

ПРОБЛЕМНАЯ СТАТЬЯ

DIETARY SALT IN THE WHIRL
OF NUTRITIONAL SCIENCE, PUBLIC HEALTH
AND FOOD PROCESSING INDUSTRY

Berislav Momčilović

Institute for Research and Development of the Sustainable Ecosystems (IRES),
Srebrnjak 59, 10000 Zagreb, Croatia

ABSTRACT. Background. The story about publishing a novelty in nutritional sciences is presented. Short-term biological indicator of urinary Na and K excretion is generally used to assess Na and K dietary exposure. In this study, we used the long-term biological indicator tissue of hair to assess Na and K nutritional status.

Methods. Hair Na and K were analyzed in 1073 healthy white adult Caucasians [734 women (♀) and 339 men (♂)] with the ICP MS. The log transformed data were analyzed with median derivatives bioassay.

Results. The median values ($\mu\text{g}\cdot\text{g}^{-1}$) were ♀Na 254 and ♂Na 371, and ♀K 74.3 and ♂K 143, respectively. The linear (adequate) ranges of the sigmoid saturation curve ranges for sodium were ♀Na 55.6–1307 and ♂Na 84.0–1450, whereas these ranges for potassium were ♀K 18.9–46.7 and ♂K 25.8–107.9. The strict homeostatic control of whole blood K and Na renders them unsuitable for assessing nutritional status. The potassium to sodium ratio (K/Na) in women appears stable across the sigmoid linear segment range, contrary to the constantly increasing of K/Na ratio in men.

Conclusions. The results suggest how hair Na concentration should not be below 55.6 and 84.0 or above 1307 and 1450 $\mu\text{g}\cdot\text{g}^{-1}$ in women and men, respectively. Similarly, hair potassium concentrations should be not below 18.0 and 25.8 and higher than 46.7 and 107.9 in women and men, respectively. Hair K/Na ratio should stay around 0.600 in men and 0.400 in women. Current general population dietary sodium exposure does not warranted for the general population dietary salt restriction; individual precision medicine is required.

KEYWORDS: potassium, sodium, hair, whole blood, nutritional status, dietary intake.

PROLOGUE

The idea on how the dietary salt acts as the etiological factor in the development of human hypertension was there since my student days at the Medical School in Zagreb back in 60th. My physical chemistry course taught the students how the sodium ions bond excessive amounts of water and that this increased volume induces the hypertension, i.e., the most common human cardiovascular disease. The obvious way to escape hypertension was thought to be to reduce the salt intake. Ever since, thousands of epidemiological studies were conducted on the entire Earth globe to prove how hypertension is related to the dietary salt intake, but the results were contradictory. Some groups of scientists showed that there is a relationship between the dietary salt and hypertension whereas the other groups of the equal credibility did not observe such effect. Even if we dismiss

the errors associated with measuring the blood pressure, many of linear extrapolation end points laid out of the directly measured observations; a No-No in the regression analysis. It should be noted that animal experiments clearly demonstrated the dietary salt induced hypertension with the doses tens of times above the normal human dietary salt intake.

Our study aimed to assess the human sodium and potassium nutritional status with the hair median derivatives bioassay (Momčilović et al., 2017). Our results on over a thousand subjects showed that sodium and potassium are deposited in the human hair and whole blood by following the sigmoid log curve. Indeed, we were able to demonstrate that sodium in the hair ($\mu\text{g}\cdot\text{g}^{-1}$) should be not below 55.6 for Women (W) and 84.0 for Men (M), or above 1307 for W and 1450 for M. Similarly, hair potassium normal range should be not below 18.9 for W and

* Corresponding author:
Berislav Momčilović
E-mail: berislav.momcilovic@gmail.com

25.8 for M or above 46.7 for W and 107.9 for M. For the first time it was possible to differentiate that there are subjects within the apparently adult healthy population who are consuming more salt (as was expected), but also that there were those who consumed the less dietary salt than should be considered necessary for them; a very novel observation. We also noted how men hair retained more Na than women and that the K/Na ratio was stable in women whereas it was increasing in men. However, there were no difference between Na and K in the whole blood between men and women. Evidently, the whole blood homeostatic control of K and Na is strictly regulated such that the concentrations of Na and K were higher in the whole blood than in the hair.

We submitted this manuscript to the prestigious New England Journal of Medicine (NEJM), and we got the manuscript rejection without a single word of the reviewing. Only the suggestion was given to try another journal. OK, NEJM is receiving thousands of the manuscripts every year and they all can't be published (they publish less than 1% of the submitted articles). Back to square one, we directed our efforts to the American Journal of Clinical Nutrition (AJCN). Here we have to wrestle with the elaborate submission instructions which have preconceived axiomatic assumptions which, I believe, are not consistent with the Goedel's proof (Naget et al., 2001). The AJCN and JN axiomatic submission protocol is good for repetitive type of research but it did not provide room for presenting new concepts or not to think "out of the box". A "cold shoulder" (rejection) again, with not a single word of a review, but with a suggestion to try another journal. The next choice was the Journal of Nutrition (JN) that have a copy paste instructions of the AJCN for manuscript submission. A new bitter cold rejection arrived with the note that they even did not submit the manuscript out to the reviewers. The rejection letter provided a new suggestion to try another more suitable journal.

In the meantime, an article appeared in the Nutrition Advancements entitled "A Systemic Review of Salt Reduction Initiatives around the World: A Midterm Evaluation of Progress Towards the 2025 Global Non-Communicable Diseases Salt Reduction Target" (Santos et al., 2021). It was quite clear that our efforts for the reliable assessment of the sodium and potassium nutritional status are on the direct collision course with the International dietary salt reduction activities. The authors took for granted that the amount of dietary salt in our diet is too high, and

that the whole developed world should aim to reduce dietary salt intake. It didn't matter that the idea of dietary salt induction of hypertension was never full proofed without a shadow of doubt. The same article informed us about the imperative that the food industry should decrease the level of salt to the diet. Moreover, as the sodium should be decreased, the dietary potassium should be increased. A whole new selection of processed foods (and with a new price tag), is now getting ready for the market (Murphy et al., 2021).

That news showed us not to give up but to try to bring our data to the public scrutiny. Indeed, we submitted our manuscript to the distinguished British Journal of Nutrition. After a long wait we finally got what we thought would be a decent review. However, the major objection was why we didn't measure Na and K in the urine instead in the hair. They claimed that assessing the Na and K urinary concentration, is the golden standard for assessing their metabolism in the human body. Practically, we were told to reject our innovative approach on how to assess the sodium and potassium nutritional status with hair median derivatives bioassay and to replace it with the "gold standard" method of measuring Na and K in the urine, i.e. the method which proved ineffective (non-conclusive) since the very start. We were amazed with such a review since we claimed to assess the sodium and potassium nutritional status by analyzing their content with the hair median derivatives bioassay. Whoever analyzed Na and K in the urine, as we did in another experiment, is well aware of the logistic hassle what is waiting for him (Momčilović et al., 1995). More important, the concentrations of Na under 135 mEq·L⁻¹ or above 145 mEq·L⁻¹ are good indicators of their respective lack or excess, but that the terms hyponatremia (low Na) and hypernatremia reflect the ratio of sodium to water and did not refer to an increase or decrease in total body sodium (Kaji, 1985). In short, judging the Na and K nutritional status by analyzing their content in the urine is to say that this is "a bridge too far" for their nutrition status assessment.

Here a new hypothesis is proposed about the origin of the essential hypertension, i.e., that the reduced function of the Na K ATPase which impedes cell capacity to expel the intracellular Na and diminish the K reentering the cells. Indeed, the complexity of Na and K moving in and out of our cells is far from being fully understood (Mita et al., 2021). This story is presented here to expose behind the scene activities of the leading nutritional journals if and

when they are influenced with the public health political voluntarism. Apparently, politicians need to show how they are working for the best public interest and what they may justify by allotting funds to science research in the years to come. The fruitful co-operation of science and politics is a very much desired situation, but not to subdue the new information on how to assess the Na and K nutritional status with a median derivatives bioassay. This is certainly not a path to follow. We should always stand “entangled” to the facts, not opinions

INTRODUCTION

Sodium and potassium are the principal extracellular and intracellular cationic elements of the human body, respectively (Gaw et al. 2004). However, the link between the habitual salt dietary intake and the general public health is still controversial (Emsley, 2003). Over the last decades, a plethora of studies informed us how excessive dietary salt intake is associated with hypertension and cerebral stroke (Mente et al., 2014; O'Donnel et al., 2014; Fillipiou et al., 2020), which led to the recent draconian recommendation for the general population for the dietary salt restriction (Institute of Medicine, 2005). However, the deeply echeloned crusade against what is now the habitual dietary salt intake is strongly criticized because of the flaws in many studies' statistical design and “cherry picking” of the data (Taube, 1998), that the basic tenants of the human physiology were either ignored or misinterpreted (Heaney, 2013) and there was too much bureaucratic political meddling in the salt restriction issues (McCarron, 2014).

The simple idea of how the reduction of sodium dietary intake may be a health protection measure for the general population against the development of hypertension and cerebral stroke is certainly a very appealing one. That idea has been tested by a vast number of authors who studied the relationship between blood pressure and dietary sodium and potassium intake and their urinary excretion (separately or in combination), which review is beyond the aim of this article. However, there are difficulties associated with the timing and assessing of the correct blood pressure readings (Kelly, McGrath, 1988) with the control of the complex dietary composition variability (Cade et al., 2004; Bankir et al., 2017), and how to adequately assess the dietary intake of either sodium or potassium (Xu et al., 2019; Dahm, 2020). Indeed, dietary sodium restriction in normotensive adults was followed by a heterogeneity of re-

sponses which were either increased, or decreased, or show no change (Miller, 1987).

The aim of this research is to assess sodium and potassium nutritional status by analyzing their frequency distribution in the hair and whole blood of adult men and women with a median derivatives bioassay (Momčilović et al., 2017). Today, a century old dictum “We are what we eat” may be modified to “Hair knows what we eat” (Ehleringer et al., 2020). Indeed, hair is the long-term biological indicator of the bioelement nutritional status, whereas urine is a short-term biological indicator (Momčilović et al., 2010). It should be noted that we used the term “bioelement” as a common denominator for the major elements such as Na and K, trace elements, and ultra-trace elements (Momčilović et al., 2017).

SUBJECTS AND METHODS

This prospective, observational, cross-sectional, and exploratory epidemiological study was approved by the Ethical Committee of the Institute for Research and Development of the Sustainable Eco Systems (IRES), Zagreb, Croatia. The study was conducted by adherence to the World Medical Assoc. Declaration of Helsinki on Human Subject Research (World Med Assoc, 1964). Every subject gave his/her written consent to participate in the study and filled out a short questionnaire on his/her health status and medical history (data not shown) (Oppenheim, 1992). Data on hair shampooing were also recorded and none declared the presence of the elements under observation.

Hair potassium and sodium were analyzed in a random sample of 1073 apparently healthy white Caucasian adults (339 men, 734 women). Whole blood K and Na were analyzed in a subset of 212 subjects (143 women and 91 men); the median age of women and men was 47 and 50 years, respectively. Our population consisted of subjects from the general Croatian population who were interested to learn about their health status; the majority of them were living in the capital city region of Zagreb, Croatia. All the subjects consumed their usual home prepared mixed mid-European diet, and none of them had reported an adverse medical health condition.

Hair K and Na and whole blood K and Na were analyzed with the inductively coupled plasma mass spectrometry (ICP-MS, Elan 9000, Perkin Elmer, Canada) at the Center for Biotic Medicine (CBM), Moscow, Russia. The CBM is an ISO Europe certified commercial laboratory for analyzing bioelements (electrolytes, trace elements, and ultra-trace

elements) in different biological matrices in health and disease. CBM is also a member of the exclusive External Quality Assessment of the UK Surrey scientific group for the quality control of trace element analysis. Hair K and Na analyses were performed following the International Atomic Energy Agency recommendations (International Atomic Energy Commission, 1980) and other validated analytical methods and procedures (Burgess, 2000).

Preparation of hair and whole blood for the ICP-MS analysis is already described (Momčilović et al., 2017). The detection limits for K and Na in the hair were 4.3 ppm for Na and 0.3 ppm for K, and in whole blood they were 0.6 ppm for Na and 0.04 for K. All chemicals were of pro analysis grade (Khimmed Sintez, Moscow, Russia).

To scrutinize the respective hair and whole blood potassium and sodium concentration frequency distribution, we used the median derivative bioassay of the log transformed data to fit the sigmoid logistic regression function (power function) (Momčilović et al., 2017; Heyes, 2017) for men and women separately:

$$A_2 + \frac{A_1 - A_2}{1 + (x/x_0)^p},$$

where A_1 is the initial value (lower horizontal asymptote), A_2 is the final value (upper horizontal asymptote), x_0 is the center (point of inflection) is the median (M_0 detected), p is power (the parameter that affects the slope of the area about the inflection point).

The OriginPro 8.0 data analysis and graphing software (OriginLab Corp., OriginPro Version 8.0., Northampton, MA) and IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA) was used for this analysis.

The deposition of a K and Na below the linear segment range of the sigmoid curve denotes a deficient hair uptake of K and Na; when their concentration is within the linear range segment that indicates safe and adequate hair K and Na uptake, and when K and Na concentrations are above the linear range segment of the sigmoid power curve, that denotes excessive level of their hair uptake (Finney, 1952). The central adequate linear segment of the sigmoid power curve may be further subdivided into low adequate, safe, and high adequate segments with a 30:60:10 ratio (Bray, 2020), but some other ratios may also be indicated. It is well known the body may adapt to the given nutrient intake so that balanced nutrition can occur at various dietary levels of the nutrients. Thus, sparse diets are not necessarily deficient ones, although they often are (Schutte, 1964).

RESULTS

To correct for the skewedness of the data, we log transformed the potassium and sodium hair and whole body concentration data for men and women separately. Such data transformation led to the classical Gaussian bell shaped frequency distribution. Hair potassium data frequency distribution for both men and women are shown in the upper left part of Fig. 1 whereas the data for sodium frequency distribution are shown in the lower left part of the same figure. Hair of both men and women gave higher concentrations of sodium than potassium. The hair sodium median concentrations were ($\mu\text{g}\cdot\text{g}^{-1}$) 371.5 for men (M, σ) and 254 for women (W, σ), whereas the comparative hair potassium concentrations were lower for both M-K 142.5 and W-K 73.7 (Fig. 2 Left). The median potassium to sodium ratio (K/Na R) was 0.385 for M and 0.298 for W, respectively (Table 1).

Table 1. **Changes of the Potassium/Sodium (K/Na) ratio in the hair ($\mu\text{g}\cdot\text{g}^{-1}$) of the linear segment of the sigmoid curve (Figs. 2A and 2B)**

Element	MEN (M)			WOMEN (W)		
	D ₂	Median	U ₂	d ₂	Median	u ₂
Potassium	10.3	155.9	1100.5	20.6	81.6	483.9
Sodium	91.2	364.3	1577.3	60.9	275.9	1377.2
K/Na	0.113	0.420	0.698	0.337	0.296	0.337

Note: d₂W Point Minimum of the Adequate linear region of the sigmoid curve for Women, D₂M ibid for men; u₂W Point Maximum of the Adequate linear region of the sigmoid curve for Women, U₂M ibid for men.

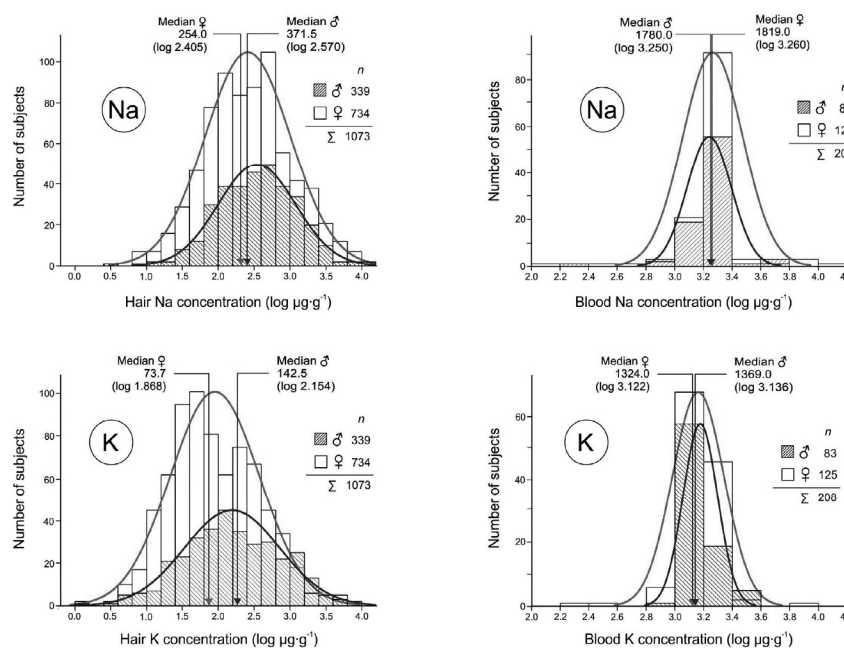


Figure 1. Gaussian hair and whole blood potassium and sodium distribution in women and men (log μg·g⁻¹)

Similarly, whole blood (WB) concentrations were also higher for sodium than potassium (Fig. 2 Right). WB medians for sodium were M·Na 1780 and W·Na 1819 μg·g⁻¹, whereas WB potassium medians were M·K 1369 and W·K 1324, respectively. The K/Na median ratios were M·K/Na 0.769 and W·K/Na 0.731 and they were almost identical with the overlapping CV intervals. It should be noted that WB potassium Gaussian distribution showed a tendency of slightly leaning to the right whereas, contrary to that, sodium showed a tendency to lean to the left, which indicates subtle sex potassium and sodium metabolic differences.

Our median derivatives bioassay allowed for transformation of the Gaussian bell shaped frequency distribution curves for hair potassium and sodium into their sigmoid saturation curves (Fig. 2. Lower Left) for K and for Na (Fig. 2. Upper Left). The sigmoid saturation curves started being linear at the points W·d3 and M·D3, but the linear upward trend started earlier in women than men. However, the linear segments for both man and women sigmoid curves for hair potassium would fuse again together at the upward point of W·u3 and M·U3. However, the linear range segments for hair sodium get merged much earlier at W·u1 and M·U1, respectively. We assume what this pattern suggests a tighter metabolic control of sodium than potassium in both men and women.

The median derivatives bioassay data for whole blood (WB) generated steep and narrow linear ranges for both sodium (Fig. 2 Upper Right) and potassi-

um (Fig. 2. Lower Right); the linear segments between men and women for the same bioelement were fully merged. However, potassium and sodium WB concentrations were both higher in men than women. The data demonstrated impressive homeostatic control of sodium and potassium in WB of both sexes, and that impedes their usefulness for assessing the dietary impact of both Na and K.

We also directly compared the relationship of hair Na to K concentrations over their linear range (Fig. 3). Indeed, we may assume that there is a difference in the degree of K and Na quantitative saturation along the hair fiber. Knowing that even sparse diets may be nutritionally adequate, we assume that the initial linear part of the sigmoid curve indicates the subclinical or low adequate nutritional response range. Therefore, we assumed that the 30–90% segment of the linear range of the sigmoid curve represents a truly adequate K and Na dietary intake range. Interestingly enough, the correlation coefficient r^2 was impressively high for individual potassium and sodium slopes, i.e., r^2 for M·Na was 0.948 and that for W·Na was 0.929, whereas r^2 for M·K it was 0.865 and W·K was 0.857. However, when comparative data for hair sodium were plotted on an X axis, and potassium data on Y axis, the combined r^2 correlation coefficient dropped to 0.487. This data indicate that there is a considerable homeostatic adaptability to the changes of the amount of Na and K available for their simultaneous deposition in the hair. Apparently, the constant and efficient homeostatic control of Na and K in the whole blood is ac-

accompanied with their highly variable concentrations in the hair, which acts as a river levee for water excess. Collected data showed a tempting impression on how hair Na and K tends to increase in women with aging whereas K and Na remained stable over the same time period (Fig. 4). Indeed, there was a significant age-dependent increase of sodium and

potassium in the hair of women (Spearman's correlation coefficient is 0.242, $p < 0.01$ for sodium, and 0.231, $p < 0.01$, for potassium), but not in men. Presumably, the number of men studied was too small to conclusively show the presumed age dependent increase of hair Na and K or we may be dealing with a problem of statistical inequality.

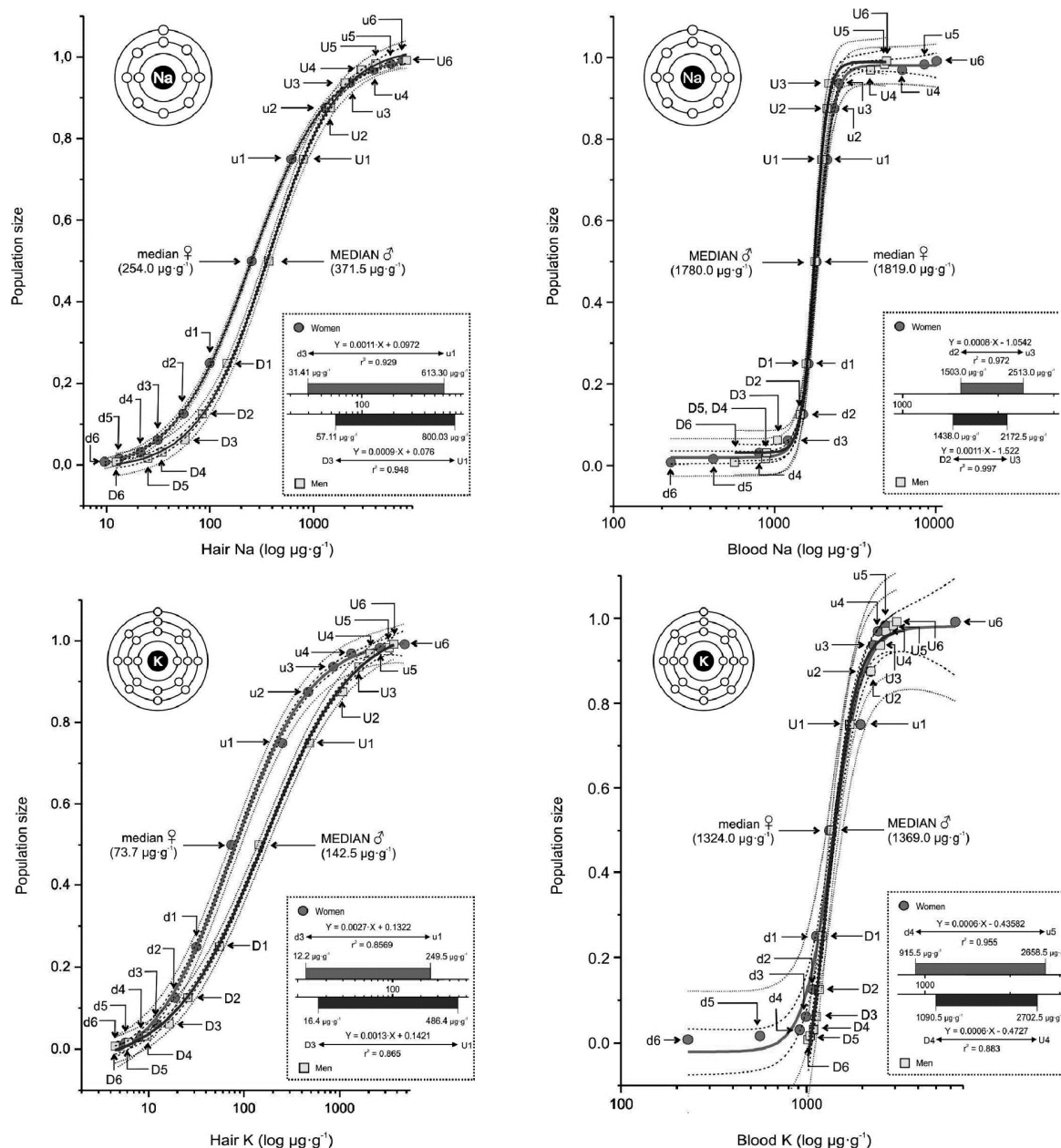


Figure 2. The power function sigmoid curve of hair median derivatives. The difference between the K-H median derivatives of men $n=339$ (■) and women $n=734$ (●). D, U men downward (D) and upward (U) median derivatives; d, u women downward (d) and upward (u) median derivatives.

Logistic function $Y = A2 + (A1 - A2) / (1 + (X/X_0)^p)$, -0.95 confidence limit, ... 0.95 prediction limit:

sodium: Men: $Y = 1.025 + (-0.011 - 1.025) / (1 + (X/363.95)^{1.302})$, $r^2 = 0.999$; women: $Y = 1.008 + (-0.018 - 1.008) / (1 + (X/247.73)^{1.179})$, $r^2 = 0.999$; Box:

Sodium linear saturation range for \bar{X} and \bar{X} (log conc):

B – Men: $Y = 1.045 + (-0.040 - 1.045) / (1 + (X/151.62)^{0.934})$, $r^2 = 0.999$; women: $Y = 1.006 + (-0.059 - 1.006) / (1 + (X/74.03)^{1.065})$, $r^2 = 0.999$;

Box: Potassium linear saturation range for \bar{X} and \bar{X} (log conc)

potassium: Men: $Y = 1.045 + (-0.040 - 1.045) / (1 + (X/151.62)^{0.934})$, $r^2 = 0.999$; women: $Y = 1.006 + (-0.059 - 1.006) / (1 + (X/74.03)^{1.065})$, $r^2 = 0.999$.

Box: Potassium linear saturation range for \bar{X} and \bar{X} (log conc)

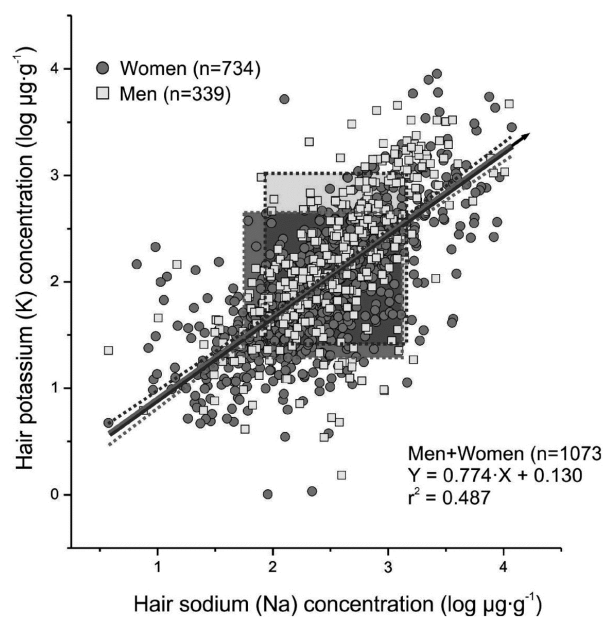


Figure 3. Optimal range of hair potassium and sodium concentration

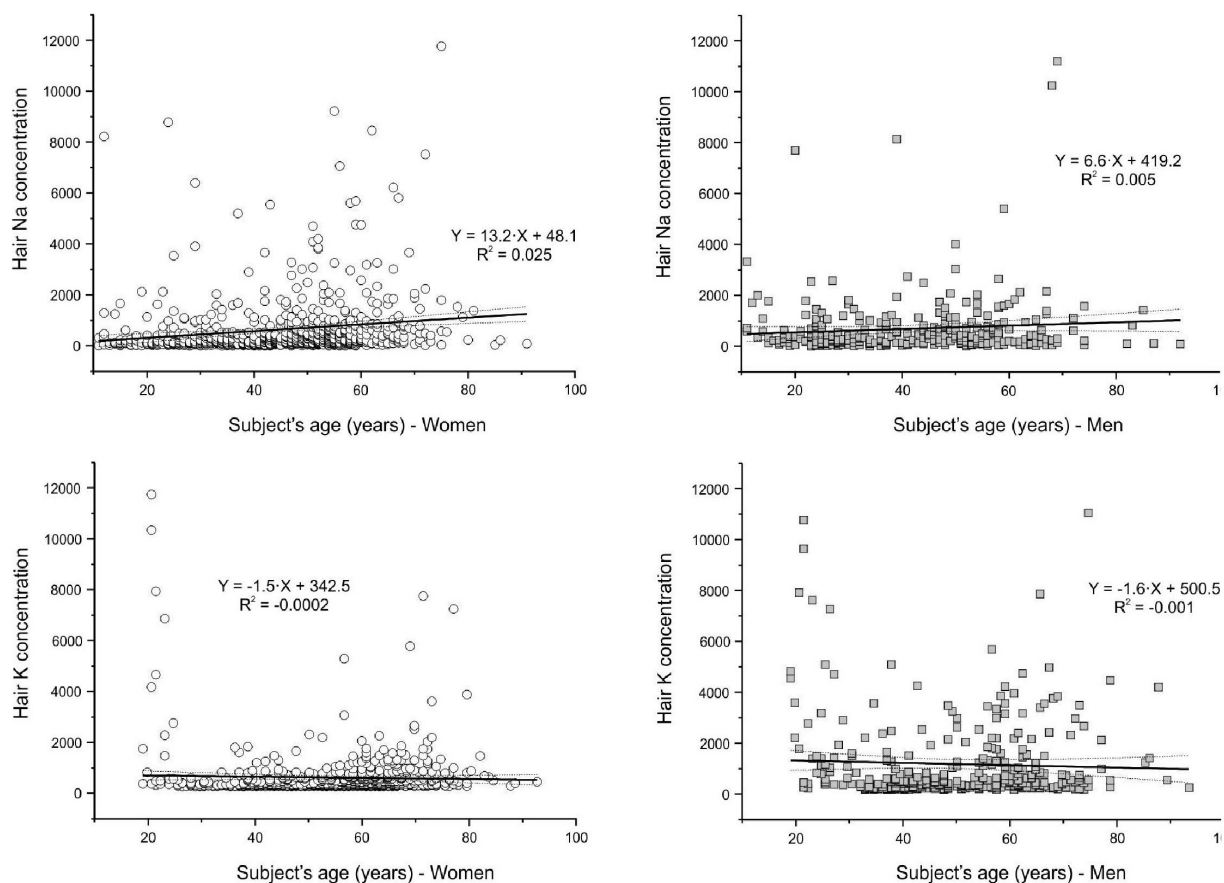


Figure 4. The effect of age on sodium and potassium accumulation in the hair

DISCUSSION

Human hair makes a valuable long term biological indicator tissue for the assessment of the essential bioelements' nutritional status (Momčilović et al., 2010). Hair growth is a unidirectional process, which in difference to the urine excretion, precludes sodium and potassium post absorption metabolic equilibration with the surrounding organs and tissues (Heaney, 2013). Indeed, natural deposition of K and Na in human hair is characterized by a sigmoid saturation curve. The results of our study demonstrated that the human nutritional status of potassium and sodium may be adequately assessed with a hair median derivatives bioassay. This assay stems from within the existing data set and not by implementing the model upon the data. Moreover, the median derivatives bioassay drew our attention to the central part of the Gaussian statistical data distribution curve, and what differs from the standard statistical approach where we focus on the tails of data distribution. Also, the median derivatives bioassay model avoids the problem of J-shaped curves transformation (Calabrese, Baldwin, 2001) and other problems associated with the no threshold assumption of the linear regression model (Sanders, 2010).

This study revealed subtle gender dependent metabolic differences in the homeostatic control of sodium and potassium metabolism. Both Na and K belong to the first column of the Periodic Table and are bio-dynamically entangled in their metabolic activity. In our study, the bio entangled K/Na ratio stays constant over the linear (adequate) part of the sigmoid saturation curve in women, but is progressively increasing in men. We already know that the increased intake of potassium suppresses the appearance of hypertension induced by the increased sodium dietary exposure (Smith et al., 1992). Apparently, being a man carries the inherited risk towards developing hypertension.

Today, average adult American men and women aged 19–71+ years are consuming 2.83–3.34 and 2.21–2.43 mg K per day, respectively. At the same time, the average daily consumption of sodium for the same age group population was 2.43–5.64 for men and 1.96–3.41 mg per day for women (Institute of Medicine, 2005). It is reasonable to assume that such amounts of potassium and sodium in the diet is adequately reflected in the hair median concentration values for both men and women. Granted, the estimated daily intake of K and Na in the healthy white Caucasians Croatian population is somewhat

higher than that of the USA population (Jelaković, Reiner, 2014); however, comparatively, that would only slide down the position of the US hair median for K and Na concentration if shown on a same linear part of the sigmoid saturation curve when shared with Croats (Dahm, 2020). Thus, since the dietary intakes of K and Na are, indeed, reflected in their hair concentration, then they would both fall well within the adequate range of their dietary intake. That leads us to the conclusion that there is no need to reduce the current level of sodium in the diet for the general population. The results urged us to provide means for the individual control of Na and K dietary intake to identify the overexposed sodium subjects or, for the first time reported here, underexposed potassium and sodium subjects, respectively. We are in no way saying that the excess dietary sodium is not the primary agent responsible for inducing increased blood pressure, especially in the salt sensitive individuals (Messerli et al., 1977). Indeed, our data indicate that there is no reason to reduce current dietary salt intake level *an block* for the general population (Graudal et al., 2015; Moore et al., 2017). Such a dietary salt reduction is a kind of “One size fit all” philosophical approach, which is not justified.

With regard to the plethora of studies searching to prove causative effect of the increased dietary salt intake to the cardiovascular system, and to hypertension in particular, we think that the respective researchers fall into the cognitive trap of Doctor Snow's water-pump handle of the cholera epidemic in London in the 19th century (Johnson, 2006). However, bioelements like Na and K, when within an adequate dietary intake, are not foreign substances to the human body such as *vibrio cholerae*, which is a xenobiotic bacterium. Sodium and potassium are very much human essential constituents. We have discussed that issue about copying the bacteriology solutions to the trace element specific problems in our article on assessing boron nutritional status (Prejac et al., 2018).

As a matter of fact, our study does not contradict other studies where increased urinary excretion in hypertension was associated with the increased dietary salt intake. Our study only indicates that it is the failure of the sodium metabolic homeostasis, and not the dietary salt intake, that may be behind the observed increased sodium urinary excretion in hypertension. Indeed, numerous studies indicate that whatever impaired the Na K ATPase function of the

cell membrane, would impede the essential sodium and potassium trans-membrane exchange and what appears to be a key pathophysiological cause behind the essential hypertension (Hamlyn et al., 1982; Kramer et al., 1985; Jailovich, Bertorello, 2010; Kita, Iwamoto, 2010). Our median derivatives bioassay provides a simple means to identify such subjects having impaired metabolism of sodium or potassium, or both, on a massive population scale.

REFERENCES

- Bankir L., Perucca J., Norsk P., Bouby N., Damgaard M. Relationship between sodium intake and water intake. *Ann Nutr Metab.* 2017; 70(Suppl1): 51–61.
- Bray G.A. In the footsteps of Wilbur Olin Atwater: The Atwater Lecture for 2019. *Adv Nutr.* 2020; doi.org/10.1039/advanques/nmz128.
- Burges C. Valid analytical methods and procedures. The Royal Society of Chemistry, Cambridge, UK. 2000.
- Cade J.E., Burley V.J., Warm D.L., Thompson R.L., Margetts B.M. Food frequency questionnaires: a review of their design, validation, and utilization. *Nutr Res Rev.* 2004; 17:5–22.
- Calabrese E.J., Baldwin L.A. U-shaped dose-response in biology, toxicology, and public health. *Ann Rev Public Health.* 2001; 22:14–33.
- Dahm C.C. Correcting measurement error in dietary exposure assessments: no piece of cake. *Am J Clin Nutr.* 2020; https://doi.org/10.1093/ajcn/nqaa130.
- Ehleringer J.R., Avalos C.A., Tipple B.J., Valenzuela V.O., Cerling T.E. Stable isotope in hair reveals dietary protein source with links to socioeconomic status and health. *PNAS.* 2020; https://10.1073/pnas.129914087117.
- Emsley J. Nature building blocks, Oxford University Press, Oxford 2003.
- Fillipiou C.D., Tsiouif C.T., Thomopoluous C.G., Mihos C.C., Dimitriadis K.S., Sotiripoulou. L.I., et. al. Dietary approaches to stop hypertension (DASH) diet and blood pressure reduction in adults with and without hypertension: A systemic review and meta analysis of randomized controlled trials. *Advance Nutrition.* 2020: 1–11.
- Finney D.J., (Forwarded by Tattersfield F.). Probit analysis. A statistical treatment of the sigmoid response curve, 2nd ed. Cambridge University Press, Cambridge, UK. 1952.
- Gaw A., Murphy M.J., Cowan R.A., O'Reilly D.St.J., Stewart M.J. Shepherd J. Clinical Biochemistry. Churchill and Livingstone, Edinburgh 2004.
- Graudal N., Hubeck-Graudal T., Jurgens G., McCarron D.A. The significance of duration and amount of sodium reduction intervention in normotensive and hypertensive individuals. A meta analysis. *Advanced Nutr.* 2015; 6: 169–167.
- Hamlyn J.M., Ringel R., Schaeffer J., Levinson P.D., Hamilton B.P., Kowarski A.V., Blaustein M.P. A circulating inhibitor of (Na⁺ + K⁺) ATPase associated with essential hypertension, *Nature* 1982; 300: 650–652.
- Heaney R.P. How and how not to set a nutrient intake. *Am J Hypertension.* 2013; 26: 1194–1197.
- Heyes B. Foolproof and other mathematical meditations. The MIT Press, Cambridge, MA. 2017.
- Institute of Medicine. Dietary reference intakes for water, potassium, sodium, chloride and sulfide. National Academies. Washington DC, 2005.
- International Atomic Energy Commission (IAEA). Elemental analysis of biological materials. IAEA-TEC.DOC 197, International Atomic Energy Agency. Vienna Austria. 1980.
- Jailovich A., Bertorello A.M. Salt, Na⁺, K⁺ -ATPase and hypertension. *Life Sci.* 2010; 86: 73–78.
- Jelaković B., Reiner Ž. Croatian action on salt and health (CRASH), *Liječnički vjesnik. Zagreb, Croatia.* 2014; 9-1: 304–305 (in Croatian).
- Johnson B.S. The ghost map. New York. Riverhead 2006.
- Kaji D.M. Hyponatremia and hypernatremia, Difficult Diagnosis (Taylor R.B., Ed), W.B. Saunders Co, Philadelphia, USA. 1985; 290–299.
- Kelly J.R., McGrath J.E. On time and method, SAGE Publications. Newbury Park, CA. 1988.
- Kita S., Iwamoto T. Mechanisms for linking high salt intake to vascular tone: role of Na⁽⁺⁾ pump and Na⁺/Ca²⁽⁺⁾ exchanger coupling. *Yakugaku Zasshi.* 2010; 130: 1300–1405 (in Japanese).
- Kramer H.J., Glanzer K., Sorger M. The role of endogenous inhibition of Na-K-ATPase in human hypertension – sodium pump activity as a determinant of peripheral vascular resistance. *Clinical Exp Hypertension A.* 1985; 7: 769–782.
- McCarron D.A. What determines human sodium intake: policy or physiology? *Am Nutr Society.* 2014; 5: 578–584.
- Mente A., O'Donnel M.J., Rangarajan S., McQueen M.J., Poirier P., Wiegelosz A., et al. Association of urinary sodium and potassium excretion with blood pressure. *New England J Med.* 2014; 371:601–611.

Acknowledgement

The initial summary of this study was partly presented at the 2015 Experimental Biology meeting (FASEB J 2015; 29: S1). The author is indebted to David F. Marshall, English language Prof. Emeritus, for his language editing of the manuscript, to Dr. sci. Juraj Prejac MD for his presentation of sigmoid data curves, and Prof. dr.sci. Ninoslav Mimica for his help in providing the book references.

- Messerli F.H., Schmieder R.E., Weir M.R. Salt. A perpetrator of hypertensive target organ disease. Arch Intern Med. 1977; 157: 2449–2452.
- Miller J.Z., Weinberger M.H., Daugherty S.A., Fineberg N.S., Christian J.C., Grim C.E. Heterogeneity of blood pressure to dietary sodium restriction in normotensive adults. J Chronic Dis. 1987; 40: 245–250.
- Mita K., Sumikama T., Iwamoto M., Matsuku Y., Shigemitsu K., Oki S. Conductance selectivity of Na⁺ and across K⁺ channel via Na⁺ trapped in tortuous trajectory. Proc Nat Acad Sci USA 2021; 116; doi:10.1073/pnas.2017168118.
- Momčilović B., Lykken G.I., Tao L., Wielopolski L. Comparative analysis of 65Zn and 40K in human urine by library least square and window methods using a personal computer. J. Radioanal Nucl Chem. 1995; 195: 315–319.
- Momčilović B., Prejac J., Brundić S., Morović S., Skalny A.V., Mimica N., Drmić S. An essay on human and elements, multi-element profiles and depression. Translational Neuroscience. 2010; 1: 122–134.
- Momčilović B., Prejac J., Skalny A.V., Mimica N. In search of decoding the syntax of the bioelements in human hair – A critical overview. J Trace Elements Med Biol. 2017; 49:1–11.
- Moore L., Singer M., Bradley M.L. Low sodium intakes are not associated with lower blood pressure levels among the Framingham offspring study adults. Experimental Biology. 1917: 446.6.
- Murphy M.M., Crafford C.G., Barraj L.M., Bi X., Higgins K.A., Jaykus L.-A., Tran N.L. Potassium chloride-based replacers: modeling effects on sodium and potassium intakes of the US population with cross-sectional data from NHNES 2015–2016 and 2009–2010. Am J Clin Nutr. 2021: 1–11.
- Nagel E., Newman J.R., Hofstadter D.R. Goodell's Proof. 2001. New York Univ Press.
- O'Donnel M.J., Yusuf S., Mente A., Gao P., Mann J.F., Teo K., et al. Urinary sodium and potassium excretion, mortality and cardiovascular events. New England J Med. 2014; 371:612–623.
- Oppenheim N. Questionnaire – design, interviewing and attitude measurement. Continuum. London 1992.
- Prejac J., Skalny A.A., Grabeklis A.R., Uzun S., Mimica N., Momčilović B. Assessing the boron nutritional status by analyzing its cumulative frequency distribution in the hair and whole blood. Trace Elements in Med. Biol. 2018; 45:50–56.
- Sanders C.L. Radiation and the linear No-threshold assumption. Springer, Heidelberg, Germany. 2010.
- Santos J.A., Tekle D., Rosewarne E., Flexner N., Cobb L., Al-Jawaldeh A., Kim W.J., Breda J., Whiting S., Campbell N., Neal B., Webster J., Trieu K. Systemic review of Salt Reduction Initiatives around the world: A midterm evaluation of progress towards the 2025 Global Non-Communicable Diseases Salt Reduction Target. Advances in Nutrition. 2021; 12: 1768–1780; <http://dx.doi.org/10.1093/advances/nmab008>.
- Schutte K.H. The biology of trace elements. Croasby, Lookwood and Son. London. 1964.
- Smith S.R., Klotman P.E., Svetkey L.P. Potassium chloride lowers blood pressure and causes natriuresis in older patients with hypertension. J Am Soc Nephrol. 1992; 2: 1302–1309.
- Taube G. The (political) science of salt. Science. 1998; 281: 898–907.
- World Med Assoc. Declaration of Helsinki human subject research (June) 1964.
- Xu J., Du X., Bal J., Fang L., Liu M., Ji N., Zhong J., Yu M., Wu J. Assessment and validation of spot urine in estimating the 24-h urinary sodium, potassium, and sodium/potassium ratio in Chinese adults. J Human Hypertension. 2019; <https://doi.org/10.1038/s41371-019-0274-z>.

ПИЩЕВАЯ СОЛЬ НА СТЫКЕ НАУКИ О ПИТАНИИ, ЗДРАВООХРАНЕНИЯ И ПИЩЕВОЙ ПРОМЫШЛЕННОСТИ

Б. Момчилович

Институт изучения и развития устойчивых экосистем,
Srebrnjak 59, 10000, Загреб, Хорватия

РЕЗЮМЕ. Представлено сообщение о новых данных в области науки о питании. Для оценки пищевого поступления Na и K обычно воспользуется краткосрочный показатель – выведение Na и K с мочой. В этом исследовании были использованы волосы в качестве долгосрочного биологического индикатора алиментарного обмена Na и K.

Методы. Волосы 1073 практически здоровых взрослых европеоидов [734 женщины (♀) и 339 мужчин (♂)] были проанализированы на содержание Na и K методом ИСП-МС. Математический анализ проводился методом оценки медианных производных после лог-трансформации данных.

Результаты. Медианные значения (мкг/г) составили: ♀Na – 254, ♂Na – 371, ♀K – 74,3 и ♂K – 143. Линейные (адекватные) интервалы сигмовидной кривой составили для Na 55,6–1307 (♀) и 84,0–1450 (♂), для K 18,9–46,7 (♀) и 25,8–107,9 (♂). Строгий гомеостатический контроль Na и K в цельной крови делает её непригодной для оценки алиментарного обмена этих элементов. Отношение калия к натрию (K/Na) у женщин выглядит стабильным на всем протяжении линейного сегмента сигмовидной кривой, в отличие от постоянно увеличивающегося отношения K/Na у мужчин.

Заключение. Результаты показывают, что концентрация Na в волосах не должна быть ниже 55,6 и 84,0 или выше 1307 и 1450 мкг/г у женщин и мужчин соответственно. Аналогичным образом, концентрация калия в волосах не должна быть ниже 18,0 и 25,8 и выше 46,7 и 107,9 у женщин и мужчин соответственно. Соотношение K/Na в волосах должно быть на уровне 0,600 у мужчин и 0,400 у женщин. Выявленный средний уровень алиментарного потребления натрия населением в настоящее время не может служить основанием для введения массовых ограничений по потреблению поваренной соли; коррекция должна носить индивидуальный характер.

КЛЮЧЕВЫЕ СЛОВА: калий, натрий, волосы, цельная кровь, статус питания, алиментарное потребление.

Dear Colleagues and Friends of ISTERH

ISTERH-14 will be held in conjunction with ICTEM in Aachen, Germany, June 5-10, 2022. It will be an in-person gathering adhering to local COVID regulations in place at the time of the meeting. The theme of the ISTERH-14 conference is "Trace Elements in Human Health and Diseases: From Benchtop Research to Clinical Investigation." Building on the ISTERH's successful conferences in Antalya, Turkey (2011), Tokyo, Japan (2013), Dubrovnik, Croatia (2015), St. Petersburg, Russia (2017), and Bali, Indonesia (2019), the upcoming ISTERH-14 will be in the historical city of Aachen, Germany, which offers wonderful opportunities to learn the ancient European history, to explore research ideas and to enjoy interacting with colleagues within and outside of ISTERH community. Please see the attached flyer on the general ICTEM information.

We welcome proposals for symposia addressing a broad range of scientific topics. Some suggestions include (but not are not limited to):

- Trace elements and COVID-19
- Transport and metabolism of trace elements in mammalian body
- Mitochondrial mechanisms of metal toxicity
- Advances in bioinformatic methods for mechanistic understanding of metals' health effect
- Psychiatric issues resulting from metal exposures
- Linking molecular and cellular mechanisms to clinical dysfunction
- Epigenetic modification as a transgenerational mechanism in metal toxicity
- Advancing risk assessment using new approach models or technology for a sustainable future
- Mechanisms by which endocrine disruption causes metal toxicity
- Epidemiological approaches for studying metal-induced toxicities
- Metals in concept of One Health: From ecology, environment, animal to human
- Alternative disease models for metal-induced disorders
- Your concept for an exciting symposium ...

The deadline for submission is November 30th, 2021. The proposals will be judged and ranked by the members of the ISTERH Scientific Committee, and the decision about acceptance or rejection will be communicated by December 31st, 2021.

Please send your proposals to Dr. Wei Zheng, Chair of the Scientific Committee, at wzheng@purdue.edu.

We look forward to receiving your proposals!

Wei Zheng (Chair, ISTERH Scientific Committee)

Anatoly Skalny (President)

John Wise (Vice President Elect)

David Fleming (Secretary)