt diet on insulin resistance in salt-sensitive versus salt-resistant hypertension. Hypertension. 2014;64(6):1384–1387. https://doi.org/10.1161/HYPERTENSIONAHA.114.03880
36. Ruppert M, Diehl J, Kolloch R, et al. Short-term dietary sodium restriction increases serum lipids and insulin in salt-sensitive and salt-resistant normotensive adults. Klin Wochenschr. 1991;69(Suppl 25):51–57.
37. Krone W, Müller-Wieland D, Nägele H, et al. Effects of calcium antagonists and adrenergic antihypertensive drugs on plasma lipids and cellular cholesterol metabolism. J Cardiovasc Pharmacol. 1987;10(Suppl 10):S199–S202. https://doi.org/10.1097/00005344-198706110-00065
38. Dzau VJ, Sacks FM. Regulation of lipoprotein metabolism by adrenergic mechanisms. J Cardiovasc Pharmacol. 1987;10(Suppl 9):S2–S6. https://doi.org/10.1097/00005344-198700109-00002
39. Gomi T, Shibuya Y, Sakurai J, et al. Strict dietary sodium reduction worsens insulin sensitivity by increasing sympathetic nervous activity in patients with primary hypertension. Am J Hypertens. 1998;11(9):1048–1055. https://doi.org/10.1016/S0895-7061(98)00126-5
40. Moan A, Nordby G, Rostrup M, et al. Insulin sensitivity, sympathetic activity, and cardiovascular reactivity in young men. Am J Hypertens. 1995;8(3):268–275. https://doi.org/10.1016/0895-7061(94)00206-Q
41. Perry CG, Palmer T, Cleland SJ, et al. Decreased insulin sensitivity during dietary sodium restriction is not mediated by effects of angiotensin II on insulin action. Clin Sci. 2003;105(2):187–194. https://doi.org/10.1042/CS20020320
42. Campión J, Maestro B, Mata F, et al. Inhibition by aldosterone of insulin receptor mRNA levels and insulin binding in U-937 human promonocytic cells. J Steroid Biochem Mol Biol. 1999;70(4–6):211–218. https://doi.org/10.1016/S0960-0760(99)00117-X
43. Petrie JR, Morris AD, Minamisawa K, et al. Dietary sodium restriction impairs insulin sensitivity in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab. 1998;83:1552–1557. https://doi.org/10.1210/jc.83.5.1552
44. Fliser D, Fode P, Arnold U, et al. The effect of dietary salt on insulin sensitivity. Eur J Clin Investig. 1995;25(1):39–43. https://doi.org/10.1111/j.1365-2362.1995.tb01523.x
45. Ames RP. The effect of sodium supplementation on glucose tolerance and insulin concentrations in patients with hypertension and diabetes mellitus. Am J Hypertens. 2001;14(7):653–659. https://doi.org/10.1016/S0895-7061(01)01310-3
46. Townsend RR, Kapoor S, McFadden CB. Salt intake and insulin sensitivity in healthy human volunteers. Clin Sci. 2007;113(3):141–148. https://doi.org/10.1042/CS20060361
47. Foo M, Denver AE, Coppack SW, et al. Effect of salt-loading on blood pressure, insulin sensitivity and limb blood flow in normal subjects. Clin Sci. 1998;95:157–164. https://doi.org/10.1042/CS19980065
48. Melander O, Groop L, Hulthén UL. Effect of salt on insulin sensitivity differs according to gender and degree of salt sensitivity. Hypertension. 2000;35(3):827–831. https://doi.org/10.1161/01.HYP.35.3.827
49. Fliser D, Nowack R, Allendorf-Ostwald N, et al. Serum lipid changes on low salt diet. Effects of alpha 1-adrenergic blockade. Am J Hypertens. 1993;6:320–324.
50. Raji A, Williams GH, Jeunemaitre X, et al. Insulin resistance in hypertensives: Effect of salt sensitivity, renin status and sodium intake. J Hypertens. 2001;19(1):99–105. https://doi.org/10.1097/00004872-200101000-00013
51. Sharma AM, Ruland K, Spies KP, et al. Salt sensitivity in young normotensive subjects is associated with a hyperinsulinemic response to oral glucose. J Hypertens. 1991;9(4):329–335. https://doi.org/10.1097/00004872-199104000-00004
52. Luther JM, Byrne LM, Yu C, et al. Dietary sodium restriction decreases insulin secretion without affecting insulin sensitivity in humans. J Clin Endocrinol Metab. 2014;99(10):E1895–E1902. https://doi.org/10.1210/jc.2014-2122
53. Lind L, Lithell H, Gustafsson IB, et al. Metabolic cardiovascular risk factors and sodium sensitivity in hypertensive subjects. Am J Hypertens. 1992;5(8):502–505. https://doi.org/10.1093/ajh/5.8.502
54. Donovan DS, Solomon CG, Seely EW, et al. Effect of sodium intake on insulin sensitivity. Am J Physiol. 1993;264(5):E730–E734. https://doi.org/10.1152/ajpendo.1993.264.5.E730
55. Fuenmayor N, Moreira E, Cubeddu LX. Salt sensitivity is associated with insulin resistance in essential hypertension. Am J Hypertens. 1998;11(4):397–402. https://doi.org/10.1016/S0895-7061(97)00490-1
56. Pollare T, Lithell H, Selinus I, et al. Application of prazosin is associated with an increase of insulin sensitivity in obese patients with hypertension. Diabetologia. 1988;31:415–420. https://doi.org/10.1007/BF00271585
57. Ferrannini E, Buzzigoli G, Bonadonna R, et al. Insulin resistance in essential hypertension. N Engl J Med. 1987;317:350–357. https://doi.org/10.1056/NEJM198708063170605

58. Ruppert M, Overlack A, Kolloch R, et al. Neurohormonal and metabolic effects of severe and moderate salt restriction in non-obese normotensive adults. J Hypertens. 1993;11(7):743–749. https://doi.org/10.1097/00004872-199307000-00010

59. Overlack A, Ruppert M, Kolloch R, et al. Divergent hemodynamic and hormonal responses to varying salt intake in normotensive subjects. Hypertension. 1993;22(3):331–338. https://doi.org/10.1161/01.HYP.22.3.331

60. Patel SM, Cobb P, Saydah S, et al. Dietary sodium reduction does not affect circulating glucose concentrations in fasting children or adults: Findings from a systematic review and meta-analysis. J Nutr. 2015;145(3):505–513. https://doi.org/10.3945/jn.114.195982

61. Stolarz-Skrzypek K, Kuznetsova T, Thijs L, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. JAMA. 2011;305(17):1777–1785. https://doi.org/10.1001/jama.2011.574

62. Ekinci EI, Clarke S, Thomas MC, et al. Dietary salt intake and mortality in patients with type 2 diabetes. Diabetes Care. 2011;34(3):703–709. https://doi.org/10.2337/dc10-1723

63. Alderman M, Sealey J, Cohen H, et al. Urinary sodium excretion and myocardial infarction in hypertensive patients: A prospective cohort study. Am J Clin Nutr. 1997;65(2):682s–686s. https://doi.org/10.1093/ajcn/65.2.682S