MARSHALL JOURNAL OF
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2016

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References with DOI

1. Segal-Lieberman G, Rosenthal T. Animal models in obesity and hypertension. Current hypertension reports 2013;15:190-5. https://doi.org/10.1007/s11906-013-0338-3

2. Landsberg L, Aronne LJ, Beilin LJ, et al. Obesity-related hypertension: pathogenesis, cardiovascular risk, and treatment--a position paper of the The Obesity Society and The American Society of Hypertension. Obesity 2013;21:8-24. https://doi.org/10.1002/oby.20181

3. Summers LK, Samra JS, Humphreys SM, Morris RJ, Frayn KN. Subcutaneous abdominal adipose tissue blood flow: variation within and between subjects and relationship to obesity. Clinical science 1996;91:679-83. https://doi.org/10.1042/cs0910679

4. Hall JE. Pathophysiology of obesity hypertension. Current hypertension reports 2000;2:139-47. https://doi.org/10.1007/s11906-000-0073-4

5. INTERSALT Study an international co-operative study on the relation of blood pressure to electrolyte excretion in populations. I. Design and methods. The INTERSALT Co-operative Research Group. J Hypertens 1986;4:781-7.

6. Elliott P, Stamler R. Manual of operations for "INTERSALT", an international cooperative study on the relation of sodium and potassium to blood pressure. Controlled clinical trials 1988;9:1S-117S.

7. Sodium, potassium, body mass, alcohol and blood pressure: the INTERSALT Study. The INTERSALT Co-operative Research Group. Journal of hypertension Supplement : official journal of the International Society of Hypertension 1988;6:S584-6.

8. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. Bmj 1988;297:319-28.

9. Rodrigues SL, Souza Junior PR, Pimentel EB, et al. Relationship between salt consumption measured by 24-h urine collection and blood pressure in the adult population of Vitoria (Brazil). Braz J Med Biol Res 2015;48:728-35. https://doi.org/10.1590/1414-431x20154455

10. Campanozzi A, Avallone S, Barbato A, et al. High sodium and low potassium intake among Italian children: relationship with age, body mass and blood pressure. PLoS One 2015;10:e0121183. https://doi.org/10.1371/journal.pone.0121183

11. Grimes CA, Baxter JR, Campbell KJ, et al. Cross-Sectional Study of 24-Hour Urinary Electrolyte Excretion and Associated Health Outcomes in a Convenience Sample of Australian Primary Schoolchildren: The Salt and Other Nutrients in Children (SONIC) Study Protocol. JMIR Res Protoc 2015;4:e7. https://doi.org/10.2196/resprot.3994

12. Lelong H, Galan P, Kesse-Guyot E, Fezeu L, Hercberg S, Blacher J. Relationship between nutrition and blood pressure: a cross-sectional analysis from the NutriNet-Sante Study, a French web-based cohort study. Am J Hypertens 2015;28:362-71. https://doi.org/10.1093/ajh/hpu164

13. Siervo M, Lara J, Chowdhury S, Ashor A, Oggioni C, Mathers JC. Effects of the Dietary Approach to Stop Hypertension (DASH) diet on cardiovascular risk factors: a systematic review and meta-analysis. Br J Nutr 2014:1-1 https://doi.org/10.1017/s0007114514003341

14. Woodruff SJ, Fryer K, Campbell T, Cole M. Associations among blood pressure, salt consumption and body weight status of students from south-western Ontario. Public Health Nutr 2014;17:1114-9. https://doi.org/10.1017/s1368980013000335

15. Singh RB, Fedacko J, Pella D, et al. Prevalence and risk factors for prehypertension and hypertension in five Indian cities. Acta Cardiol 2011;66:29-37. https://doi.org/10.1097/00004872-201106001-01321

16. Ortega RM, Lopez-Sobaler AM, Ballesteros JM, et al. Estimation of salt intake by 24 h urinary sodium excretion in a representative sample of Spanish adults. Br J Nutr 2011;105:787-94. https://doi.org/10.1017/s000711451000423x

17. Venezia A, Barba G, Russo O, et al. Dietary sodium intake in a sample of adult male population in southern Italy: results of the Olivetti Heart Study. Eur J Clin Nutr 2010;64:518-24. https://doi.org/10.1038/ejcn.2010.22

18. Haghighatdoost F, Sarrafzadegan N, Khosravi A, et al. Is the association between salt intake and blood pressure mediated by body mass index and central adiposity? Arch Iran Med 2013;16:167-71.

19. Hoffmann IS, Cubeddu LX. Salt and the metabolic syndrome. Nutr Metab Cardiovasc Dis 2009;19:123-8.

20. Heymsfield SB, Arteaga C, McManus C, Smith J, Moffitt S. Measurement of muscle mass in humas: validity of the 24-hour urinary creatinine method. The American journal of clinical nutrition. 1983;37(3):478-94.

21. Brenner BM. Nephron adaptation to renal injury or ablation. Am J Physiol 1985;249:F324-37.

22. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. Am J Physiol 1981;241:F85-93.

23. Moore DR. Keeping older muscle "young" through dietary protein and physical activity. Adv Nutr 2014;5:599S-607S. https://doi.org/10.3945/an.113.005405

24. Deutz NE, Bauer JM, Barazzoni R, et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr 2014;33:929-36. https://doi.org/10.1016/j.clnu.2014.04.007

25. Atkins JL, Whincup PH, Morris RW, Wannamethee SG. Low muscle mass in older men: the role of lifestyle, diet and cardiovascular risk factors. J Nutr Health Aging 2014;18:26-33. https://doi.org/10.1007/s12603-013-0336-9

26. Xie JX, Shapiro AP, Shapiro JI. The Trade-Off between Dietary Salt and Cardiovascular Disease; A Role for Na/K-ATPase Signaling? Front Endocrinol (Lausanne) 2014;5:97. https://doi.org/10.3389/fendo.2014.00097

27. Dial L, Liu J, Shapiro JI. Cardiotonic steroids in adaptation to dietary salt intake. Curr Clin Pharmacol 2014;9:298-309. https://doi.org/10.2174/1574884708666131111204031

Why Does Obesity Lead to Hypertension? Further Lessons from the Intersalt Study

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Abstract:

Objectives:
To analyze correlations between major determinants of blood pressure (BP), in efforts to generate and compare predictive models that explain for variance in systolic, diastolic, and mean BP amongst participants of the Intersalt study.

Methods:
Data from the Intersalt study, consisting of nearly 10,000 subjects from 32 different countries, were reviewed and analyzed. Published mean values of 24 hour urinary electrolyte excretion (Na+, K+), 24 hour urine creatinine excretion, body mass index (BMI, kg/m^2), and blood pressure data were extracted and imported into Matlab™ for stepwise linear regression analysis.

Results:
As shown earlier, strong correlations between urinary sodium excretion (UNaV) and systolic, diastolic and mean blood pressure were noted as well as between UNaV and the age dependent increase in systolic blood pressure. Of interest, BMI and urinary creatinine excretion rate (UCrV) also both correlated with systolic blood pressure, but the ratio of BMI/UCrV, constructed to be a measure of obesity, correlated negatively with systolic blood pressure.

Conclusions:
Our results offer population-based evidence suggesting that increased size due to muscle mass rather than adiposity may correspond more to blood pressure. Additional data bases will need to be sampled and analyzed to further validate these observations.

Keywords: Hypertension, salt, blood pressure, creatinine, sodium

Introduction:

The determinants of blood pressure across populations is an important public health topic. As hypertension is one of the most common and important health conditions worldwide, a population-based strategy to reduce its prevalence is a medical and epidemiological necessity.

Extensive animal and clinical evidence support obesity's multifaceted role in the pathogenesis of hypertension.(1,2) While this association is quite complex and not fully understood, in one respect, the presence of excess adipose tissue warrants increased blood flow to meet the increased metabolic demands of these areas.(3) This, alone, increases the workload placed upon the cardiovascular system. Additionally, altered renal sodium handling has also been implicated in obesity, often associated with irregular sodium retention and increased risk for hypertension. (4)

In the 1980s, the Intersalt study was designed and implemented to examine major dietary factors in blood pressure regulation. Across the world, 52 centers were selected and each center enrolled approximately 200 patients across the adult age spectrum. Among the most prominent findings, the investigators observed significant positive correlations between sodium intake (measured by 24 hour UNaV) and individuals' systolic, diastolic, and mean blood pressure. This finding was further supported across populations, and the level of 24 hour UNaV was seen to correspond with age dependent increases in systolic blood pressure. Conversely, potassium intake was inversely related to blood pressure. Independent from electrolyte analysis, body mass index was also seen to significantly relate to patients' blood pressure. (5,6)

Although the Intersalt data provide expansive population-based insight regarding few dietary and lifestyle determinants of blood pressure, there still remains a necessity for more accurate predictive models to better identify patients at risk for developing hypertension. Data published from this study were further analyzed to examine the correlations between different laboratory and examination methods and systolic as well as diastolic blood pressure.

Methods:

Results from the Intersalt study published in 1988 (7,8) were used for data analysis. As mentioned above, data summarized from approximately 200 subjects studied from the 52 centers were copied from published reports and placed into an Excel database (Office 2013 Microsoft). These data were subsequently imported into Matlab™ (R2014, The Mathworks, Inc.) for linear regression analysis. These data included 24 hour urine sodium excretion, 24 hour urine potassium excretion, 24 hour urine creatinine excretion, BMI calculated as the weight in kg/height in meters^2 and systolic, diastolic and mean blood pressure all determined as described in the published Intersalt methods. (5) Since the data consists of means, the regression methods used are an estimation of the average of the means with standard error of means. Within Matlab™, stepwise linear regression was performed with the stepwise routine resident within the Statistics Toolbox. The ratio of explained variance to total variance adjusted for the variable range (adjusted R2) was used as an index of correlation. Statistical significance was reported at the $p<0.05$ and $p<0.01$ levels.

Results:

As previously shown, we found strong linear relationships between systolic blood pressure and 24 hour urine sodium excretion (adjusted r2=26.3, p<0.01) and BMI (adjusted r2=26.5, p<0.01). Creatinine excretion had an even stronger positive correlation with systolic blood pressure (adjusted r2 = 44.3, p<0.01) but surprisingly, the ratio of BMI to creatinine excretion had an inverse, strong correlation with systolic blood pressure (adjusted r2 = 34.0, p<0.01). This variable was developed to provide some index of "fatness/obesity", i.e., size that was inversely dependent on creatinine excretion (body weight per unit surface area per unit excretion of creatinine), the latter being a well-known correlate to muscle mass. This is seen clearly on the scatterplots shown in Figure 1. This inverse correlation may also be secondary to a complex interplay between body weight, body composition, surface area and urinary creatinine excretion. Since persons with greater weight have an increased surface area, too, that might interfere in the calculation of the ratio. In addition, persons with greater surface area may also have greater associated increase in muscle mass.
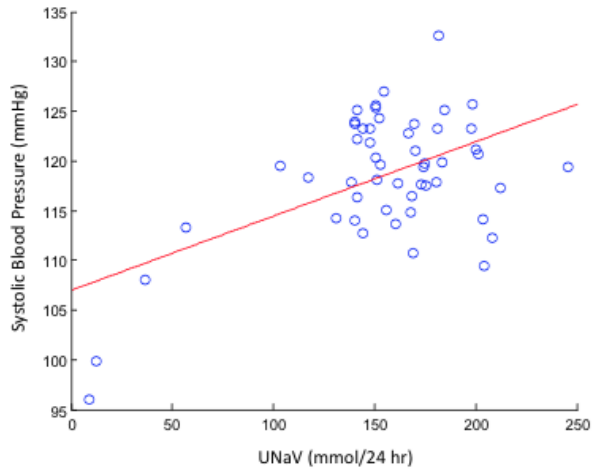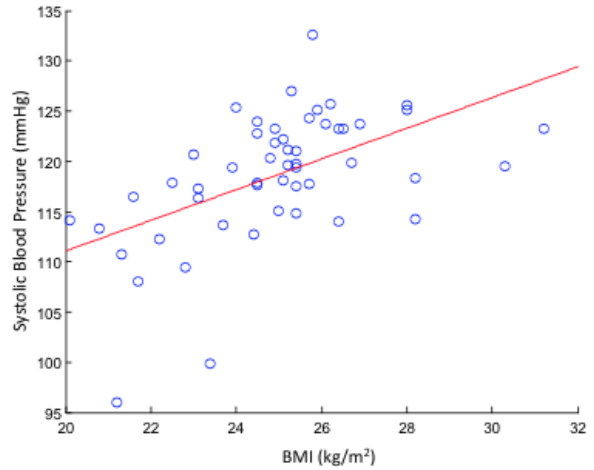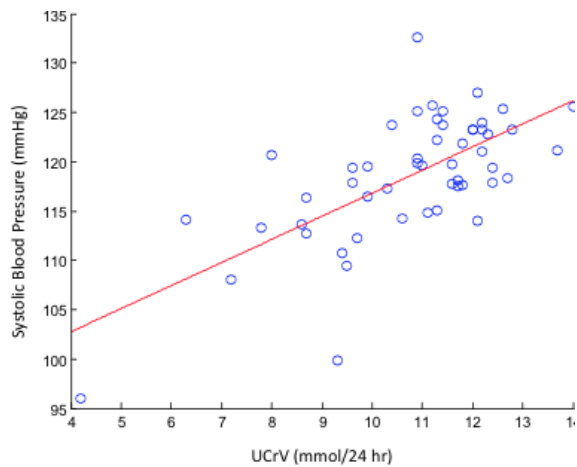
Figure 1a

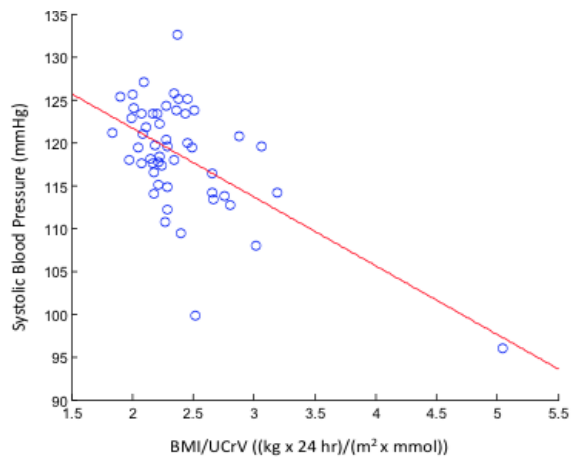**Figure 1b**

Figure 1c

Figure 1d

**Figure 1.** Panel A shows the scatterplot from the 52 centers of systolic blood pressure (mmHg) against urinary sodium excretion (UNaV, mmol/24 hr). Panel B shows systolic blood pressure against BMI (kg/m2). Panel C shows systolic blood pressure against urinary creatinine excretion (UCrV, mmol/24 hr). Panel D shows the plot of systolic blood pressure against the ratio of BMI/UCrV ((kg x 24 hr)/(m2 x mmol)).

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Figure 2a

Figure 2a.
Panel A shows the plane of prediction of systolic blood pressure from BMI and UNaV. Both prediction plane and scatterplot of data are shown.
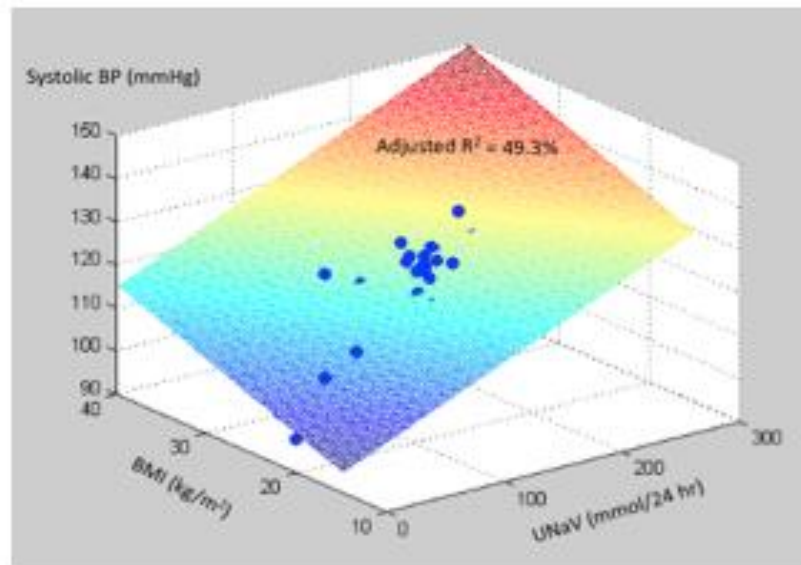
Figure 2b

Figure 2b.
Panel B shows the plane of prediction of systolic blood pressure from UCrV and UNaV. Again, both prediction plane and scatterplot of data are shown.
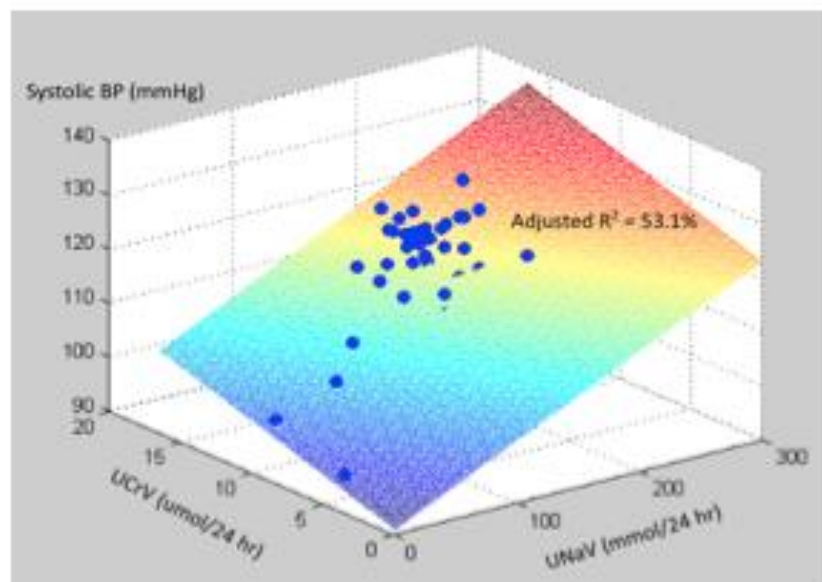
Urinary sodium excretion and BMI had no correlation (data not shown) and the combination of these two produced a predictive plane that explained 49.3% of the variance in systolic blood pressure (Figure 2a). Urinary sodium excretion also did not correlate with creatinine excretion, and the predictive plane generated by a linear combination of these variables predicted 53.1% of the variance in systolic blood pressure (Figure 2b). After either combining with urinary creatinine excretion, BMI and urinary sodium excretion or the ratio of urinary creatinine excretion to BMI, BMI and urinary sodium excretion predicted 55.7% of the variance in systolic blood pressure among the centers participating in the Intersalt study. Urinary potassium excretion was a poor predictor of systolic blood pressure Prediction of diastolic blood pressure

and mean arterial pressure was quite similar to that seen with systolic blood pressure (Table 1). Combining urinary creatinine and sodium excretion with BMI led to a prediction of just under 50% for diastolic blood pressure (adjusted R2 = 48.8%) and mean arterial pressure (adjusted R2= 57.3%). Pulse pressure was less well predicted by the variables studied (Table 1). Interestingly, the change in systolic blood pressure with age was predicted satisfactorily by urinary sodium excretion (Table 1), but no other variables either correlated well on their own or added to the prediction of urinary sodium excretion in a stepwise analysis.

Table 1: Correlation between major determinants of blood pressure

	UNaV (mmol/24 hr)	BMI (kg/m^2)	UCrV (mmol/24 hr)	UKV (mmol/24 hr)	BMI/UCrV (kg x 24 hour/mmol x m^2)
Systolic Blood Pressure (mmHg)	26.3**	26.5**	44.2**	NS	34.1**
Diastolic Blood Pressure (mmHg)	16.6**	28.2**	42.6**	NS	25.6**
Pulse Pressure (mmHg)	12.7**	NS	10.0*	NS	12.7**
Mean Arterial Pressure (mmHg)	22.7**	30.6**	47.9**	NS	32.2**
BP/Age (mmHg/year)	28.0**	NS	NS	NS	NS

NS implies adjusted R^2 has p value > 0.05. * $p<0.05$, ** $p< 0.01$

Discussion:

The Intersalt study may be among the most reviewed and critiqued studies of blood pressure determination ever. If one performs a PubMed search on the term "Intersalt", 102 papers come up. The "main" report from this study (8) has been cited well over 1000 times. With such extensive coverage, it seemed unlikely we would see anything truly novel from this data set.

As others had noted with this population, we found that sodium intake, reflected by the amount of urinary sodium excretion and BMI correlated well with systolic, diastolic and mean blood pressure among the centers studied. (7) Of interest but not terribly surprising, the combination of BMI with urinary sodium excretion provided for an even better predictive model. In addition to the Intersalt study, a number of studies have found positive relationships between both BMI or sodium intake and blood pressure in different populations. (9-17) Alternatively, combining urinary sodium excretion with creatinine excretion, an index of muscle mass, also predicted blood pressure better than either variable alone. Combining urinary sodium and creatinine excretion with BMI led to a predictive model explaining about 50% of the variance in systolic, diastolic and mean blood pressure among the centers. We must clearly state that the quality of

the prediction with this population is greater than we would observe among individual patients as each center participating in Intersalt averaged 200 subjects with each measurement. (8)

What was quite surprising was the artificial variable we created. We looked at a ratio of BMI to urinary creatinine excretion with the idea that such a ratio would be a measure of size due to adipose rather than muscle tissue. Creatinine is believed to form from the non-enzymatic breakdown of creatine which is present largely in muscle tissue and thus, creatinine excretion has been used to infer muscle mass. (20) It was our initial thinking that since both BMI and waist circumference both correlate with blood pressure, the adiposity of the patients rather than their size would be more dominant. (11,18,19) In other words, we had the initial prejudice that muscle mass might be a "good thing" regarding blood pressure whereas adipose would likely be "bad." This, however, is not what our analysis would suggest. That said, we should stress that the ratio of BMI/UCrV was a construct of our imagination, and, to the best of our knowledge, has not been subjected to validation. We should also stress that although we used urinary creatinine excretion as an index of muscle mass to formulate this construct, we acknowledge that this may be an oversimplification. Specifically there are racial and gender differences in creatinine excretion which suggest that this variable may have determinants other than muscle mass.

If we take it on faith that muscle mass corresponds more to blood pressure than adiposity, there may be some physiological basis. Some years ago, studies in the laboratory of Brenner suggested that protein intake induced glomerular hyperfiltration and hypertension which, in turn, led to progressive renal injury. (21,22) It is not beyond speculation that blood pressure might be a marker for such renal injury in patients consuming more protein as this is a likely companion for increased muscle mass. (23-25) However, our observation with the Intersalt data taken at face value suggests that muscle mass (and presumably protein intake) convey essentially all of the blood pressure risk of increased size. Clearly, work with other data bases will need to be performed to further explore this surprising finding.

As other investigators have noted, the dietary intake is actually better correlated with the change in systolic BP with age than it is with systolic BP alone. Specifically, the association between systolic blood pressure and urinary sodium excretion loses significance if one excludes the four low salt intake centers whereas an association between age dependent change in systolic blood pressure and urinary sodium excretion is not so sensitive. This is consistent with ideas related to adverse consequences of hormones involved in sodium excretion such as cardiotonic steroids also known as digitalis like factors. (26,27) While a failure to find a correlation doesn't exclude a relationship, the lack of correlation between BMI, UCrV and the ratio of BMI/UCrV with age dependent change in systolic blood pressure does argue against our proposed theory.

Limitations

The major limitation is that the published Intersalt data set is limited to the use of mean values from the different participating centers. This certainly limits variance and potentially obscures correlations which might have been significant while potentially exaggerating the relationship between other variables. We are therefore most interested in whether other data sets that includes 24 hour creatinine excretion, BMI and systolic BP validate our intriguing observation.

Acknowledgements:

References:

1.   Segal-Lieberman G, Rosenthal T. Animal models in obesity and hypertension. Current hypertension reports 2013;15:190-5.
2.   Landsberg L, Aronne LJ, Beilin LJ, et al. Obesity-related hypertension: pathogenesis, cardiovascular risk, and treatment--a position paper of the The Obesity Society and The American Society of Hypertension. Obesity 2013;21:8-24.
3.   Summers LK, Samra JS, Humphreys SM, Morris RJ, Frayn KN. Subcutaneous abdominal adipose tissue blood flow: variation within and between subjects and relationship to obesity. Clinical science 1996;91:679-83.
4.   Hall JE. Pathophysiology of obesity hypertension. Current hypertension reports 2000;2:139-47.
5.   INTERSALT Study an international co-operative study on the relation of blood pressure to electrolyte excretion in populations. I. Design and methods. The INTERSALT Co-operative Research Group. J Hypertens 1986;4:781-7.
6.   Elliott P, Stamler R. Manual of operations for "INTERSALT", an international cooperative study on the relation of sodium and potassium to blood pressure. Controlled clinical trials 1988;9:1S-117S.
7.   Sodium, potassium, body mass, alcohol and blood pressure: the INTERSALT Study. The INTERSALT Co-operative Research Group. Journal of hypertension Supplement : official journal of the International Society of Hypertension 1988;6:S584-6.
8.   Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. Bmj 1988;297:319-28.
9.   Rodrigues SL, Souza Junior PR, Pimentel EB, et al. Relationship between salt consumption measured by 24-h urine collection and blood pressure in the adult population of Vitoria (Brazil). Braz J Med Biol Res 2015;48:728-35.
10.   Campanozzi A, Avallone S, Barbato A, et al. High sodium and low potassium intake among Italian children: relationship with age, body mass and blood pressure. PLoS One 2015;10:e0121183.
11.   Grimes CA, Baxter JR, Campbell KJ, et al. Cross-Sectional Study of 24-Hour Urinary Electrolyte Excretion and Associated Health Outcomes in a Convenience Sample of Australian Primary Schoolchildren: The Salt and Other Nutrients in Children (SONIC) Study Protocol. JMIR Res Protoc 2015;4:e7.
12.   Lelong H, Galan P, Kesse-Guyot E, Fezeu L, Hercberg S, Blacher J. Relationship between nutrition and blood pressure: a cross-sectional analysis from the NutriNet-Sante Study, a French web-based cohort study. Am J Hypertens 2015;28:362-71.
13.   Siervo M, Lara J, Chowdhury S, Ashor A, Oggioni C, Mathers JC. Effects of the Dietary Approach to Stop Hypertension (DASH) diet on cardiovascular risk factors: a systematic review and meta-analysis. Br J Nutr 2014:1-1
14.   Woodruff SJ, Fryer K, Campbell T, Cole M. Associations among blood pressure, salt consumption and body weight status of students from south-western Ontario. Public Health Nutr 2014;17:1114-9.
15.   Singh RB, Fedacko J, Pella D, et al. Prevalence and risk factors for prehypertension and hypertension in five Indian cities. Acta Cardiol 2011;66:29-37.
16.   Ortega RM, Lopez-Sobaler AM, Ballesteros JM, et al. Estimation of salt intake by 24 h urinary sodium excretion in a representative sample of Spanish adults. Br J Nutr 2011;105:787-94.
17.   Venezia A, Barba G, Russo O, et al. Dietary sodium intake in a sample of adult male population in southern Italy: results of the Olivetti Heart Study. Eur J Clin Nutr 2010;64:518-24.
18.   Haghighatdoost F, Sarrafzadegan N, Khosravi A, et al. Is the association between salt intake and blood pressure mediated by body mass index and central adiposity? Arch Iran Med 2013;16:167-71.
19.   Hoffmann IS, Cubeddu LX. Salt and the metabolic syndrome. Nutr Metab Cardiovasc Dis 2009;19:123-8.
20.   Heymsfield SB, Arteaga C, McManus C, Smith J, Moffitt S. Measurement of muscle mass in humas: validity of the 24-hour urinary creatinine method. The American journal of clinical nutrition. 1983;37(3):478-94.
21.   Brenner BM. Nephron adaptation to renal injury or ablation. Am J Physiol 1985;249:F324-37.
22.   Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. Am J Physiol 1981;241:F85-93.
23.   Moore DR. Keeping older muscle "young" through dietary protein and physical activity. Adv Nutr 2014;5:599S-607S.

24. Deutz NE, Bauer JM, Barazzoni R, et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr 2014;33:929-36.
25. Atkins JL, Whincup PH, Morris RW, Wannamethee SG. Low muscle mass in older men: the role of lifestyle, diet and cardiovascular risk factors. J Nutr Health Aging 2014;18:26-33.
26. Xie JX, Shapiro AP, Shapiro JI. The Trade-Off between Dietary Salt and Cardiovascular Disease; A Role for Na/K-ATPase Signaling? Front Endocrinol (Lausanne) 2014;5:97.
27. Dial L, Liu J, Shapiro JI. Cardiotonic steroids in adaptation to dietary salt intake. Curr Clin Pharmacol 2014;9:298-309.