Journal of Health Science 2016, 6(5): 77-86
DOI: 10.5923/j.health.20160605.03

Hair Zinc Level Affects Nociception in Humans: A Cross-sectional Study

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Abstract Purpose: This study aims to investigate the relationship between hair zinc levels and nociception/ pain tolerance in reference to dietary preferences, smoking and/or alcohol consumption and exercise in young men, aged 19-40 years old. Methods: Hair samples were collected from 42 recruited healthy soldiers, aged 19-40 years old. All subjects were asked to complete a detailed questionnaire including demographic data, education status, dietary preferences, smoking and alcohol use, exercise or athletic habits and then were submitted to a stress test. Data were subjected to statistical analysis via the SPPS program. Results: Zinc levels and pain tolerance were found linearly and positively correlated ($r=0.293$, $sig<0.05$), higher levels of zinc were observed in athletes ($t=-2.534$, $sig<0.05$) and a significant positive relation was registered between hair zinc levels ($rho=0.366$, $sig<0.05$), pain tolerance ($rho=0.291$, $sig<0.05$) and frequency of athletic activity. Foods providing high zinc levels, to the consumers, such as red meat ($r=0.324$, $sig<0.05$), white meat ($r=0.361$, $sig<0.05$) and legumes ($r=0.346$, $sig<0.05$) revealed higher correlation scores to pain tolerance, whereas consumption of red meat ($r= 0.447$, $sig<0.05$) and legumes ($r=0.355$, $sig<0.05$) showed also higher hair zinc levels. Persons performing athletic activity consumed more often red meat, legumes and seafood and presented higher zinc levels ($r=0.430$, $sig<0.05$) and higher pain tolerance ($r=0.428$, $sig<0.05$). Finally a negative relation between hair zinc levels and age ($rho=-0.337$, $sig<0.05$) was registered. Conclusions: Zinc seems to modulate somatosensory function, nociception and pain tolerance in relation to a variety of lifestyle parameters.

Keywords Zinc, Nociception, Pain tolerance, Physical exercise, Smoking, Alcohol, Diet

1. Introduction

Zinc is a key element in the pyramid of micronutrients [1]. More than 500 enzymes and 3000 transcription factors need zinc for their actions, highlighting the importance of zinc in homeostasis, immune function, oxidative stress, apoptosis and aging [2-4]. Zinc also mediates transmission of nociceptive stimuli from peripheral (PNS) to central nervous system (CNS). As regards the peripheral nervous system, it affects a variety of receptors and ion channels involved in the transmission of noxious stimuli towards more central structures, such as GABA (gama-aminobutyric acid) receptors [5], glycine receptors [6], NMDA (*N*-Methyl-D-aspartic acid) receptors, purinergic receptor P2X [7], the ASIC (Acid-Sensing Ion Channel) channel and some of TRP (Transient Receptor Potential) channels and voltage-gated Ca^{2+} and K^{+} channels which are required for neuronal excitability and neurotransmitter release [8]. In the CNS, zinc stored in the vesicles of the final endings of glutamatergic neurons, is released along with glutamate in the synapses, adjusting signal and neural plasticity [9]. Levels of trace elements, such as Zn, in blood serum are related to gender, age, smoking, alcohol consumption, sports and frequency of exercising and in particular to the dietary intake of antioxidant nutrients [10].

Skin components' (nails, hair) zinc level, reflect the recent exposure 2-3 months to the trace element and represent the body burden to Zn. [11].

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Published online at http://journal.sapub.org/health

2. Materials and Methods

2.1. Human Volunteers

Sixty two (62) recruited soldiers, 19-40 years old, voluntarily joined the research, after obtaining Institutional Ethical Approval, getting volunteers informed about the aim of the study and have them signing a declaration of consensus. Soldiers suffering any recent or chronic disease were excluded from this research. Finally, after careful inspection of the medical history, forty six (46) healthy persons were included and registered in the present study.

2.2. Questionnaire

a. General informations

Full name:

Somatometric/anthropometric data:

Height:
Weight:

Age group:

18-28: ❑
> 28: ❑

Birth place:

Residence place during the last five (5) years:

Education level:

Primary school graduate: ❑
Secondary school graduate: ❑
High school graduate: ❑

Graduate from

Vocational Training Institutes: ❑
University graduate: ❑
Post graduate studies: ❑

Occupation:

Where did you work the last two years?

b. Nutrition Habits

How often do you consume, in a weekly basis, each of the food categories below:

FOODS	DAI LY	5-6 TIMES	3-4 TIMES	1-2 TIMES	NEVER
Red meat					
White meat					
Seafood					
Legumes					
Pasta					
Vegetables					
Fruits					
Dairy					
cereals					
Oil/ olives					
Nuts					

Food categories according to Zn content and bioavailability:

RED (high) -> red meat (pork, calf), seafood (fishes, oysters, mussels), legumes, nuts

BLUE (medium) -> white meat, pasta, dairy products

GREEN (lower) -> vegetables fruits, whole grain cereals, oil/olives

c. Life Style Habits

Do you smoke? :

Yes: ❑
No: ❑

If the answer is yes, how many cigarettes do you smoke? :

10 cig./ day: ❑
20-25 cig./day: ❑
Over 25 cig./day: ❑

If the answer is yes, when did you start smoking? :

Less than a year: ❑
Between 1 to 5 years: ❑
Between 5 to 10 years: ❑
Over 10 years: ❑

ow often do you consume alcohol beverages? :

Never: ❑
Rarely: ❑

Only in social events and interactions: ❑

Often: ❑
Daily: ❑

hich kind of beverages do you prefer? :

Low alcohol content: ❑
Middle alcohol content: ❑
High alcohol content: ❑

Do you practice exercise / sport

(Basketball, football, volleyball, water polo, gym, etc):

Yes: ❑
No: ❑

If you do, how often? :

1-2 times per week: ❑
3-4 times per week: ❑
Daily: ❑
Never: ❑

d. Medical History

Do you have you any recent health problems? :

Yes: ❑
No: ❑

If the answer is yes, what kind of?

Are you under any medical treatment? :

Yes: ❑
No: ❑

If the answer is yes, what kind of?

How long are you under medication? :

1-2 weeks: ❑
2-4 weeks: ❑
Over 4 weeks: ❑

Do you take any Nutrition Supplements (NS)?:

Yes: ❑
No: ❑

If the answer is yes, what kind of?

How long do you take NS? :

1-2 weeks: ❑
2-4 weeks: ❑
More than 4 weeks: ❑

Are you allergic to? :

medicaments:

Yes: ❑
No: ❑

food:

Yes: ❑
No: ❑

anything else:

Yes: ❑
No: ❑

Have you undergone any surgery? :

Yes: ❑
No: ❑

Do you suffer any chronic disease such as:

Diabetes mellitus: ❑
Arterial hypertension: ❑
Skin diseases: ❑
Blood diseases: ❑
Gastrointestinal diseases: ❑
Arthralgia: ❑
Spine problems: ❑
Hepatitis A, B, C: ❑
Anything else: ❑
None of the above: ❑

Does any member of your family suffer a health problem? :

Yes: ❑
No: ❑

2.3. Sample Collection, Preparation and Zn Detection

Hair samples, 2-3 cm long, were taken from the occipital protuberance of each participant and collected in plastic polyethylene containers (zip). The procedure was carried out using stainless scissors and disposable gloves. Each container was labelled with a code-number corresponding to each participant as well as to the questionnaire completed by him. Volunteers were submitted to a stress test, by repetitively lifting (1 lift/sec) a 5 kg dumbbell with the hand, after the application of 180 mm Hg tourniquet pressure around the left arm if the participant was right- handed and vice versa, by means of a sphygmomanometer's cuff. Pain stimuli evoked due to ischemic fatigue and time between stress test initiation and pain perception were registered for each participant. Hair samples were analyzed in the laboratory of Physiology of the Medical Department of the University of Ioannina by Atomic Absorption Spectroscopy (AAS). Each hair sample was processed into acid digestion and then zinc content was detected. Reference material for the detection of the metal was Human Hair certified reference material NCS ZC81002b. Data were processed into statistical analysis, listed and coded by the SPPS program. Basic descriptive measures of position and dispersion (mean, standard deviation, median and minimum-maximum) were produced for quantitative - continuous variables, as well as frequency and relative frequency were calculated for each quantitive and nominal variable (smoking, educational level, etc.), Shapiro-Wilk test were used to identify if variables are normally distributed, as regards the independent variables, independent sample t-test was used to test the equality of the average of the answers, *coefficient of correlation* Pearson and Spearman was used to test bivariate correlations, the value of which shows the intensity of the linear relationship and their sign shows the direction of their relationship and finally the procedures were completed by graphical representations such as scatter diagrams and bar diagrams in the name of nominal and continuous variables respectively.

3. Results

3.1. Correlation between Zinc Level and Time of Pain Display

According to the results, time of pain display and hair zinc level are linearly and positively correlated ($r=0.293$, $sig<0.05$), indicating that the higher the hair zinc level the more the time of pain display is registered in healthy young males, aged 19-40 years old.

Table 1. Correlation coefficient between time of pain display and hair zinc level in healthy male humans (19-40 y)

		TIME OF PAIN DISPLAY (sec)	ZINC LEVEL (mg/dl)
TIME OF PAIN DISPLAY(sec)	Pearson Correlation	1	.293
	Sig. (2-tailed)		.048
	N	46	46
ZINC LEVEL(mg/dl)	Pearson Correlation	.293	1
	Sig. (2-tailed)	.048	
	N	46	46

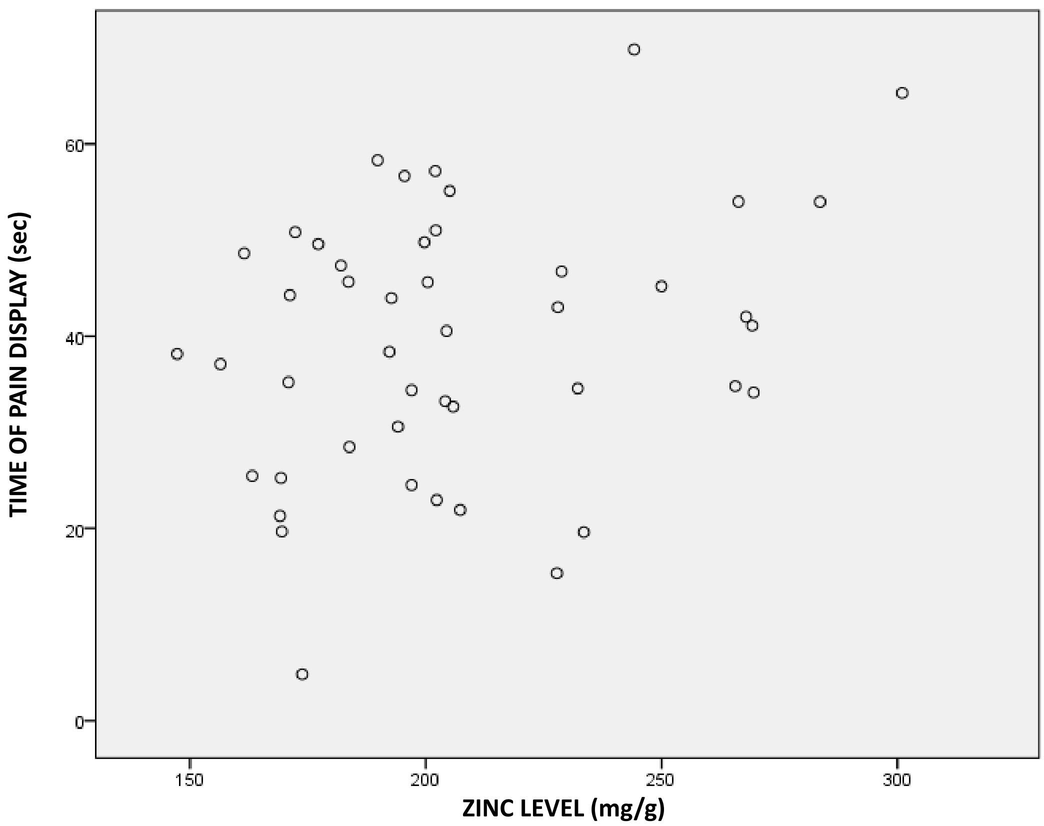

Figure 1. Hair Zn level vs time of pain display

3.2. Correlation between Time of Pain Display, Hair Zinc Level, Rate and Content of Alcohol Consumption, in Alcohol Consumers

Table 2. Correlation between time of pain display and hair zinc level and alcohol consumption and alcohol content. (Alcohol consumption 5 categories: never, often, daily, rarely, in social events)

		FREQUENCY OF ALCOHOL CONSUMPTION 5	CONTENT OF ALCOHOL
TIME OF PAIN DISPLAY (sec)	Correlation Coefficient	.363	.391
	Sig. (2-tailed)	.013	.007
	N	46	46
ZINC LEVEL (mg/gr)	Correlation Coefficient	-.006	.035
	Sig. (2-tailed)	.967	.818
	N	46	46

Results presented above show that time of pain display is linearly and positively correlated to the rate of alcohol consumption (rho=0.363, sig<0.05) as well as to the alcohol content (rho=0.391, sig<0.05).

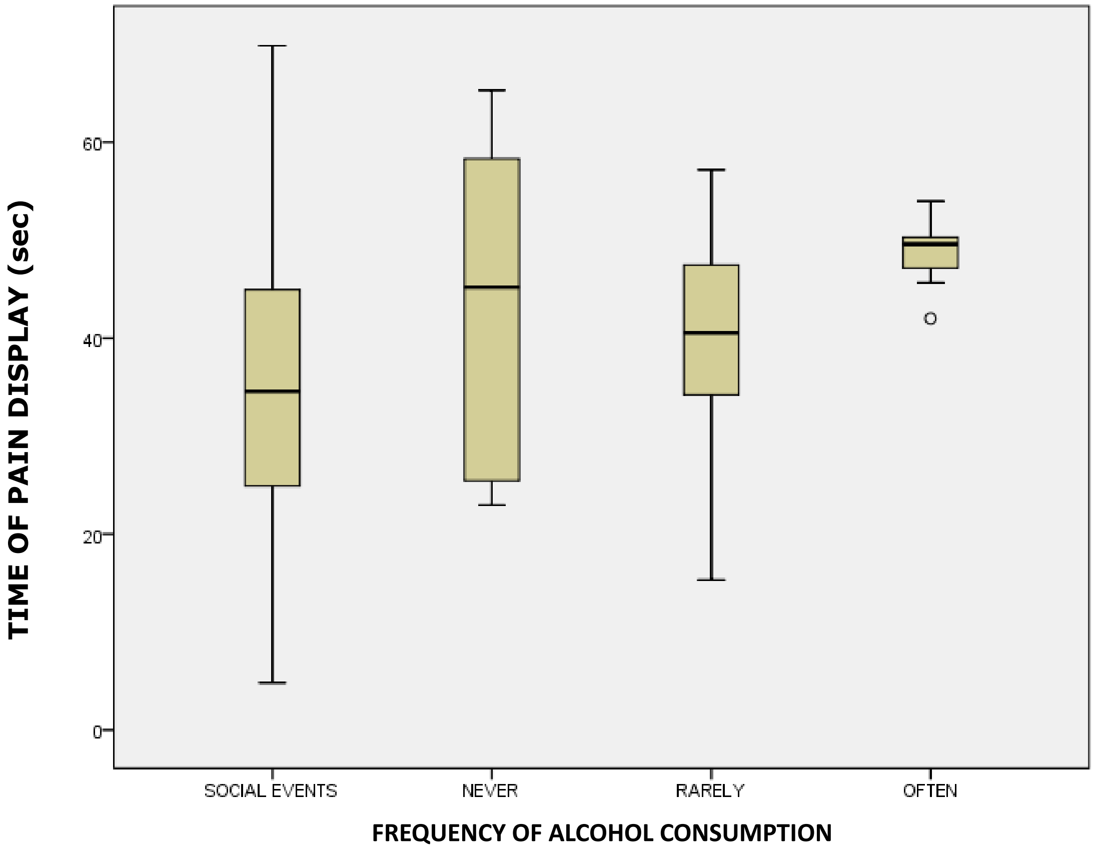

Figure 2. Comparative box plot of time of pain display and frequency of alcohol consumption

3.3. Correlation between Hair Zinc Level, Time of Pain Display and Exercise Practice

Table 3. Survey on the mean rates of time of pain display and hair zinc levels, between volunteers practicing (+) and not practicing (-) exercise

EXERCISE PRACTICE		*N*	*M*	*S.D.*	*t (sig.)*
TIME OF PAIN DISPLAY (sec)	–	20	36.0	13.5	-1.562 (0.125)
	+	26	42.3	13.7	
ZINC LEVEL(mg/gr)	–	20	192.5	25.5	-2.386 (0.021)
	+	26	217.7	41.4	

Statistical analysis via t-test for equality of means shows that significantly higher hair Zn level, is registered, in those participants who are practicing exercise (+) compared to those who are not (-) ($t=-2.386$, $sig<0.05$).

3.4. Correlation between Hair Zinc Level, Time of Pain Display and Frequency of Practicing Exercise

Table 4. Correlation between time of pain display, hair Zn level and frequency of practicing exercise

		FREQUENCY OF PRACTISE
TIME OF PAIN DISPLAY(sec)	Correlation Coefficient	.291
	Sig. (2-tailed)	.050
	N	46
ZINC LEVEL(mg/gr)	Correlation Coefficient	.366
	Sig. (2-tailed)	.012
	N	46

Results listed in table 4 show that there is statistically significant linear correlation between time of pain display and frequency of practicing exercise (rho= 0.291, sig<0.05). Statistically significant linear correlation is also registered between hair Zn level and frequency of practicing exercise (rho= 0.366, sig< 0.05).

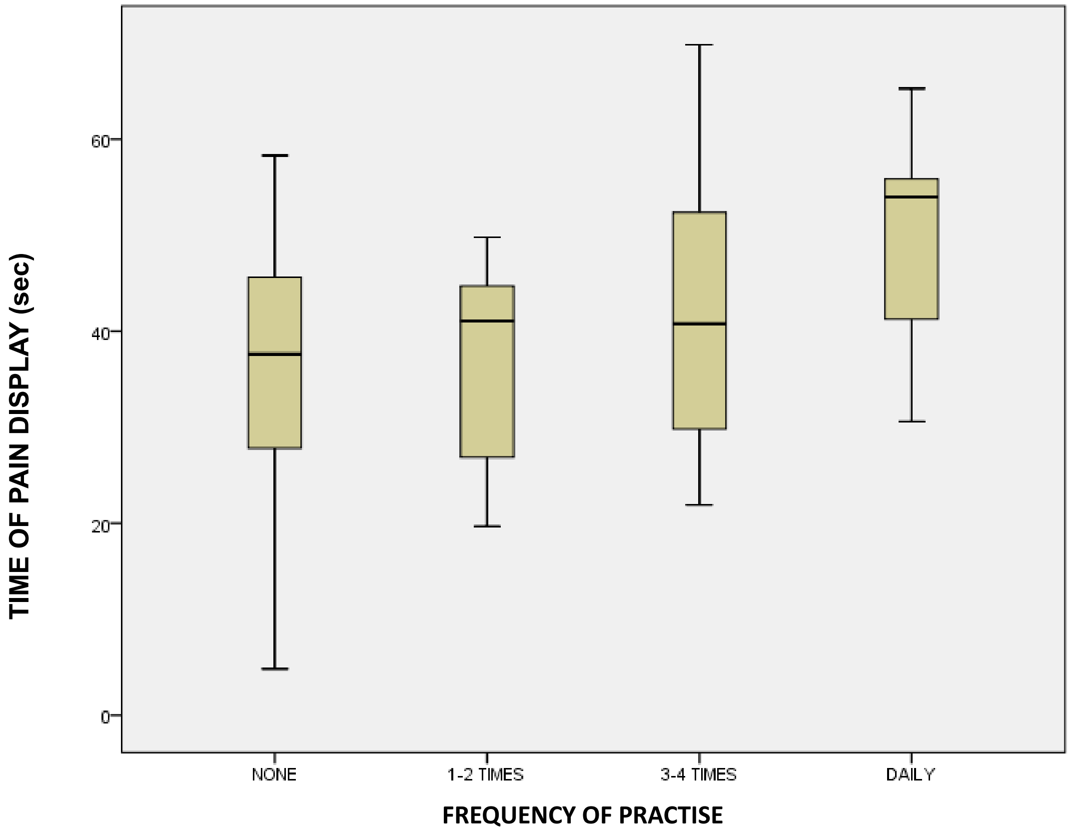

Figure 3. Comparative box plot of frequency of practise and time of pain display

3.5. Correlation between Hair Zinc Level and Time of Pain Display in Smokers and Non Smokers

Table 5. Correlation of time of pain display, zinc level and number of cigarettes

		CIGARETTES (whole sample)	CIGARETTES (smokers)
TIME OF PAIN DISPLAY(sec)	Correlation Coefficient	0.244	0.242
	Sig. (2-tailed)	0.103	0.254
	N	46	24
ZINC LEVEL(mg/gr)	Correlation Coefficient	0.179	-.440
	Sig. (2-tailed)	0.235	0.031
	N	46	24

Based on the results above, significant negative linear correlation was observed between zinc level and number of consumed cigarettes in smokers (24 persons) (rho=-0.44, sig<0.05). No significant differences were observed between smokers and non smokers, either to time of pain display or to zinc level (table 6).

Table 6. Means rates and standard deviation of time of pain display and zinc levels between smokers and non smokers

	SMOKING			
	NO		YES	
	Mean	S.D.	Mean	S.D.
TIME OF PAIN DISPLAY (sec)	36.83	13.99	41.99	13.45
ZINC LEVEL (mg/gr)	200.8	40.4	212.2	33.9

3.6. Correlation between Hair Zinc Level, Time of Pain Display and Diet

a. Food categories according to Zn content and bioavailability

Table 7α. Correlation between time of pain display, hair zinc level and food categories

(RED food = high, BLUE food = medium, GREEN food=low)

		RED (Red Meat, Seafood, Legumes, Nuts)	BLUE (White Meat, Pasta, Dairy)	GREEN (Vegetables, Fruits, Cereals,Oil)
TIME OF PAIN DISPLAY (sec)	Pearson Correlation	.375	.125	-.082
	Sig. (2-tailed)	.010	.406	.589
	N	46	46	46
ZINC LEVEL (mg/gr)	Pearson Correlation	.347	.141	-.104
	Sig. (2-tailed)	.018	.348	.492
	N	46	46	46

Based on the results above (table 7a)significant positive linear correlation appeared between time of pain display and "red" colored nutritional products, rich in Zn (r=0.375, sig<0.05)as well as significant positive linear correlation between zinc level and "red" foods (r= 0,347, sig<0.05).

b. Foods

Table 7b. Correlation between time of pain display and zinc level and certain foods

		RED MEAT	WHITE MEAT	LEGUMES
TIME OF PAIN DISPLAY (sec)	Pearson Correlation	.324	.361	.346
	Sig. (2-tailed)	.028	.014	.018
	N	46	46	46
ZINC LEVEL (mg/dl)	Pearson Correlation	.447	.037	.355
	Sig. (2-tailed)	.002	.808	.015
	N	46	46	46

Based on the results above important linear correlation was observed between time of pain display and consumption of red meat (r=0.324, sig<0.05), white meat (r=0.361, sig<0.05) and legumes (r=0.346, sig<0.05).

Significant linear correlation between zinc level and consumption of red meat (r=0.447, sig<0.05) or legumes (r=0.355, sig <0.05) was also registered.

3.7. Correlation between Zinc Level and Time of Pain Display and Age

Table 8. Correlation between time of pain display, zinc level and age

		AGE
TIME OF PAIN DISPLAY (sec)	Correlation Coefficient	.052
	Sig. (2-tailed)	.732
	N	46
ZINC LEVEL (mg/gr)	Correlation Coefficient	-.337
	Sig. (2-tailed)	.022
	N	46

Significant negative linear correlation between zinc level and age (rho=-0.337, sig<0.05) was registered.

3.8. Correlation between Zinc Level, Time of Pain Display and Food Consumption by Athletes

Table 9. Correlation between time of pain display, zinc level and food consumption by athletes

		RED (Red Meat, Seafood, Legumes, Nuts)	BLUE (White Meat, Pasta, Dairy)	GREEN (Vegetables, Fruits, Cereals,Oil)	FREQUENCY OF PRACTISE 4	FREQUENCY OF PRACTISE 3
ZINC LEVEL (mg/gr)	Pearson Correlation	.430	.259	.187	.286	.237
	Sig. (2-tailed)	.028	.201	.361	.157	.244
	N	26	26	26	26	26
TIME OF PAIN DISPLAY (sec)	Pearson Correlation	.428	.103	-.057	.354	.273
	Sig. (2-tailed)	.029	.617	.784	.076	.178
	N	26	26	26	26	26

Frequency of practice, 4 categories: not at all, 1-2 times, 3-4 times, daily

Both Zinc level and time of pain display presented significant positive correlation to consumption of "red" foods in subjects practicing exercise (r=0.430, sing<0.05), (r= 0.428, sing<0.05) respectively.

4. Discussion

Hair zinc level is positively correlated to pain endurance (r=0,293, sig<0,05) (Table 1, Fig. 1). Correlation between several forms of chronic pain and inadequacy of zinc as well as the beneficial role of zinc supplements in these maladies has been revealed by many researchers [12, 13]. Zinc administration in animals improved analgesia levels [14, 15]. Moreover, in vitro research has shown that zinc may provide a general mechanism regulating the neuronic stimulation in the central nervous system by inhibiting the NMDA receptors [16].

Our results showed that time of pain display is linearly and positively correlated to frequency of alcohol consumption (rho=0.363, sig<0.05) and to alcohol concentration of consumed beverages (rho=0.391, sig<0.05) (Table 2, Fig. 2). Alcohol affects a wide spectrum of neurotransmitters, most important of them being GABA and glutamic acid [17-19]. Chronic alcohol use leads to decrease of GABA's receptors function and increase of the NMDA's receptors activity resulting to neurodegeneration and neuronic damage [17].

The present study showed that zinc level differs among individuals practicing exercise compared to not practicing exercise (t=-2.386, sig<0.05) (Table 3). It was also shown that the higher the frequency of exercise the higher the hair zinc levels (rho=0.366, sig<0.05) and pain endurance (rho=0.291, sig<0.05) (Table 4, Fig. 3). Recent studies have shown that zinc's plenty metabolic roles, such as energy production, immune defence system and organism protection towards oxidative stress [20, 21] were increased after high-intensity exercise [22-23] maybe due to lipids mobilization. Parallel increase of zinc and leptin also appears after intense exercise [24].

Regarding frequency of exercise and pain endurance, Scheef L et al, 2012 and Tesarz J. et al, 2013, showed through functional magnetic resonance imaging (fMRI) that exercise such as running but not walking leads to control of perception and pain resistance due to mediation of endogenous nociception mechanisms and specifically of opioids since increased b endorphins levels in the athletes blood were detected [25, 26].

In addition, our results showed that hair zinc levels were reduced inversely to the number of consumed cigarettes in smokers (rho=-0.44, sig<0.05) (Table 5, Table 6). Smoking intervenes in human metal homeostasis [27] affecting body mineral levels and especially zinc [28] resulting in disorders such as arterial hypertension, atherosclerosis [29] and male's spermatic distortion [30].

The present study showed that consumers of red foods revealed higher zinc levels (r=0.347, sig<0.05) and higher pain resistance (r=0.375, sig<0.05) compared to white and green food consumers (Table 7a). In particular, consumers of red meat and legumes revealed higher pain resistance (r=0.324, sig<0.05) (r=0.346, sig<0.05) and higher zinc level (r=0.447, sig<0.05) (r=0.355, sig<0,05) respectively, compared to other groups of consumers (Table 7b). Recent research showed that meat-based diets such as seafood and shellfish, veal, beef and lamb meat, chickens, dairy, cereals and cereal products and their combination with legumes resulted to higher body zinc level in comparison to diets based on vegetables [31-33].

The present study showed that body zinc level is reduced during aging (rho=-0,337, sig <0.05) (Table 8). Research shows that serum zinc levels increase during the third decade and then decline [34], teenagers seem to hold the 80% of the appropriate zinc level while elders hold only the 37% [35]. Zinc's decrease influences the human immune system and leads to susceptibility to immune function disorders [3] but this may be improved by zinc supplementation [34].

In conclusion, the present research showed that individuals practicing exercise and consuming red meat, legumes and seafood revealed higher hair zinc level (r=0.430, sig<0.05) and higher pain resistance (r=0.428, sig<0.05) comparatively to the other group of the study (Table 9). Our results corroborate to research findings showing that athletes often adopt an unusual diet in an attempt to enhance performance, which is an excessive increase in carbohydrates and low intake of foods rich in zinc such as meat, eggs and seafood, proteins and fat. As a result they appear having 90% zinc deficiency as well as deficiency of other minerals such as phosphorous, magnesium and iron [36-38].

5. Conclusions

Zinc is correlated to nociception and pain resistance and may be used in the treatment of various painful conditions. Alcohol consumption extends the time of pain display. Long term smoking influences negatively zinc levels due to toxic metal accumulation and competition to zinc. Consumption of red meat and legumes-combined to protein foods leads to increased body zinc level. Moreover, an inverse correlation between age and body zinc level plays an important role in human immune system regulation. Exercise is correlated to high hair zinc level and individuals, exercising systematically and regularly, appear to have higher pain resistance compared to other groups. Regarding athletes, high rate ignorance is observed concerning their nutrition sources and is necessary a proper diet plan accompanied with the right nutrition and mineral taking for the improvement of their preparation and their health. In conclusion, results of the present study highlight zinc's role in nociception and pain resistance, in correlation to significant lifestyle parameters.

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