Low-Salt Diet and Diuretic Effect on Blood Pressure and Organ Damage

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Abstract. This review focuses on some aspects of the complex relationship among dietary salt intake, BP, organ complication, and genetic factors. First, the reason regarding the debate in the effect of a low-salt diet on BP and organ damage is discussed. Certainly, the lack of controlled long-term studies, taken together with the opposite effect of a low-salt diet on cardiovascular risk factors, justifies the contrasting opinions about the opportunity to reduce the sodium (Na) content in the diet of the general population. Second, the contribution that the genetic polymorphisms may furnish to explain the BP response in studies that apply either a moderate or a brisk reduction of salt intake is considered. Finally, the long-term effects of diuretics that produce a decrease in body Na similar to that achieved by moderate long-term dietary salt reduction are examined. Diuretics are able to reduce organ complications in the general population. However, these beneficial effects may be the net results of opposite effects in a subset of patients. Recently, the results of an observational study on hypertensive patients who were treated with a variety of antihypertensive drugs have been published. These results show that in carriers of the 460Trp ADD1 allele (38% of the population), the administration of diuretics halves the incidence of myocardial infarction and stroke when compared with other antihypertensive treatments that produce similar reduction of BP. These data support the notion that matching of the genetic mechanism with the drug mechanisms of action produces a clear therapeutic benefit.

Several decades of debate on the opportunity to reduce the dietary sodium (Na) content to lower BP in the general population have not yet produced any definitive conclusion (1,2). Some authors believe that the reduction is useful; others disagree. This debate is kept alive by the lack of a long-term controlled study showing that the reduction of dietary Na can lower not only BP but also the organ complications associated with it (3). This demonstration is crucial, because a low-salt diet may produce a moderate decrease in BP, but this effect is associated with an increase of other risk factor such as sympathetic activity; rennin-angiotensin-aldosterone system (RAAS) activation; and increase in cholesterol, triglycerides, and insulin resistance (4). Therefore, the beneficial effect of lowering BP must be weighed against the increase of these cardiovascular risk factors. The results so far obtained with diuretics may be useful in this regard, because diuretics produce a decrease of body Na similar to that achieved by the low-salt diet and increase the cardiovascular risk factors in parallel with the fall in BP. It is proved that diuretics are able to reduce organ complications when administered for a sufficiently long period of time (5), even though their effect on risk factors seems particularly evident only in a subset of patients who do not respond with a fall in BP (6). Therefore, it is likely that the benefits on organ complications demonstrated on the overall population of hypertensives results from opposite effects in subsets of patients. No data are available in this regard for dietary salt restriction, which certainly differs from diuretics as far as the mechanism of reduction of body Na is concerned. However, some heterogeneity among subsets of patients has been reported concerning the ability of this maneuver to increase cardiovascular risk factors (7). Similarly, heterogeneity in the magnitude of BP decrease under a low-salt diet is observed in individual subjects (8). The benefits on organ complications theoretically could be expected by reducing salt intake in subsets of patients who exhibit a significant fall in BP associated with a minimal change in the cardiovascular risk factors. For instance, the activation of the RAAS system with a low-salt diet has been considered a phenomenon that may limit the BP fall (9) and also the ability of this intervention to protect from organ damage. In fact, it has been proposed that both Na⁺ depletion by activation of RAAS and Na⁺ load, per se, may increase reactive oxygen species (ROS) production that is considered an important mechanism of organ damage (10). Therefore, for minimizing ROS activation, an optimal set point of body Na must be achieved in the individual patient (10) (Figure 1). Clearly, we do not have the appropriate measurements to assess this set point in individual patients or in a subgroup of them. Therefore, we may try to evaluate the effects either of diuretics or of reduction in dietary Na⁺ in different genetic and environmental backgrounds. Even though the application of the genetic methods to these phenomena is at its infancy, there is no any alternative approach for defining the individual characteristics of the patients as far as the response
to variations in body Na is concerned. In fact, all previous studies based on various indexes of RAAS activity failed to furnish conclusive data about this issue. Because the available published data are contrasting, it is important to assess to what extent this confusion may arise because of weaknesses in the experimental design or interpretation of the data.

Considering the BP changes after the reduction of dietary Na, examining the genotype-BP relationship, two type of studies can be considered: 1) studies that applied a moderate reduction of Na intake for a relatively long period of time (≥2 mo) (11–13) and 2) studies that produce a brisk (within 24 h) large reduction of Na intake (from the normal-salt diet of 150 to 200 mmol NaCl to 50 or lower) for a short period of time (≤2 wk) (14–16). It has been demonstrated that the latter protocol produces several physiologic modifications that, per se, may affect the genotype BP response relationship. In fact, a recent careful study (17) examined the relation between the pressor response and GFR to angiotensin I and II at normal- and low-salt diet (50 mmol for 1 wk) according to the angiotensin-converting enzyme (ACE) I/D genotypes. The results demonstrate that the BP response to angiotensin II is not affected by the genotype or by the reduction in Na intake. Conversely, the DD-ACE carriers show a greater pressor response to angiotensin I than the II ACE carriers, when measured at normal-Na diet, but this genotype-dependent responsiveness to angiotensin I disappears at low-salt diet (Figure 2).

Thus, the RAAS activation consequent to this abrupt and large reduction of Na intake blunts the genotype influence of the generation of angiotensin II from angiotensin I. The low-salt diet also increases the expression of Na⁺ transporters in tubular cells, thus affecting the overall renal Na reabsorption capacity (18,19). Besides the two changes illustrated above, a low-salt diet increases sympathetic activity and catecholamine, insulin resistance, and plasma lipids (4).

The crucial question is whether the velocity, magnitude, and duration of the dietary Na decrease may affect, per se, the influence of genotype on BP fall. Considering, for instance, the angiotensinogen polymorphism, the genotypes that increase the production of this protein are associated with a greater fall in BP or a lower incidence of hypertension when mild reduction in Na diet is adopted for a relatively long period of time (11–13). This finding is consistent with the observation that chronic infusion of suppressor doses of angiotensin II are able to transform a Na-resistant dog to a Na-sensitive one (20).

Conversely, carriers of the angiotensinogen genotypes associated with a lower plasma level of this protein experience a large fall in BP, when a much greater reduction in Na intake is applied, for a short period of time (14–16). Thirty years of studies regarding the relation between RAAS and body Na on BP regulation yielded data that may be consistent with both types of genetic influences. Namely, a moderate steady-state activation of RAAS may increase the BP response to body sodium reduction, as mentioned above (20), or, conversely, the RAAS activation may limit such a fall if it exceeds a critical level (9).

The BP effect of diuretics is certainly more comparable to that achieved by moderate, long-term dietary Na reduction, even though other differences may occur between the two types of interventions. From this point of view, the magnitude of BP fall with diuretics is associated with those gene variants that tend to increase Na reabsorption (21) with some influence of other factors such as age, gender, and race (22,23).

However, it would be naive to consider only the relationship between the cellular effects of the genotype (e.g., the increase in Na transport across renal tubules associated with 460Trp ADD1 or G Protein β3 subunit 825T alleles) and the cellular effect of the intervention such as the reduction in (I) renal tubular reabsorption with diuretics or (2) reduction in the availability of dietary Na. As pointed out above, many counterregulatory mechanisms may limit or affect the BP response to these interventions; therefore, other genotypes may be involved. For instance, when the BP response to diuretics in never-treated hypertensive patients is analyzed (21), the responders (mean BP fall ≥15 mmHg) were 14% in Gly/Gly ADD1 carriers compared with 38% in Gly/Trp +Trp/Trp ADD1 carriers (previous data show that carriers of the latter genotype have an increased tubular Na reabsorption compared with the former). When the I/D ACE genotypes are also taken into account, these values became 4 and 47%, respectively.

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**Figure 1.** Relationship between salt consumption and reactive oxygen species (ROS). A random distribution is suggested in the relationship between salt consumption and ROS production. However, the distribution may depart from random by being skewed toward low (left) or high (right) salt consumption. An individual’s salt consumption, yielding the least accumulation of oxidative end products (arrow), would reflect the genetic makeup of an individual and environmental factors. (Reprinted from reference 10, with permission.)
The II ACE genotype favors the BP fall, and the DD genotype contrasts it. Although these data must be confirmed by larger studies, they are consistent with the idea that the genetic influence underlying the counterregulatory mechanisms must also be taken into account.

Considering all of the above-mentioned factors affecting different directions the magnitude of the global cardiovascular risk and the lack of solid data on the long-term effects of the reduction of dietary Na on cardiovascular complication, the persistence of the debate and the uncertainty about the beneficial effect of a low-salt diet are not surprising. Again, from the experience on diuretics, some information along this direction may be obtained.

Recently (24), the results of an observational study on 1038 hypertensive patients who were followed for approximately 10 yr and treated with a variety of antihypertensive drugs have been published (Figure 3). These results show that in carriers of the 460Trp ADD1 allele (38% of the population), the administration of diuretics halves the incidence of myocardial infarction and stroke when compared with other antihypertensive treatments that produce a similar reduction of BP. The selective beneficial effect of diuretics over the other drugs was not present in carriers of the Gly/Gly ADD1 genotype. These data support the notion that matching of the genetic mechanism with the drug mechanisms of action produces a clear benefit probably because the magnitude of the counterregulatory mechanism, hence the global cardiovascular risk, may be minimized. Before a widespread clinical application, these findings need additional confirmation on a large cohort of patients.

In conclusion, the available data do not support the notion
that a widespread application of a low-salt diet to the general population will result in the reduction of organ complication even though a mild reduction in BP may be obtained. Of course, this conclusion does not contradict the very large body of data, either experimental or clinical, supporting the view that an excess of Na in the diet may be harmful both to BP and to organ damage. In the authors’ opinion, a dietary Na context fluctuation of approximately 100 to 130 mmol/d must be applied to hypertensive patients.

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References

5. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blockers vs diuretic. JAMA 288: 2981–2997, 2002