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RELATIONSHIP BETWEEN DIET AND HEAVY METALS IN HIGH RISK OF THE ENVIRONMENTAL TOXICITY AREAS. IMPLICATION FOR CANCER PREVENTION

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ABSTRACT: Background: *The continuous exposure of the population to xenobiotics inevitably leads to accumulation along with the resulting increased inflammation, related chronic diseases and cancer risk. The authors aim to study dietary factors which modulate the effects of environmental toxicity related to the presence of "heavy metals" in order to minimize the risk of chronic damage in subjects who are exposed to high-toxicity risk areas.*

Patients and Methods: *Sixteen subjects living in the high-risk pollution in areas between Caserta and Naples which had received a diagnosis of heavy metal poisoning for various reasons were recruited. The following assays were carried out: i) analysis of the composition of membrane lipids, as biomarker of cellular metabolic imbalance; ii) bioelectrical impedance analysis for the evaluation of phase angle and sodium/potassium exchangeable ratio, as biomarkers of inflammatory and metabolic alterations; iii) mineralogram to assess the levels of heavy metals accumulated in hair.*

Results: *After ninety days of diet and supplementation, there was a significant reduction in the average levels of toxic metals. In particular, 81% of partecipants reported a decrease in the value of lead, 69% in the value of cadmium, 44% in the value of aluminium, 31.3% of participants shown a decreasing in the normal range of mercury due the food plan. In addition, statistical analysis were performed.*

Conclusions: *The results show that proper food hygiene which leads to fundamental changes in lifestyle can effectively counter bio-accumulation, thereby representing not only a primary prevention strategy but also acquiring real drug value given the therapeutic effects it produces in existing cases of overt pathology.*

KEY WORDS: *Heavy metal assay, Pollution in Caserta and Naples Area, Lipidomic profile, Hair Mineralogram profile.*

INTRODUCTION

Toxic metals are ubiquitous pollutants that enter our bodies through smoking, food, drink, air, water, cosmetics, dyes, orthopaedic implants, piercings, tattoos, drugs, clothes, paints and daily objects which tend to bioaccumulation[1,2], thereby representing an emerging health and environmental hazard[3]. In fact, when not balanced by adequate detoxification, the continuous exposure of the population to these toxins inevitably leads to accumulation along with the resulting increased inflammation risk and related chronic diseases[4-8]. Given the high intoxication rates in subjects, including those living outside high-risk

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areas[9], food selection must be based on quality of predominantly plant origin[10], despite the fact that the danger of contamination is notable even with proper nutrition (which calls for 5 servings of vegetables per day). This choice must prevail over other food choices[11] in spite of the fact that there is also the possibility of fruit and vegetable contamination for crop areas which meet "organic" protocols – i.e. where the use of pesticides, herbicides and fertilizers is not allowed – since foods deriving from these crops may contain traces of heavy metals (from contamination with polluted water, acid rain, non-organic areas surrounding the organic farm)[12].

In this study, the authors evaluated the associations between the dietary habits of subjects living in high risk areas (the so-called "land of fires", the area between Caserta and Naples), bioaccumulation, and the extent to which diet can reduce the effects of "bioaccumulated" metal toxicity[13]. Personalized recommendations for each study subject and, when necessary, nutraceutical integration were formulated based on the cross-evaluation of the following parameters: the FFQ (Food Frequency Questionnaire), the study of fatty acids in mature red blood cell membranes[14,15] and the study of toxin bioaccumulation in hair (a technology that uses atomic emission spectrometry, mineralogram reported by WHO as the most accurate measure for revealing heavy metal toxicity)[16,17].

The assessment was repeated after 90 days. Sixteen residents of the Caserta/Naples urban area were selected, homogeneous for lifestyle and education. All 16 subjects completed the integrated food plan (consuming mostly vegetables, legumes, seeds, roots and pumpkins), showing significant benefits in terms of bioaccumulation (as evidenced by the mineralogram) despite living in a highly contaminated region[13]. Previous research had suggested that some nutrients present in raw vegetables – such as selenium, vitamin A, iron, folic acid and zinc – may help the body defend itself against the attack of toxic metals[18,19].

The mechanism through which phytonutrients are able to chelate minerals and detoxify the body is not clear. Given the importance of nutrition as "intoxicating/detoxicating" factor, this topic undoubtedly requires further research in order to validate its potential application and inclusion in the guidelines for primary prevention. To this end, further studies should include significant sample sizes and be conducted using double-blind *versus* placebo controls. As shown by the results attached herein, the combination of micronutrients contained in our protocol had an undisputed "gentle" chelating action despite the presence of toxic minerals in the vegetables consumed several times per day. Finding integrated strategies that can mitigate toxic impacts and translate them in guidelines is therefore of primary importance. To date, the scientific evidence on dietary approaches which mitigate the risk of toxic metals is scarce[20]. This study brings a positive message to the people living in high-risk areas, revealing that plant-based diets correspond to health and wellness, thereby motivating the population to make a conscious food selection of local origin[21].

PATIENTS AND METHODS

Sixteen subjects aged 3-73 living in the high-risk areas between Caserta and Naples which had received a diagnosis of heavy metal poisoning for various reasons were recruited. The following assessments were carried out for the purposes of recruitment:

1. Food Analysis and FFQ followed by analysis of the quantitative/qualitative composition of membrane lipids, as biomarker of cellular metabolic imbalance.
2. Bioelectrical impedance analysis for the evaluation of phase angle and sodium/potassium exchangeable ratio, as biomarkers of inflammatory and metabolic alterations.
3. Mineralogram to assess the levels of heavy metals in hair.

The bioelectrical impedance analysis and mineralogram were repeated after ninety days of diet and personalized nutraceutical supplements. The mineralogram was carried out using atomic emission spectrometer (ICP-OES) with ultrasonic nebulizers following microwave mineralization in acid solution (HNO_3). Given that metal activity in terms of ROS production (so-called free radicals) and consequent oxidative damage is well known in literature, this phenomenon was studied by observing the modification of fatty acids in the membrane of mature red blood cells.

Study duration

Ninety days, starting 19/06/2014

Inclusion criteria

Subjects aged 3-73 living in high-risk areas between Caserta and Naples who spontaneously and who had received a diagnosis of heavy metal poisoning for various reasons. From the moment of inclusion, all subjects suspended existing therapies with the exception of life-saving medication.

Exclusion criteria

Pregnant women, patients undergoing immunotherapy treatment, patients residing outside the province of Naples and Caserta.

Number of subjects

16 (originally 18, however two did not complete follow up in accordance with protocol)

Study methodology

- Informed consent from patient or parents (for minors);
- Medical visit, food history with FFQ and lipid analysis of mature red blood cells;
- Bioelectrical impedance for the assessment of body composition;
- Mineralogram.

Protocol

Each participant started their personalized food plan and received training on how to keep a daily food diary and a journal for any signs or symptoms considered important. Subjects were summoned every thirty days. After ninety days, participants were visited and the information from their journals was taken into consideration.

Food plan

Balanced diet as follows: Complex Carbohydrates 55%; Protein 20%; Lipids 25%. The food plan administered to participating subjects was predominantly made up of proteins from plant origin with a limitation of those from animal sources. Furthermore, it had the following characteristics:

a. Calorie levels and macronutrient balance were calculated by combining the analysis of the basal metabolic rate, obtained through bioelectrical impedance (direct method), and the use of the most reliable mathematical formulas available in literature (indirect method).
b. Main sources of macronutrients (pumpkin, roots, whole grains rich in fibre and vegetable protein): brown rice, buckwheat, barley, spelt, quinoa. Fish meat. Eggs and white meat, one portion per week.
c. Main sources of Micronutrients: seasonal fruits and vegetables, whole or as juice (obtained by centrifugation/extraction). These foods come from local markets, suggesting a rotation of vegetable type and place of purchase.
d. Other foods: non-creamy plain yogurt, miso rice, turmeric, ginger, bitter almonds, walnuts, green tea, 50% blend of extra virgin olive oil and flaxseed oil. Still water of low residue, slightly alkaline pH and low temperature at source.

RESULTS

It has been estimated that the subjects followed the treatment plan to 70% at most.

The data reported reveals that there is a correlation between food choices and concentration of toxic minerals in the hair. As stated in the methodology, all subjects participating in the study filled out an evaluation questionnaire on the diet they had followed up until that moment. The "food frequency questionnaire" was chosen as its validity has been recognized by the Ministry of Health. Analysis of the questionnaires revealed that there was a strong imbalance in excess animal protein, presumably for reasons related to the high water and land pollution in the subjects' area of residence (Figure 1). Specifically, prior to receiving our food rebalancing protocol, the 16 subjects participating in the study, respectively, from the ideal Mineral Test, all had an excess of mercury (Hg), 50% of them showed an excess of lead (Pb), 68,8% of an excess of aluminum (Al), 12.5% of an excess of chromium and

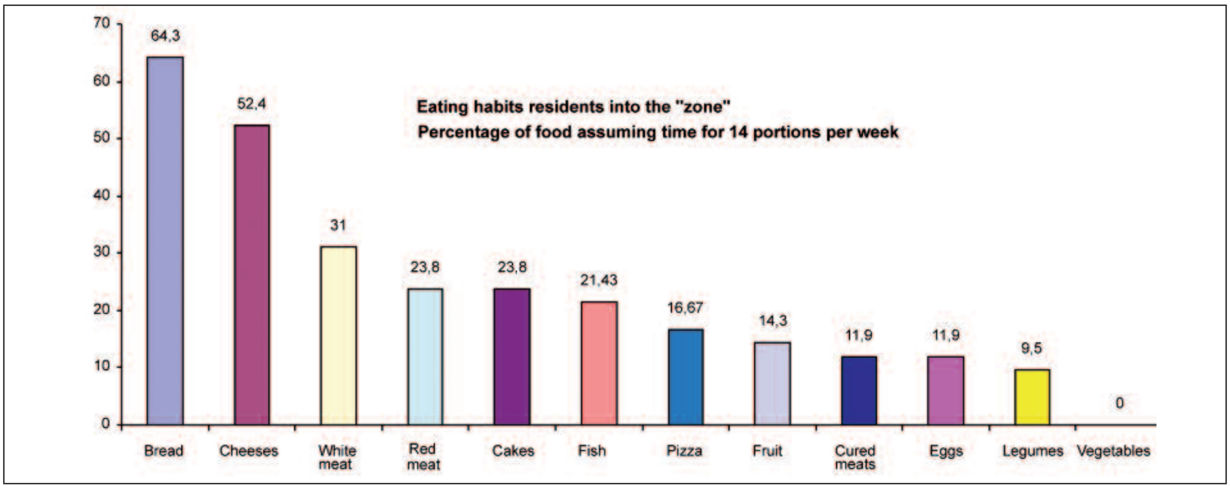

Figure 1. Percentage of food assuming time for 14 portions per week by residents into the "zone".

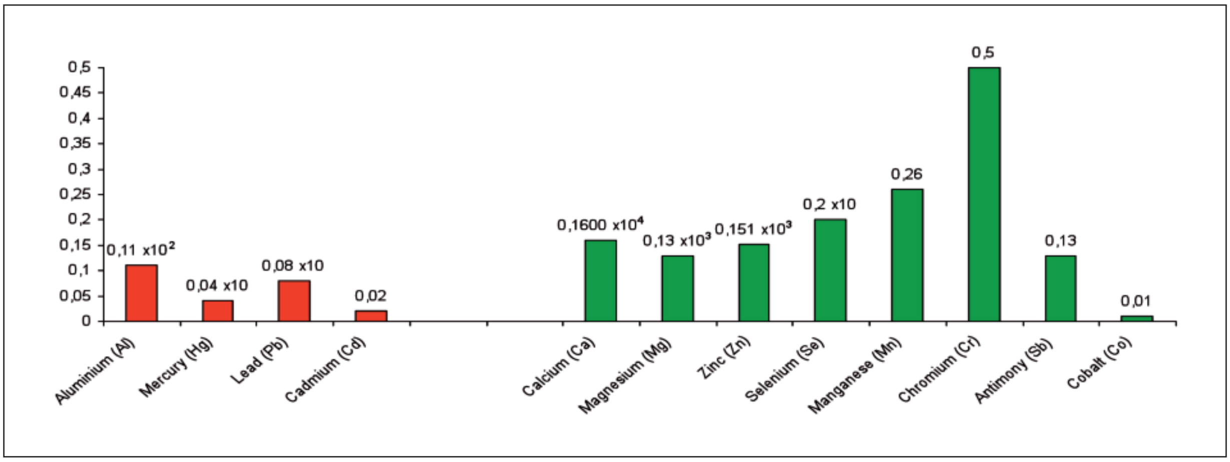

Figure 2. First test of mineralogram.

6.3% of an excess of tin (Sn), while for the cadmium (Cd) all values where within the ideal interval. Furthermore, 68.8% of them showed a deficiency of chromium (Cr) and tin (Sn) (Figure 2).

After ninety days of diet and supplementation, there was a significant reduction in the average levels of toxic metals. Although additional studies are needed, the tendency to rebalance key minerals in nutritional deficiency (Ca, Zn, Mn, Mg, Co, Sn) has been shown in all subjects (Figure 3, Table 1).

In particular, 81% of partecipants reported a decrease in the value of lead, 69% in the value of cadmium, 44% in the value of aluminium, 31.3% of participants reported a decrease in the value of mercury after following the food plan, thereby returning in the ideal range. The percentage of subjects with lead values in excess rose from 50% to 75%. Moreover, the percentage of subjects with excess aluminium (Al) slightly decreased from 68.8% to 56.3. The nutritional minerals, instead (Ca, Cr, Zn, Mn, Mg, Co, Sn) have returned to the normal range.

STATISTICAL ANALYSIS

In order to have an estimate of the statistical significance (with a confidence level of 95%) of changes in the distribution of the values of individual trace elements recorded in subjects under examination, before and after following the protocol of rebalancing, we chose to make the non-parametric test for dependent samples, Wilcoxon test, as typically the distribution of values of trace elements is nonparametric (the normality test of Shapiro-Wilk has given a positive result, ie, there are significant differences between the distribution of these values and the standard normal distribution/parametric).

From the results of the Wilcoxon test performed for each individual trace element, has emerged that there is a statistically significant difference ($p < 0.05$) between the mean of the distribution of the values of chromium (Cr) at the first examination and the mean of the distribution of the values of

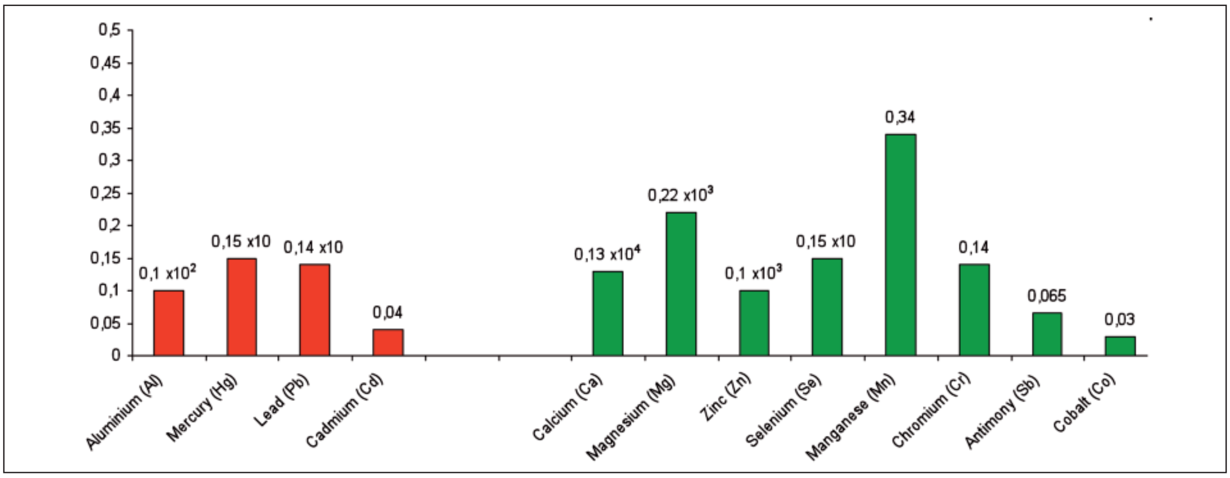

Figure 3. Second test of mineralogram.

TABLE 1. PERCENTAGE OF SUBJECTS IN EXCESS OR SHORTAGE FOR SINGLE MINERAL.

In excess at 1° test	In excess at 2° test	Deficiency at 1° test	Deficiency at 2° test
Mercury 100 %	Mercury 62.5 %	Manganese 50 %	Manganese 43.75 %
Aluminium 68.75 %	Aluminium 56.25 %	Magnesium 37.5%	Magnesium 6.25%
Lead 56.3 %	Lead 75 %	Calcium 31.25 %	Calcium 18.75 %
Calcium 50 %	Calcium 62.5 %	Cobalt 81.25%	Cobalt 6.25%
Magnesium 43.75 %	Magnesium 68.75 %	Chromium 68.75%	Chromium 56.25%
Selenium 75 %	Selenium 25 %	Platinum 25%	Platinum 12.5%
Antimony 87.5 %	Antimony 18.75 %	Tin 68.75%	Tin 68.75%
Tin 6.25 %	Tin 6.25 %	Zinc 31.25%	Zinc 68.75%

chromium (Cr) at the second examination after following our protocol ($z = -2.017$, $p = 0.044$). Furthermore, were found two differences tend significant with respect to the distribution of the values of lead (Pb) ($z = -1.810$; $p = 0.070$) before and after following our diet rebalancing. In fact, in particular, chromium (Cr) is reduced from an average of 0.5354 ppm to an average of 0.1384 ppm, from the ideal average value to an average value in slight deficiency. The lead (Pb) is increased from an average of 0.8065 ppm to an average of 1.3889 ppm, ie, in excess of the average interval ideal is increased. The mercury (Hg) is increased from an average of 0.3913 ppm to an average of 1.4644 ppm, in other words, on average excess than the interval ideal is significantly increased after treatment. Cadmium (Cd) is slightly increased from an average of 0.0221 ppm to an average of 0.0398 ppm, or, in the average level of cadmium (Cd) has remained the ideal range. The aluminum (Al) is slightly decreased from an average of 11.7045 ppm to an average of 10.1530 ppm while remaining on average considerably in excess of the ideal interval. Finally, tin (Sn) is increased from an average of 0.5555 ppm to an average of 0.7829 ppm, in other words, on average, by a slight deficiency has passed ideal interval.

DISCUSSION

The current literature, accounting the relationship between diet and bioaccumulation of toxic elements, is still very lacking. However, the few works published in this field, are extremely significant. Micronutrients intake have a significant effect on the toxicity and carcinogenesis caused by various chemical substances[22]. In addition Jia et al[23] concluded that a diet low in micronutrients is predisposing to metal toxicity.

The kind of diet we suggested to our patients, is very close to macrobiotic diet, such as whole grains beans, seasonal vegetables raw and cooked, vegetables, seasonal fruits, fish and white meat. The presence of minimal quantity of animal protein is essential, on second hand, because under some conditions the aminoacids can modulate the absorption of toxic metals (e.g. Taurine)[24]. We also introduced short periods of caloric restriction, in which we used water and oils (occasionally butter) to stimulate the mobilization of persistent lipophilic substances in oil reserves and to influence the enterohepatic circle to reduce the re-absorption of xenobiotic[25].

In addition to the comparison of the percentages of subjects in shortage/excess and the ideal range in the first test and the retest, a control group (benchmark) consisting of residents of the Campania region that supposedly follow a standard diet (library Mineral Test) was also used. The statistical significance of the differences in distribution of individual trace elements was carried out between the study group at the first test and the control group (benchmark) and between the distributions of trace elements of the study group on the retest and the control group (benchmark). The purpose was to provide a statistical significance that went beyond differences in percentages but which considered the entire distribution of individual trace elements recorded in the study group at the first test and second test (retest) and compare them with a "typical" distribution, ie, that of a population living in the same area that follows a standard diet (control group) (Figure 4, Table 2).

Similarly to the first examination of the study group, the Mineral Test control group has a nearly all subjects with excess mercury (Hg), a totality of subjects with cadmium (Cd), the ideal range, an equilibrium between the percentage of subjects in the range of ideal and excess of lead (Pb), a majority of subjects with excess aluminum (Al) and a majority of subjects with deficiency of chromium (Cr) and Tin (Sn). The purpose was to provide a statistical significance that, besides the sun percentage differences, consider the entire distribution of the values of individual trace elements

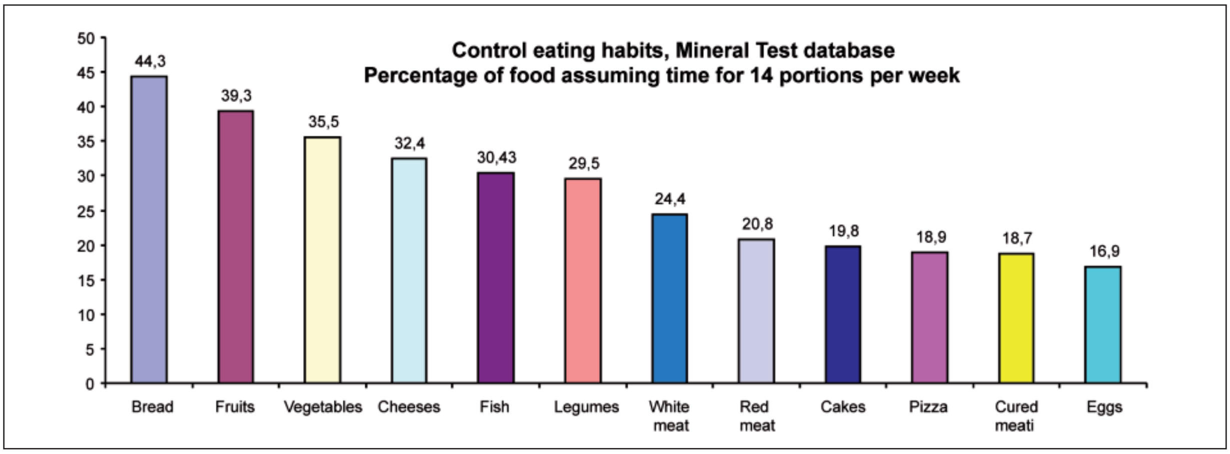

Figure 4. Mineral test database. Percentage of food assuming time for 14 portions per week.

recorded in the study group at the first test and the second test (retest), compared with the distribution "typical" or that of the population of the same territory that is assumed to follow a standard diet (control group).

To this end, given the non-parametric distributions of trace elements, nonparametric testing was also carried out between the two independent samples, i.e, the Mann-Whitney U test for each individual trace element with a confidence interval of 95% in order to test the statistical significance ($p < 0.05$) of the differences between the two groups, the study on the first test and the control (benchmark) and between that of the study according to the test and the control (benchmark).

The case-control analysis with the Mann-Whitney U test between the study group at the first test and the control group (benchmark) reveals a statistically significant difference for mercury (z = -2.612; p = 0.009), for cadmium (z = -2.338; p = 0.017) and a potential difference for vanadium (z = -1.668; p = 0.095). On the first test the study group showed an average mercury and cadmium level below that of the control group (benchmark) but nevertheless higher than the maximum value of the ideal range (Table 2). The two groups had similar mineral profiles for Cadmium (Cd), Lead (Pb), aluminium (Al), Chromium (Cr), Tin (Sn) and a significantly different mineral profile for mercury (Hg) and cadmium (Cd).

The 95% confidence level obtained in the Wilcoxon test and the Shapiro-Wilk test is the controlled variation between the distribution of the values of individual trace elements on the first hair test and the retest 90 days later (Table 3).

The Wilcoxon reveals that there is a statistically significant difference for each individual trace element ($p < 0.05$).

TABLE 2. STATISTICAL SIGNIFICANCE AND DISTRIBUTION OF INDIVIDUAL TRACE ELEMENTS RECORDED IN THE STUDY GROUP AT THE FIRST MINERAL TEST

Categorical demographic variables		Control group resident in the same province (benchmark) (mineral test database first test) (135 subjects) N(%)	Group study (16 subjects) N(%)	χ2 Pearson	*p*-value (Liv. Sign. must be <0.05)
Sex	Male	73 (54.1%)	7 (43.8%)	0.612	0.434
	Female	62 (45.9%)	9 (56.3%)		
City	Napoli (NA)	92 (68.1%)	6 (37.5%)	5.898	0.015
	Caserta (CE)	43 (31.9%)	10 (62.5%)		

TABLE 3. VARIATIONS BETWEEN THE DISTRIBUTION OF THE VALUES OF INDIVIDUAL TRACE ELEMENTS ON THE FIRST HAIR TEST AND THE RETEST 90 DAYS LATER.

Continuous demographic variables	Control group resident in the same province (benchmark) (mineral test database first test) (135 subjects)				Group study (16 subjects)				Student's *t* test	*p*-value (Liv. Sign. must be <0.05)*
	Mean	Std.	Dev.	Min	Max	Mean	Std.	Dev.	Min	Max
Età	38.5	18.583	3	72	35.23	19.212	1	75	0.646	0.519

*Between the mean of the distribution of the values of chromium (Cr) at the first examination and the mean of the distribution of the values of chromium (Cr) at the second examination (z = -2.017, p = 0.044). Tend significant for the vanadium (V) (z = -1.706; *p* = 0.088), lead (Pb) (z = -1.810; p = 0.070), chromium (Cr) from 0.5354 ppm to 0.1384 ppm), mercury (Hg), increased from an average of 0.3913 ppm to an average of 1.4644 ppm (greatly increased after the treatment), cadmium (Cd) passes from an average of 0.0221 ppm to an average of 0, 0398 ppm, aluminum (Al) from 11.7045 to 10.1530 ppm.

CONCLUSIONS

This pilot study allows us to state that a change in lifestyle and adequate nutrition education can significantly improve reproducible metabolic parameters.

The purpose of the diet treatment was, ultimately, promote cell physiology, membrane integrity and the rebalancing of nutritional minerals, in order to increase the cellular capacity to defend against exogenous substances known to be hazardous[26-28]. Our hypothesis, to be confirmed with further studies, is that by changing lifestyle and diet, it is possible to influence the phytonutrients and the intestinal flora (microbiota), promoting detoxification, thanks to the activity of specific bacterial strains[29-32].

This experience can also be assessed in terms of political economy. Published studies on the cost/benefit conducted with algorithms validated internationally, pose economic and ethical problems and allow to quantify economically illnesses or deaths spared[33-34]. The use of these algorithms could contribute to the maximization of resources devoted to the protection of environment and health, transforming a context of uncertainty in a calculable risk[35]. Those who today are cost, will become tomorrow in a gain for illnesses and deaths spared. Assuming that the benefits are observed after twenty years, and will last for the next thirty years, the algorithms allow to estimate and quantify the resources to invest, which must be proportional to the expected result in order to avoid waste and poorly investments[36]. This is, in our view possible, first by diet control.

Conflict of Interests:

The Authors declare that they have no conflict of interests.

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