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Research Article

The Hair Golden Range Yardstick for Assessing the Optimal Bio Element Nutritional Status

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Abstract

Background: The bio element nutritional status may be defined as deficient, adequate, or excessive/toxic. Non-invasive method of hair collection makes it a tissue of choice for multi bio element analysis in precision medicine and nutritional epidemiology.

Methods: Hair multi bio element profiles of healthy 1073 subjects (339 Men, 734 Women) were analyzed with the ICP MS. The frequency distribution of the hair log concentration data was used to assess the bio element nutritional status with the median derivatives bioassay. The assay allows for the reliable assessment of the bio element deficiency, adequacy, and excess.

Results: Nutritional status of P, Zn, and the bio element pairs of I and Se, Ca and Mg, and Na and K are fully exposed and illustrated. The nutritional status of all twenty-two hair bio elements is presented in Table 1 in their decreasing order of abundance (μg•g-1): Calcium, Zinc, Phosphorus, Sodium, Potassium, Magnesium, Silicon, Copper, Iron, Aluminum, Boron, Strontium, Chromium, Iodine, Selenium, and in (ng•g-1) for Nickel, Manganese, Molybdenum, Silver, Lithium, Cobalt and Gold.

Conclusion: Hair bio element median derivatives bioassay proved to be a rapid, reliable, accurate, and fully reproducible method for assessing the bio element nutritional status, the nutritional health surveillance, and maintenance in precision medicine.

Keywords: Hair; Bio elements; Entanglement; Interactions; Median derivatives bioassay; Reference standards; Reliability; Nutritional status

Introduction

In the last three quarters of a century the definition of malnutrition has evolved from a simple "Faulty and imperfect nourishment" [1], to the current elaborate WHO definition "Malnutrition refers to deficiencies, excesses or imbalances in a person's intake of energy and/or nutrients. The term malnutrition covers two broad groups of conditions. One is "under nutrition". This includes stunting (low height for age), wasting (low weight for height), underweight (low weight for age) and lack of micronutrient vitamins and minerals, their deficiencies or insufficiencies. The other diet related malnutrition subgroups are the no communicable diseases, such as heart disease, stroke, diabetes, and cancer" [2]. This broad WHO definition of malnutrition tells us that too much of the nutrients are as bad as is too little of them. Moreover, a complex situation may arise, like having one nutrient in excess and the other being deficient. Today, the time has come that everybody may look for his personal bio element precise nutrition or so-called Rx (receipt) nutrition. And beyond the current Recommended Dietary Allowances (RDA's).

The aim of this article is to demonstrate how to assess the bio element nutritional status and to allow us for acceptable level of differentiation between the deficient, adequate and excessive bio element nutritional status. Here the term bio element is used as a common denominator for the major elements (electrolytes), trace elements and ultra-trace elements. Some of the bio elements are essential, some are conditionally essential, some were not shown to actively participants in the metabolism, and some are considered to be toxic at the extremely low concentrations. The situation is even the more complex since the essential bio elements may be also toxic depending upon their concentration [3]. Indeed, the rate at which the same dose of the bio element is administered may result in their different metabolic response [4]. Thus, the purpose of this article is to define how the level of the nutritional bio element exposure, i.e., its nutritional status, can be accurately assessed over their entire spectrum of ranges, from a bio element deficient, adequate, and excessive dietary intake, respectively.

Our biological indicator tissue of choice for assessing the bio element nutritional status is human hair [5]. Hair is a biological indicator tissue that can be non-invasively (painlessly) sampled with a simple scissors, and the collected hair samples are easily stored and transported to be later analyzed at some adequately equipped

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analytical laboratory [6,7]. Hair follicle is a natural collector of the bio elements in our body (Figure 1), some kind of our, always running, personal metabolic ward facility. The numbers shown are the logarithms since the hair bio element concentrations ranges over the eight orders of magnitude. The hair bio element analysis has an advance in comparison with the alternative bio indicators. The superiority of hair iodine against the iodine in the whole blood and urine biological indicator tissues is demonstrated in (Figure 2a and b). The highest concentrations of iodine were observed in the hair, then in urine, and they were the lowest in the whole blood. Today, urinary iodine is considered to be the bio indicator tissue of choice, the so called "golden standard", for assessing the iodine bio element body status, but the difficulties in collecting, transporting, and analyzing urinary samples are notorious [8]. Of all the here tested twenty-two hair bio elements, only the blood iron concentrations were higher in the whole blood than they were in the hair. However, great hopes for broader use of the hair bio element analysis in the bio-medicine wane soon when the actual analytical data of supposedly replicated samples, were shown to be unacceptably dispersed. This article shows that the observed unacceptable dispersion of the analytical data between the replicates is not due to the chemical analysis inadequacy, but due to the inappropriate way of analyzing their frequency distribution. Indeed, the hair samples from even the same head are not homogenous entities, as it was taken for granted, but a sex dependent mixture of hair treads in different stages of hair cyclic follicular growth [9].

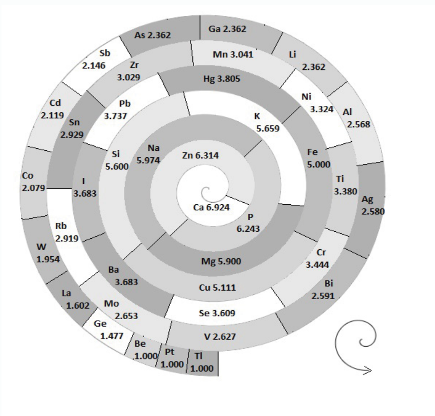

Figure 1: Hair bio element abundance (log μg·g-1).

Subjects and Methods

In this article we studied multi bio element profile in the hair of 1073 apparently healthy men (n=330) and women (n=734) in Croatia (Figure 1) in order to assess their bio element nutritional status for the precision medicine [10]. All the hair bio elements in this study were analyzed at the Center for Biotic Medicine (CBM), Moscow, Russia. CBM is an internationally accredited commercial bio element analytical laboratory. Data on hair preparation for analysis are shown separately in Appendix 1.

Median derivatives bioassay

The skewed cumulative exponential distribution curve of the initial data set was log transformed, what generated a standard Gaussian bell shaped data distribution. Such "normalized" frequency data distribution of the hair bio elements was analyzed with the median derivative bioassay. This log transformed data were fitted to form the sigmoid logistic regression function (power function) [5,11].

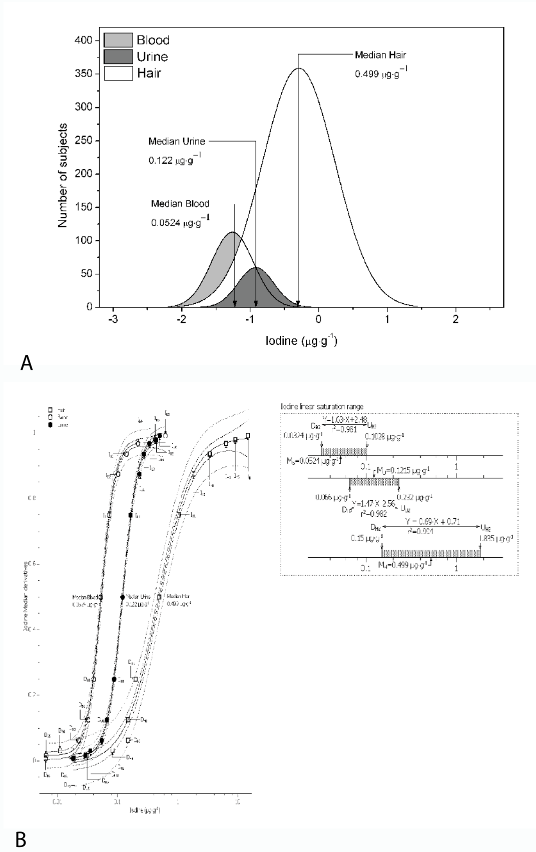

Figure 2: A) Iodine in the hair, whole blood and ur. Gaussian (μg·g-1). B) Iodine in the hair, whole blood and urine. Golden range yardstick (log μg·g-1).

$$A2+(A1-A2)/[1+(x/x0)p]$$

Where A1 is the initial value (lower horizontal asymptote), A2 is the final value (upper horizontal asymptote), x0 is the center (point of inflection) of the detected median (M0), p is the power (the parameter that affects the slope of the area about the inflection point). The Origin pro 8.0 data analysis and graphing software was used for this analysis (Origin Lab Corp., Origin Pro Version 8.0., Northampton, MA). As a rule, one standard deviation of the total tested population formed the emerged linear segment of the sigmoid saturation curve.

Visual examination of the bioassay sigmoid dose-response saturation curve allows for the determination of the natural cut off points of the central linear portion and their upper (Maximum, Max) and lower (Minimum, Min) tails. The central linear segment indicates the adequate range of a given bio element hair incorporation. That linear segment is considered to reflect the phase of a transient equilibrium between the input of the available circulating bio elements to the hair follicle, and the bio element actual uptake by the hair follicle. Thus, the level of a bio element below that cut off point of linearity is considered to be a border separating the deficient and adequate nutritional status. Similarly, the bio element concentrations above the linear portion of the sigmoid saturation curve, represents an excessive nutrient (bio element) intake which is no more regulated in a linear fashion. Indeed, the central linear portion of the sigmoid saturation curve is considered to represent the adequate bio element nutritional status. It should be noted that this natural bio element response pattern, suggests that the adequate nutritional status reference values, need to be presented in the range format [12].

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Also, by identifying this linear segment of the sigmoid saturation curve allows us to further subdivide the adequate nutritional status, into the different sub-segments, i.e., low adequate, Adequate Golden Range (conditionally optimal range), and supra-adequate regions. The low adequate segment would be comparable with the concept of a subclinical deficiency, whereas the supra-adequate region, or the sub pharmacological region, would be more important to the environmental exposure studies. In this study the adequate nutritional status range is divided into (a) low adequate, (b) Adequate Golden Range, and (c) supra-adequate regions with a 30:60:10 percent ratio. All the defined cut off points for every tested bio element are shown in Table 1, where they are assigned as Minimum (Min) and Maximum (Max). All the concentrations below the Minimum are considered to be overtly deficient, whereas all the concentrations above the Maximum are considered to be excessive.

Vignette 1: Solving the Riddle of Analytical Variability of Calcium in Hair Replicate Samples

Miekeley et al. [42], published an article which discussed how reliable are human hair reference intervals for trace elements. They gave (supposedly) the same hair samples to five different analytical laboratories.

Human hair reference intervals for trace elements from five different analytical laboratories.

Laboratory	Mean	1	2	3	4	5
Calcium ($\mu g \cdot g^{-1}$)	802 ± 37	844	1555	431	686	1024

Numerous studies showed similar inconsistency in analyzing duplicate hair samples, and what is used as a principal objection for wider use of hair bio elements in clinical medical practice.

However, Dinh K et al. [9], revealed that the replicate samples are not a homogenous set of hair threads, but a complex mixture generated by hair follicles in different phases of their sex dependent hair cell cycle. Indeed, the here presented study showed that hair calcium has a distinct sex dependent statistical data distribution, which resulted in a wide range of adequate nutritional status concentrations.

Shows hair calcium has a distinct sex dependent statistical data distribution.

Calcium ($\mu g \cdot g^{-1}$)		Men		Women			
Min	Median	Max	Optimum	Min	Median	Max	Optimum
281	492	816.4	599-761	487.7	1721.4	4426	971-4195

This study proved the sex dependent difference in calcium intermediary metabolism. Apparently, women have a higher internal turnover of calcium than men. Also, our results revealed substantial difference between duplicate hair samples in Miekeley et al. [42] study. Our study indicates that Labs 1 and 4 analyzed mostly the mixed men and women hair, Lab 2 and 5 analyzed mostly women hair, and Lab 3 analyzed predominantly men hair. Thus, the reported inadequacy in the analysis of calcium in the hair of replicates or duplicates reflects the inhomogeneity of the analyzed hair threads mix.

Results

The results of assessing the bio element nutritional status with the aid of the median derivatives bioassay are

shown for phosphorus and zinc (Figure 3 Left column), for the hair phosphorus invariance across the Earth globe (Figure 4), and for the physiologically entangled bio element pairs of iodine (Figure 5 Left) and selenium (Figure 5 Right), for sodium and potassium (Figure 3 Middle column), and calcium and magnesium (Figure 3 Right column). The combined comparative box-plot of Ca, K, Mg, Na, P, and Zn is shown in (Figure 6). The assessment of the nutritional status of the other tested bio elements is presented in the tabular form without the graphic presentation. The other tested bio elements have identical pattern of sigmoid saturation curves, i.e., in decreasing order of concentration: Silicon, Copper, Iron, Aluminum, Boron, Strontium, Chromium, Nickel, Manganese, Molybdenum, Silver, Lithium, Cobalt and Gold. All the hair bio element concentration data are expressed in $\mu g \cdot g^{-1}$ and in $ng \cdot g^{-1}$ for Cr, Ni, and Co (Table 1). The so far studied bio element interactions are shown in (Figure 7). The hair median derivatives bioassay is presented in (Table 2).

Phosphorus and zinc (Figure 3 left column)

Major bio element phosphorus and the trace element zinc are two essential bio elements [13]. The low limit threshold of adequate phosphorus nutritional status is ($\mu g \cdot g^{-1}$) 121.9 in men and 124.5 for women, respectively (Table 1). That is shown in a Minimum (Min) column and it is considered to represent a breaking point between the deficient and adequate phosphorus nutritional status, respectively. From that Min point or lower limit, the hair phosphorus concentration rises straight up to its Maximum (Max) or upper tolerance limit of 194.1 and 199.2 for men and women, respectively (Table 1). The entire adequate (linear) range may be further subdivided by a 30:60:10 ratios, the first 30% of that subdivision of the phosphorus linear segment of the sigmoid saturation curve, represent the sub-adequate or sub-clinical bio element nutritional status. The next subdivision of 60% represents the true Adequate Golden Range (Conditionally Optimal Range) of the bio element phosphorus nutritional status, and the final upper 10% of the subdivision is a supra-adequate phosphorus nutritional status. Let us remind that all of these three subdivisions actually belong to the adequate phosphorus nutritional status range. Indeed, hair phosphorus concentrations were almost identical for both men (M) and women (W) in two different population groups in Croatia (initials J and V), North Macedonia (M), Japan, and the US (Texas) where mostly Mexican were involved (Figure 4) [14]. Apparently, sex and race does not measurably affect the human races phosphors nutritional status. It is pertinent to note here that both phosphorus and zinc showed almost identical hair zinc concentration invariance. Indeed, zinc is like phosphorus, an essential bio element, but zinc was never directly associated with the metabolic cycling of ADP and ATP, respectively.

Since zinc is very much involved in body growth. i.e., an energy high demanding process, it is not surprising that zinc and phosphorus are so tightly related. Indeed, zinc essentiality was recognized after stunted growth of Iranian children was proved back in 60' to be due to zinc nutritional deficiency. The border between the deficient and adequate zinc nutritional status, as assessed with the median derivatives bioassay is Min 126 and 131 for men and women, respectively, whereas, the upper Max level off of the linear part of the sigmoid saturation curve, is 184.1 and 247 for men and women, respectively. The optimal hair zinc nutritional status, lies between 173 to 198 and 191 to 224 for men and women, respectively. The previous idiorrhythmic experiments demonstrated that dietary zinc reference values should be considered in their range format and beyond their current daily defined dietary allowances [12].

Thus, the hair phosphorus concentrations below 121.9 or above 199.3 should be considered as ominous warning sign of somebody

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metabolic health. Apparently, the invariant stability of hair phosphorus may serve as an internal standard against which other bio elements may be compared, like namely Na and K, Mg and Ca. The summary comparative box-plot enlist six pairs of bio elements, i.e., P-Zn, Ca-Mg, and Na-K are visually displayed; an intriguing network pattern comparing several bio elements simultaneously (Figure 8).

Iodine and Selenium (Figure 5a and b)

Historically, iodine is the first identified trace element (oligo element in French, spurn element in German), or bio element in this article annotation [15]. Although the iodine deficiency was known since the end of the 18th century, it was rampant in the Great Lakes of the USA all the way in the 20th century and even now is a problem in the lowlands of Holland and Belgium, but also in the river Poe valley in Italy, Himalayan countries, and wide areas of China and India. All over the world, iodine deficiency is frequently observed but preventable human health deficiency. The iodine status is so far, mostly assessed by analyzing its urine concentrations; a cumbersome and low sensitivity biological indicator tissue, often missing to detect a low urine iodine concentration, even when analyzed with a highly sensitive analytical instrument like the ICP MS. When our Croatian hair iodine analytical data were subjected to a median derivatives bioassay analysis, the characteristic sigmoid saturation curve was obtained (Figure 5a). Our data showed that adequate linear region of the sigmoid saturation curve covers the range starting at Min of 0.150 for both men and women, whereas the Max appears to be at 0.765 and 0.509 for men and women, respectively.

The linear part of the iodine sigmoid dose-response saturation curve may be further divided into its subclinical, optimal (Golden Range), and supra saturated part with a 30:60:10 partition ratio, as already explained. Indeed, the follicular hair is growing linearly, but the rate of hair follicular iodine incorporation depends upon the equilibration of blood iodine with iodine hair follicular uptake.

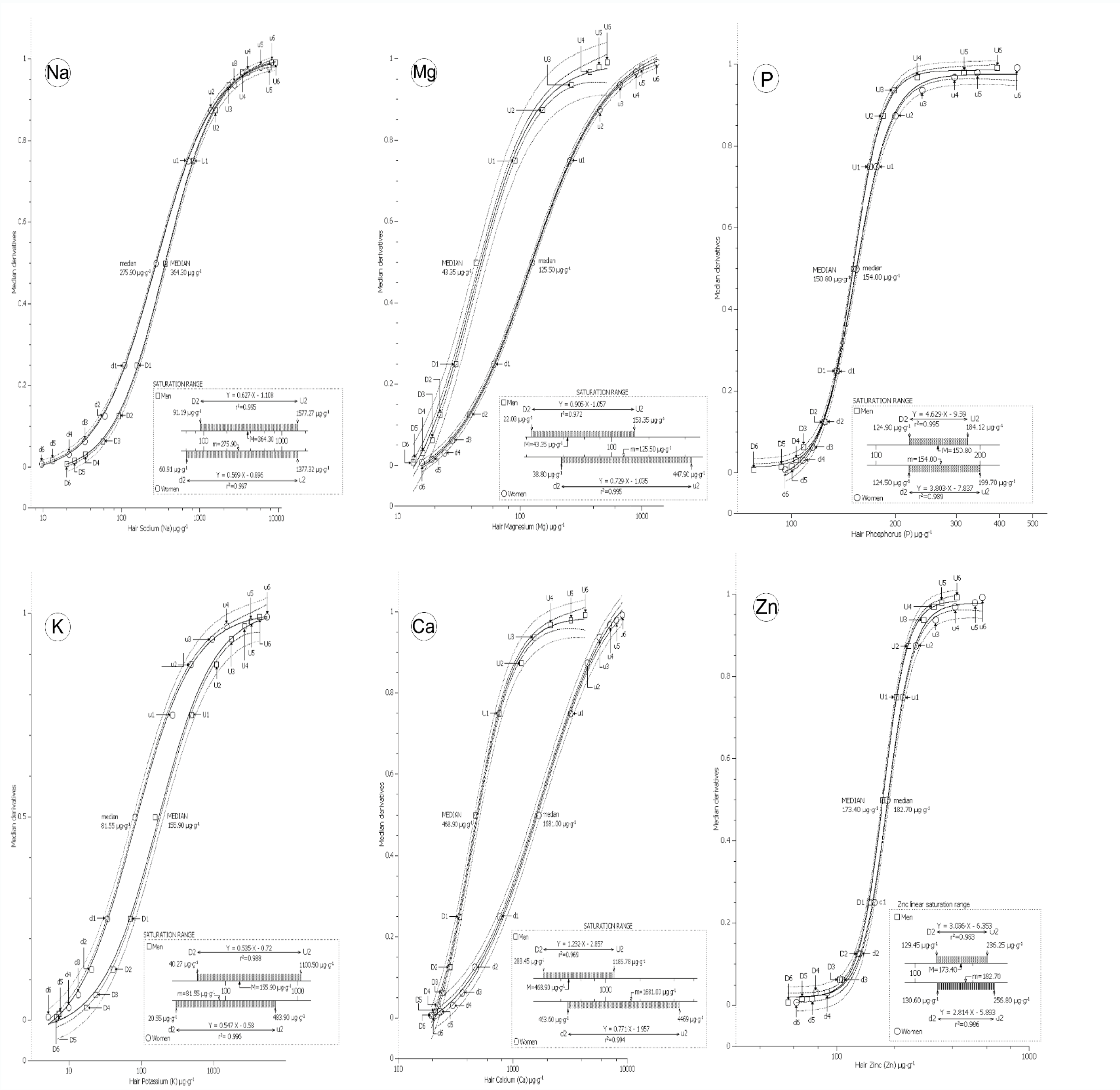

Figure 3: Hair (log µg·g-1), sodium and potassium (left column), magnesium and calcium (middle column), magnesium and calcium, phosphorus and zinc (right column).

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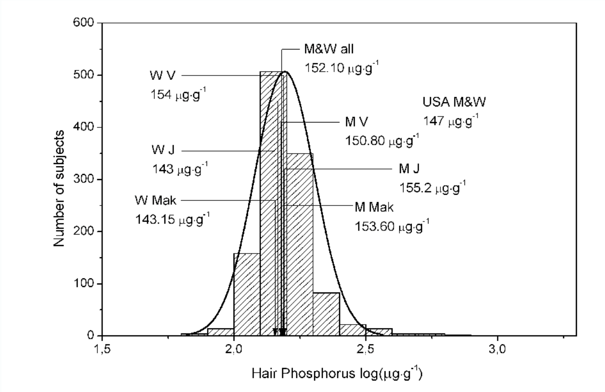

Figure 4: Invariance of hair phosphorus (µg·g-1). W Mak. women Northern Macedonia, WJ· women from Japan, WV· Croatian women, All M&W· all Croatian men and women, MV· Croatian men, UM&W· Texas men and women, MJ· Japan men, M Mak· men Northern Macedonia.

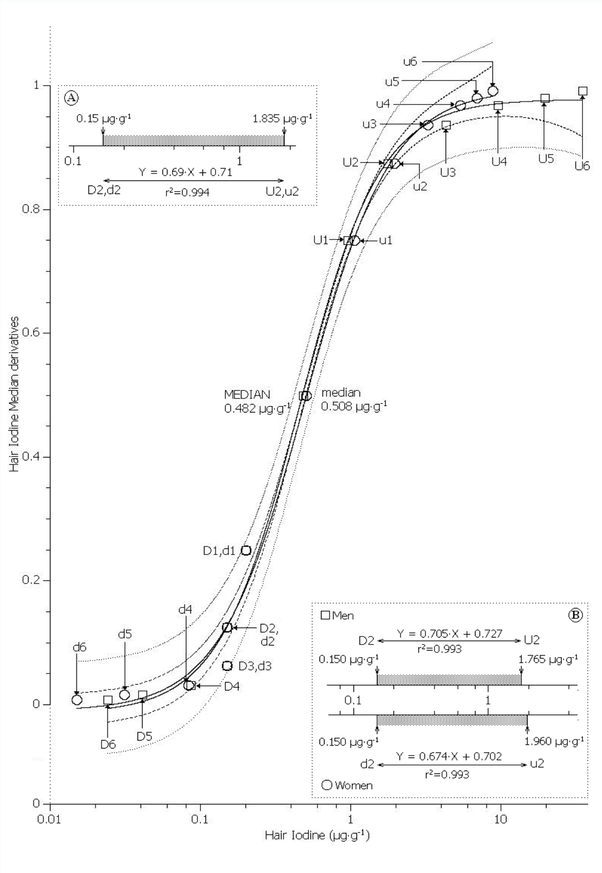

Figure 5a: Hair iodine sigma.

Indeed, the iodine hair incorporation changes depending upon the already reached level of the hair iodine saturation. Here we are facing a currently ill-defined area of diagnosing the subclinical bio element deficit, and its antipode of the bio element over abundance (the upper end of the linear part of the sigmoid dose-response saturation curve). Therefore, we propose that the area of the initial 30% of the linear range of the iodine dose-response sigmoid saturation curve should be considered as a subclinical iodine (and other bio elements) nutritional status. Similarly, the liner region above the 90% of the upper part of the linear range should be considered as an over saturated region. Indeed, the position of any given bio element median, may slide up or down along the tilted linear segment of the sigmoid saturation curve. Essentially, the tilting angle of the median derivatives slope is constant for a bio element, so that the bio element medians from the various parts of the world would be sliding up or down along it. However, the linear bio element tilt may vary with sec, as is demonstrated in this study.

Selenium

Selenium is another we may call a "proper" essential trace element, or what we here name the bio element. Selenium is shown here paired with iodine, since both of these bio elements are critical partners involved in the normal thyroid hormone biosynthesis [16,17]. Hair selenium sigmoid saturation curve is shown in Figure 5b. The adequate linear part of the selenium sigmoid dose-rate saturation curve Min to Max range lies between 0.134 and 0.078 (Min) and 0.701 and 0.623 (Max) for men and women, respectively. The suggested optimal Golden Range for selenium nutritional status lies between 0.304 to 0.644 and 0.233 to 0.569 for men and women, respectively. The subjects who belong to the upper 10% part of the supra-adequate linear part of the sigmoid saturation curve, have the increased risk of developing diabetes, as observed in China. So, the supra-adequate level of a bio element in the human body may be a "mixed blessing". In the case of Se, when our bio element nutritional status is supra-adequate, we may have to pay for this good result by having the increased chance of getting ill with the diabetes mellitus [17]. One more fact is interesting. When data on position of the hair median Se along the adequate linear range of the sigmoid response curve were plotted for various countries, Croatia and Tajikistan appeared to have similarly positioned their selenium medians, whereas it was different in comparison with Italy [18,19]. Thus, the hair bio element median derivatives allow for direct visual comparison of the bio element nutritional status across the different countries (Vignette 2).

We assume that the lower 30% of the adequate selenium linear part of the sigmoid curve should be considered as subclinical deficiency, whereas the upper 10% of the sigmoid linear part should be considered as an over saturated. Thus, the suggested optimal selenium nutrition status is 0.304 to 0.644 for men, and 0.233 to 0.569 for women (Table 1).

It should be noted that hair follicles do not actively discriminates between iodine and selenium (Figure 6). This is an important point how it is essential to control the iodine nutritional status if somebody supplements him with selenium, and *vice versa*.

Vignette 2: International Selenium Nutritional Status

Golden range Croatia (LM Low limit, UM Upper limit) [17-19, 43-48].

Nutr Status	Sub adequate	Adequate		Supra adequate	
Grading (%)	0%-30%	Min	30%-90%	Max	90%-100%
Men	LM 0.134	0.304-	[Median 0.346]	0.664-	UL 0.701
Women	LM 0.078	0.233	[Median 0.269]	-0.569	UL 0.623

Selenium nutritional status from Europe to Central Asia (Golden Range).

	Belgium	Croatia	Tajikistan	Italy	France	Asia
Women	0.1	0.346	0.369	0.37	0.39	0.54
Men	0.269	0.34	0.394	0.78	60.54e	0.60g

Hair selenium nutritional status appeared satisfactory for tested

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countries except Belgium where it was at the bottom of the subclinical adequate selenium nutritional status zone. We recommend selenium supplementation for all subjects whose hair selenium is in the subclinical selenium nutritional status range. For hair selenium levels above the subclinical adequate selenium nutritional status but below the median derivative concentration, selenium supplementation is optional. We consider hair selenium supra-adequate concentrations should not attempt selenium supplementation [17-19, 43-48].

Sodium and potassium (Figure 3 middle column)

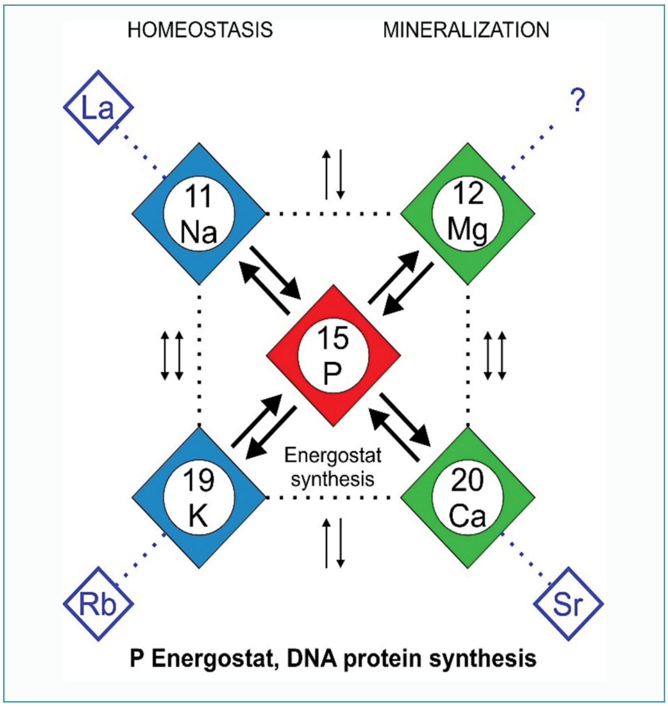
These two major electrolytes of the human body are essential bio elements that we found in the human hair [20,21]. The Min sodium hair concentrations are 94.0 and 56.6 for men and women, respectively, whereas their Max hair concentrations are 1450 and 1357 for men and women, respectively. It is amazing how our metabolism operates under such a concentration gap range (over the two orders of (magnitude). However, the suggested optimal sodium concentrations linear segment of the dose-response sigmoid curve is 411 to 1313 and 272 to 1117 for men and women respectively. These two essential bio elements, sodium and potassium, are the key participants in maintaining the cell membrane osmotic gradient. Indeed, sodium and potassium intracellular metabolic balance is a dynamic state of constant cellular membrane out flux of sodium with exchange for potassium cellular influx. Indeed, it was quite unexpected to see how these two bio elements of fundamental importance were increased in the hair of depressed people [22]. Evidently, the metabolic cause of that, the most prevalent human mental health impairment, needs further elucidation. Moreover, and contrary to the currently prevailing understanding, dietary sodium apparently is not the cause of the idiopathic essential hypertension, but the consequence of the failure of the cell membrane Na K ATPase regulation of in and out cellular Na and K transport [23]. Evidently, this observation opposes the current hysterical international crusade to decrease the sodium dietary intake, and increase that of potassium in our daily diet. Indeed, studying the role of Na, K, ATPase as a fundamental core set conformer factor in the idiopathic hypertension human disease, requires a rigorous biomedical study [24]. At this moment, it should be noted, that decreased hair sodium, but adequate hair potassium, was observed in cystic fibrosis, a chlorine ionic channel disease [25]. This finding should greatly improve the diagnosis of that inherited genetic disease. Indeed, cystic fibrosis is currently definitively confirmed only by finding high levels of chlorine in the human sweat, a technically very demanding diagnostic procedure that may be carried on in only a few laboratories in the entire world. It is pertinent to note here, that according to our congress reported data, the bio element lanthanum somehow mimics sodium metabolism, whereas the bio element rubidium acts like a potassium internal metabolic "shadow" (Vignette 3). Here presented data suggests that the optimal Golden Range sodium concentrations along the linear segment of the dose-response sigmoid saturation curve are 411 to 1313 and 272 to 1117 for men and women, respectively. Similarly, the optimal hair potassium concentrations are 315 to 974 and 137 to 330 for men and women, respectively (Table 1).

Vignette 3: Phosphorus Metabolic Node (hub)

The field of bio element metabolic interactions is waste and complex (Figure 7). Moreover, these interactions were studied by following the paradigm that we may vary only one parameter at a time. However, the life is evidently a much more complex phenomenon than the simple mechanical cause and effect relationships. Indeed, our bodies are simultaneously exposed to numerous metabolic stimuli of varied intensity. And all these metabolic stimuli are dispersed across the other numerous metabolic receptors. Evidently, the life is not a simple linear flow process, but a network of numerous different streams which may changeably mingle to keep the organ homeostasis steady.

After studying hair multi bio element profiles with principal component analysis, we identified their grouping in definitive clusters [5]. Two clusters were prominent (a) sodium and potassium cluster (Na-K) and (b) magnesium and calcium cluster (Mg-Ca). However, we also observed that beside the Na-K and Mg-Ca pairing, the members of this affinity pairs have around themselves the other elements of similar chemical characteristics, some kind of their "shadow". Indeed, we need a new way shown in this Vignette to present bio element interactions and beyond the current model of linear diagonal display. Apparently, a web-like cross-balanced models like this where Na-K and Mg-Ca pairs are cross=balanced over the centrally positioned phosphorus as shown in this Vignette. Here, we have a model involving five elements at a time. New statistical methods need to be developed to handle such web-like structures.

It is reasonable to assume that energy production has evolved around phosphorus, and that this energy drives the homeostatic energy necessary for Na-K ionic exchange, and signal transduction and ossification mediated by Mg-Ca.



Calcium and magnesium (Figure 3 middle column)

Calcium and magnesium are another two essential electrolytes in our family of bio elements [26,27]. The Min adequate hair calcium concentrations are 291.0 and 487.7 for men and women, respectively. Calcium is evidently the most abundant mineral bio element in the human hair (Figure 2), and also it is a bio element that has a distinctly high sex dependent accumulation in the women hair. Indeed, hairs Max for calcium concentrations are 816.4 and 4426.0 for men and women, respectively. It is really amazing how our metabolism operates

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Table 1: Adequate bio element nutritional status: adequate bio element nutritional status of men (m) and women (w) as assessed with a hair median derivatives bioassay.

Element		Adequate (Linear Portion of a Sigmoid Curve) Range ($\mu g \cdot g^{-1}$)							
		Minimum (Min) (Lower Limit)		Median		Maximum (Max) (Upper Tolerance Limit)		Golden Range Yardstick Conditionally optimal range (30%-90% of Adequate range)	
		Men	Women	M	W	Men	Women	Men	Women
Calcium	Ca	291	487.7	492	1721.4	816.4	4420	599-761	971-4195
Zinc	Zn	126	131	179	183	247	234	103-198	181-224
Phosphorus	P	121.9	124.5	150.8	154	184.1	199.2	131-188	147-177
Sodium	Na	84	55.6	471.4	254	1450	1397	411-1313	272-1117
Potassium	K	25.8	8.9	31.5	14.25	1079	467	315-974	137-330
Magnesium	Mg	20.5	29.7	47.1	137.2	90.2	279.6	23.9-32.2	75.0-254.6
Silicium	Si	11.01	11.58	12.99	30.58	59.86	85.76	14.67-54.97	23.21-78.34
Copper	Cu	8.5	9.11	11.1	11.8	19	18	15.85-17.95	15.33-17.11
Iron	Fe	6.09	6.11	12.72	32.19	28.23	12.42	8.4-26.02	6.74-11.79
Aluminum	Al	2.7	1.86	6.54	4.74	17.49	14.29	5.14-16.01	5.59-13.06
Boron	B	0.771	0.472	2.21	1.04	6.51	3.89	2.49-5.94	1.48-2.55
Strontium	Sr	0.42	0.85	0.867	1.28	3.12	7.26	1.23-2.85	2.77-6.62
Chromium	Cr	0.212	0.389	0.397	0.317	0.867	0.626	0.197-0.588	0.231-0.395
Iodine	I	0.15	0.15	0.482	0.508	1.765	1.96	0.436-1.603	0.257-0.531
Selenium	Se	0.134	0.078	0.346	0.269	0.701	0.623	0.304-0.644	0.233-0.569
Nickel	Ni	0.098	0.15	0.215	0.351	0.432	0.926	0.100-0.300	0.233-0.600
Manganese	Mn	0.09	0.091	0.1	0.118	0.749	0.628	0.288-0.863	0.253-0.574
					nano $g \cdot g^{-1}$				
Molybdenum	Mo	34	27	49	39	71	57	45-67	44-76
Silver	Ag	15	15	50	76	22	69.5	75-195	22-63
Lithium	Li	15	14	28	25	100	86	42-92	36-79
Cobalt	Co	6	9	14	28	22	74	49-74	41-79
Gold	Au	7	7	30	34	61	90	16-55	27-87

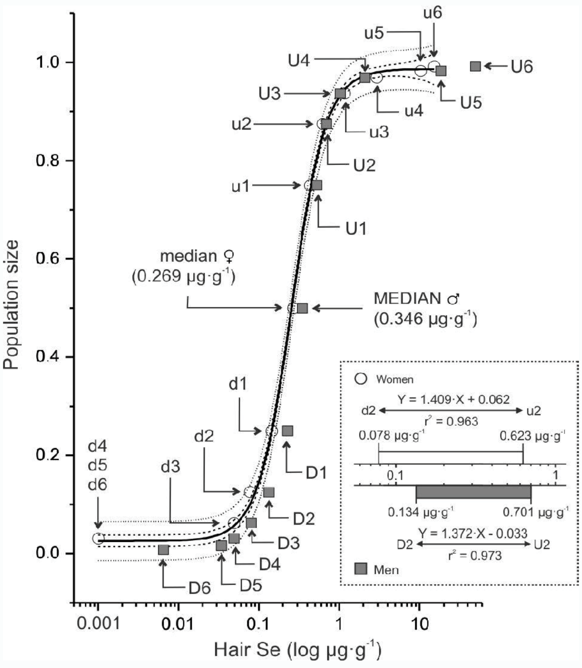

Figure 5b: Hair selenium sigma.

under such concentration diversity (over the two orders of magnitude). What are the energy costs of maintenance of such a homeostasis range and its adaption capacity remains to be explored. However, the suggested Golden Range optimal calcium concentrations range along the linear segment of the dose-response sigmoid saturation curve is 591 to 761 and 971 to 4195 for men and women respectively. At the same time, the corresponding Golden Range hair magnesium levels were Min 20.5 and 29.7 for men and women, respectively, whereas

Table 2: The median derivatives bioassay for assessing the bio-elements nutritional status.

Median (M0, $\mu g \cdot g^{-1}$)			
Median Derivative Downward (Descending)		Median Derivative Upward (Ascending)	
Branch (D0, PS/2=0.500)		Branch (U0, PS/2=0.500)	
Descending Median Derivatives		**Ascending Median Derivatives**	
D1=D0/2	0.25	U1=U0+U0/2	0.75
D2=D0/4	0.125	U2=U1+U0/4	0.875
D3=D0/8	0.062	U3=U2+U0/8	0.937
D4=D0/16	0.03	U4=U3+U0/16	0.969
D5=D0/32	0.016	U5=U4+U0/32	0.983
D6=D0/64	0.008	U6=U5+U0/64	0.992

the hair magnesium Max were 90.2 and 270.6 for men and women, respectively. The suggested optimal Golden Range hair magnesium concentrations were 21.9 to 32.2 and 75.0 to 254.6 for men and women, respectively. Our results showed a marked sex difference in the hair concentration of calcium and magnesium; both bio elements were higher in women than men.

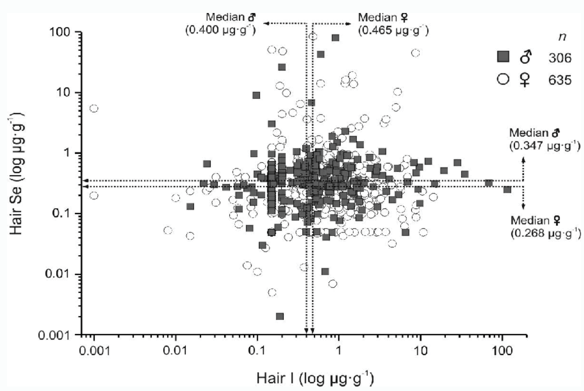

Figure 6: Hair Se and I.

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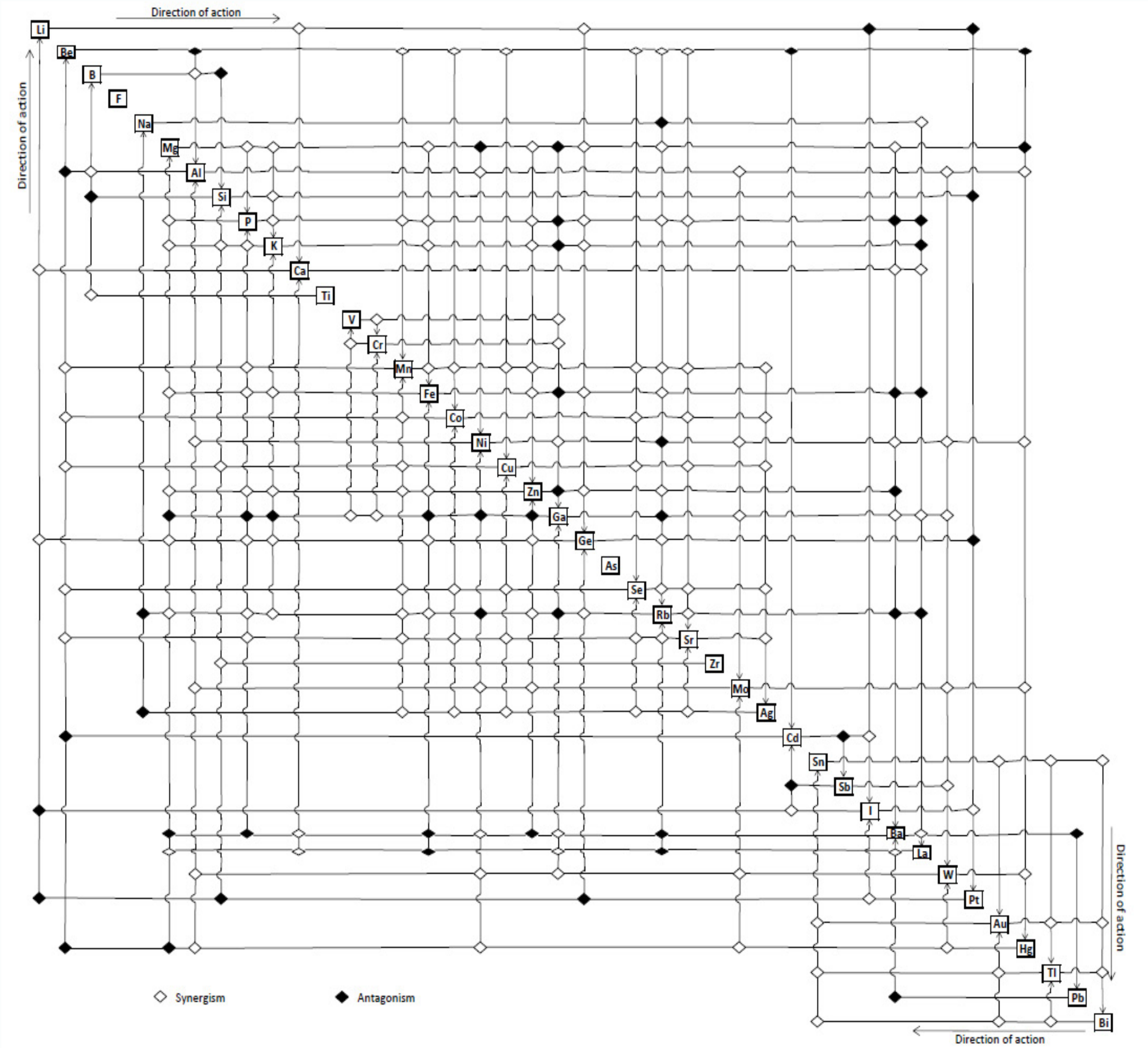

Figure 7: Bio element interactions.

Of course, there is a wide overlapping area between the two bio elements for both sexes, but the linear segments of the sigmoid saturation curves for these two bio elements were distinctly different in their slope tilts (Figure 3). Indeed, some human diseases, especially the stone forming pathology, are more prevalent in women than men [28]. As a matter of fact, the mineral metabolism differences of calcium in men and women, were sporadically observed and reported in the literature, but generally neglected and avoided in discussion.

We also observed an illustrative case of a women subject (No. 161) who had very high Ca hair concentrations (above 4200) in two separate hair sample analysis. Further medical diagnostic procedures revealed that she had a hyperparathyroidism. It should be noted that diagnosing hyperparathyroidism is a considerable diagnostic endeavor [29]. Later on, it was found, that our hair multi bio element profile analysis confirmed other author findings of high hair calcium in hyperparathyroidism [30]. Also, the osteotrophic bio elements (bone seekers), like Sr showed identical sex dependent behavior as did Ca and Mg; they are all higher in women. The sex dependent differences in bone metabolism need to be acknowledged since osteoporosis is more prevalent in women. Moreover, Hans Selye, the father of the human “stress” health paradigm, demonstrated how the systematic tissue calcification, i.e., calciphylaxis (internal calcification of tissues). may be induced with the combined administration od high doses of calcium, parathyroid hormone, and vitamin D. Interestingly enough, such a calciphylaxis may be avoided or alleviated by concurrent administration of magnesium salts [31]. We may consider calciphylaxis to be a special case of malnutrition where the complex high and imbalanced doses of the participant nutrients may induce disastrous health effects.

The box-plot Figure 8 is shown here to allow a cross comparison of the entangled bio element pairs P-Zn, Ca-Mg, and Na-K. Essentially, the Figure 8 demonstrated the potential role of the hair as an integrative multi bio elements sensor organ in the human body.

Silicon, copper, iron, aluminum, boron, strontium, chromium, nickel, manganese, molybdenum, silver, lithium, chromium, nickel, cobalt and gold

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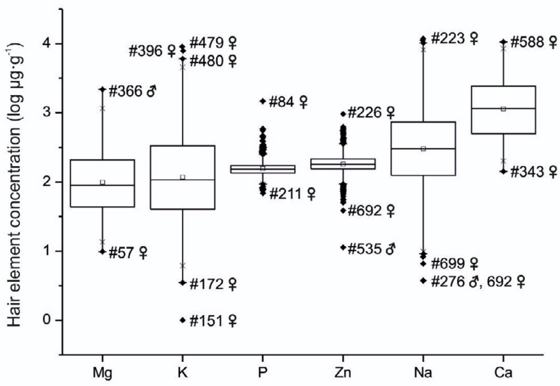

Figure 8: Box-plot comparison of six bio element pairs: Mg-Ca, K-Na and P-Zn.

In the preceding text, the eight exemplary bio element pairs, i.e., P-Zn, I-Se, Na-K, and Ca-Mg, in the human hair were analyzed in a great detail and accompanied with figures. For the rest of the fourteen bio elements, i.e., Silicon, Copper, Iron, Aluminum, Boron, Strontium, Chromium, Nickel, Manganese, Molybdenum, Silver, Lithium, Cobalt, and Gold, the respective reader will find their defined nutritional status determinants in (Table 1). There, the data are shown as reference values to differentiate between the bio element deficiency and excess, and (more important), what is their boundaries of the adequate and optimal nutritional status for men and women, respectively. The more detailed information about the metabolic role off these bio elements in the human body, health and the diet may be found in a WHO informative book on vitamins and minerals [32] and on their toxicity [3].

Indeed, bio elements are involved or help us image numerous health impairments like the relationship of zinc deficiency and alopecia [33], the great allergy inducing potential of Co, Cr, and Ni [34]; the role of copper in urticaria [35], the place of boron in the rheumatic diseases [36], the role of skin absorption of bio elements [37], the metabolic role of metals in human depression [38], and the effect of sub-pharmacological doses of Li in depression [39]. The sensitivity of infant brain on lead exposure [40], and olfactory route of vectored bio element particle matter in the brain [41], to name a few related research subjects. Special attention needs to be paid to the study of the physiology of bio element entanglement phenomenon alike that observed for Na and K, and Ca and Mg, in this paper.

This story on bio element metabolic peculiarities may go on, from bio element to the bio element, and it will only show how lacking is our knowledge about their mutual interactions in a complex body metabolic "internet" network (Figure 7). It should be noted that the here shown metabolic bio element interactions were induced with the high doses of the bio elements that were unusually high in comparison to those that we may find in the normal human diet. Moreover, the question of the various bio element composed mixtures on their nutritional status also needs a novel approach for its elucidation.

Conclusion

At the end of this article on assessing the bio elements nutritional status we may conclude how hair is a superb biological indicator tissue of a great potential in precision medicine. Once we accurately did the chemical analytical work, there remains for us to focus our mind and reflect on the biological meaning of our analytical chemical results. The hair median derivatives bioassay provides us with an insight of how much of a dietary bio element became actually incorporated in our body. Hair is itself a complex biological multi-sensor of the bio element metabolic behavior, and, in a way our personal metabolic study laboratory. Now, we get the possibility to fully control an individual dietary bio element intake and tailor made an Rx and, moreover, to control bio element nutritional supplementation. Indeed, surveying the multi bio element profiles proves to be a useful simple screening diagnostic test for numerous metabolic and other health disturbances. Let us conclude with a statement, that adequate, quantitative and qualitative, bio element precision medicine nutrition, is the essential prerequisite for human health.

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Appendix

Hair bioelement analysis

A strand of hair 5 cm to 7 cm long and weighting less than one gram would be cut with titanium coated scissors over the anatomically well-defined bone prominence at the back of the skull (lat. *protuberantia occipitalis externa*). The individual hair samples were further minced into strands less than 1 cm long prior to chemical analysis, stirred 10 min in an ethyl ether/acetone (3:1, w/w), rinsed three times with the deionized H_2O (18 MΩ·cm), dried at 85°C for one hour to constant weight, immersed one hour in 5% EDTA, rinsed again in the deionized H_2O, dried at 85°C for twelve hours, wet digested in HNO_3/H_2O_2 in a plastic tube, sonicated, and microwaved. The digested solutions were quantitatively transferred into 15 ml polypropylene test tubes. They were rinsed three times with the deionized water, and the rinses were transferred into the individual test tubes. These test tubes were filled up to 15 ml with deionized water and thoroughly shaken to mix. The samples were run in NexION 300+NWR 2013 spectrometer (Perkin Elmer, USA). Graduation of the instrument was carried out with a nonelement Perkin Elmer reference solution. We used certified GBW09101 Human Hair Reference Material (Shanghai Institute for Nuclear Research, Academia Sinica, Shanghai 201849, China) to validate the quality of the analytical work.

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