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.
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.
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

![Figure 2. Mean BP (MAP) responses to infusions of angiotensin I and angiotensin II with a low sodium (□) and liberal sodium (■) diet according to angiotensin-converting enzyme genotypes. (Reprinted from reference 17, with permission.)](image)

![Figure 3. Incidence of myocardial infarction (MI) and stroke during 10-yr follow-up in treated patients with hypertension according to the adducin genotype and the inclusion of diuretics into the antihypertensive treatment. (Reprinted from reference 24, with permission.)](image)
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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