Pendrin abundance was observed in aldosterone-infused animals. Additionally, chloride's role was highlighted during an oral kidney session at the conference. Dr. Puyol (Buenos Aires, Argentina) presented the effect of the anion chloride on the induction of oxidative stress on a high-salt diet. This revealed the chloride anion was associated with more glutathione peroxidase activity than the sodium cation in the kidney cortex, favoring a prooxidative state.

Outside of the kidney, Dr. Constantino Iadecola (NY, USA) revealed the mechanisms associated with high salt intake and cognitive impairment. In animal studies, high salt, independently of blood pressure levels, induces endothelial dysfunction in the brain. This process is mediated by IL-17 generated in TH17 lymphocytes at the intestine, highlighting the role of the gut-brain axis. Thus, IL-17 in cerebral arteries decreases endothelial nitric oxide synthase (eNOS), decreasing cerebral blood flow but also increasing accumulation of

the phosphorylated Tau protein. These elegant studies showed that the salt-induced Tau protein, induced by high salt, and not decreased blood flow, induced the cognitive impairment. Thus, future clinical trials should translate these findings to prevent cognitive impairment in patients.

Overall, the ESH-ISH Meeting has contributed new concepts and translational evidence on the role of a high-salt diet in hypertension and hypertension-mediated organ damage.

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Salt and Hypertension – Clinical Aspects

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The clinical importance of high blood pressure has been recognized for almost two centuries now¹ but its etiopathogenesis is still a matter of continuing intense research. Although effective treatment is available, control of blood pressure (BP) remains a global challenge and hypertension continues to be the main risk factor for morbidity and mortality around the world². The simplified and concise 2020 International Society of Hypertension Global Hypertension Practice Guidelines will harmonize the management for worldwide healthcare providers³ while the search for more effective ways of preventing and controlling hypertension continues. It is well established that the onset of hypertension may be prevented, or at least delayed, by healthy lifestyle choices⁴, which is also the first line of antihypertensive treatment.

Salt intake is considered the most important dietary risk factor for hypertension, and, in fact, a large body of evidence supports the strong association between high Na intake and raised BP⁵. Nevertheless, the susceptibility to the BP-raising effects of salt, called salt sensitivity of BP (SSBP), is a physiological quantitative trait that varies between individuals and the mechanisms that mediate the pressor effects of salt are not fully explained⁶. Furthermore, although the associations between high sodium intake and increased BP as well as between hypertension and cardiovascular (CV) morbidity and mortality are well established and undisputed, the question of impact of dietary salt reduction in hard CV outcomes (stroke, myocardial infarction or death) remains unanswered, with several studies presenting opposed results⁵. As

such, it remains a matter of continued attention and discussion. Recently, Professor Franz Messerli and colleagues analysed the relationship between sodium intake and life expectancy and survival⁷. Global health estimates of 181 countries were used to analyse the relationship between country-specific average sodium consumption with healthy life expectancy (at birth and at 60 years), death due to non-communicable diseases and all-cause mortality for the year of 2010. The authors found a positive correlation between sodium intake and healthy life expectancy (including when the analysis was restricted to 46 high income countries) but not for death due to non-communicable diseases. An inverse correlation with all-cause mortality was also observed. Though such findings suggest that high sodium intake does not shorten life span or increase premature death, a large number of potential confounders and several other limitations of the study, as well acknowledged by the authors, preclude its use as a guide for nutritional interventions. Unfortunately, conducting an adequate trial to evaluate the lifespan effect of high dietary salt in humans, which could raise definitive evidence on hard CV outcomes and mortality, is very difficult, requiring a large sample of the population, followed for a long time, with strict control of several variables. Based in current evidence, the World Health Organization recommends a daily salt intake <5 g⁸. In fact, SSBP is considered an important public health problem, independently of BP^{6,9} but the lack of clear mechanisms and biomarkers for this trait prevents the identification of individuals at higher risk, who could benefit from early intervention.

Promising results were presented at the joint meeting ESH-ISH 2021. Chen C. and colleagues, based on bioinformatics approaches, identified several potential biomarkers of SSBP, though pending confirmation in humans¹⁰. On the other hand, an emerging new scientific view states that the problem in SSBP is not the level of salt in the diet but an abnormal BP response to salt. Opposing to previous knowledge that there is an impairment in renal function, recent studies have shown that the changes in sodium balance and cardiac output in salt-sensitive (SS) individuals are no different from those in salt-resistant normotensives. Instead, there is an abnormal vascular resistance response to high salt intake ("vasodysfunction theory"). In effect, Professor Kurtz and colleagues argued that instead of reducing salt in food, what should be corrected is the mechanism causing such abnormal response. Taking into account

previous evidence showing that in SS individuals there is an abnormal reduction of nitric oxide activity that impairs vascular relaxation leading to hypertension, their studies showed that the administration of small amounts of nitrates (in the form of sodium nitrate or beetroot juice) and nitrite (in the form of sodium nitrite) protects against salt induced increases of BP, in Dahl salt sensitive rats and Spontaneously Hypertensive Stroke Prone (SHRSP) rats, respectively¹¹. Tiny amounts of nitrate protected against large amounts of salt, with nitrates appearing to be 100 times more potent than potassium for protecting against salt-induced hypertension. Accordingly, salty food fortification with small amounts of nitrate-rich vegetable extracts was proposed as a strategy to prevent salt-induced hypertension without changing the diet.

Though this may be a way forward to protect against the effects of high salt intake in BP, what was not evaluated in these studies and should be considered when designing public health interventions and in future research, is that increasing BP is not the only deleterious health effect of high salt intake. It has been shown that salt can damage target organs by several other pathways, being independently associated to the risk of numerous other important public health problems¹². In practice, the ideal strategy would require the identification of the SS individuals and the main mechanisms of salt-induced hypertension in their specific settings (accounting for the influence of ethnicity and culture in the BP response to salt), to inform tailored interventions. Presently, no simple, accurate and widely accepted method of estimating dietary sodium intake and no clear guidance as to how to manage the patient are available. Pending further evidence, for the health professional in front of the patient, the use of questionnaires to assess individual salt intake, such as the one presented by Bortolotto L. et al (sodium consumption questionnaire with photographic manual), is an accessible alternative to the 24-hour urinary collection and can guide individualized dietary advice. It could be adapted and validated for specific contexts.

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