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Research Article

SYSTEMIC SENESCENCE AND ENVIRONMENTAL FACTORS: INFLUENCE OF HEAVY METALS IN SURFACE WATER AND SEDIMENTS OF THE AL-GHADIR RIVER (MOUNT OF LEBANON) ON TELOMERE LENGTH

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ABSTRACT

Al-Ghadir River (length 15 km, width <3m) is considered one of the most polluted rivers in Lebanon and is the primary source of pollution to the Mediterranean Sea. Different sources of pollution have identified that the water and the sediments of this river have significant levels of heavy metals. These metals were infiltrated to groundwater and then used by the population near the river and probably induces health problems to populations. Telomere length is considered a marker for biological aging. Exposure to heavy metals like lead and cadmium may be associated with premature aging. To test the hypothesis that subjects living beside the polluted river experience accelerated telomere shortening, telomere length was measured using a Real-time quantitative polymerase chain reaction (QPCR)-based method, and plasma levels of various heavy metals in 100 subjects living beside the polluted river and 100 age- and sex- matched control subjects. Median (range) telomere length ratio was significantly lower in subjects living beside the polluted river than in control subjects. The difference remained highly significant when using logistic regression analysis adjusted for age, sex, and tobacco exposure. Both females and males living beside the polluted river had shorter telomere length than same-sex control subjects.

INTRODUCTION

Rivers in Lebanon have always been the most important freshwater resources and most developmental activities are still dependant on river water. However, rivers have also been used for cleaning and disposal purposes. Huge loads of waste from industries, domestic sewage and agricultural activities find their way into rivers resulting in the deposition of contaminants, large scale deterioration of water quality and elevation of sediment concentrations that have the potential to cause toxicity to aquatic biota (Khair *et al*., 1994).

The main sources of Al-Ghadir water pollution are the releases of solid and liquid wastes containing heavy metals and organic pollutants from different plants, as well as the direct discharge of domestic sewages and household wastes especially in the lower course where the river runs through crowded residential neighborhood slurry and poor in sanitation. Other sources contributing to the pollution of the water have been identified such as air emissions, traffic, atmospheric deposition, runoff from streets; in addition to the Agricultural impacts through the use of Metals in food supplement fertilizers and pesticides. The water of this river, polluted by heavy metals, is used by residents for domestic use and watering their vegetables. The exposure to heavy metals like zinc may be associated with premature aging related to amplification of the mechanisms that underlie aging (Cipriano *et al*., 2009). Mcheik *et al*., 2015 has demonstrated that the leaching of the metals at the contaminated sites and showed that their leaching was very low in the calcareous sediment column and varied between metals. This leaching has been accelerated by the stimulation of the endogenous bacterial activity by the addition of complex nutritive media and which mimics the wastewaters released continuously in the Al-ghadir river. The analysis of the distribution profile of the heavy metals in the incubated sediment columns has showed that the metals have leached

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from the sediments during incubation in a homogenous manner, but since the system is continuous, the arrival of the leachate rich in solubilized metals has led to the re-adsorption of the metals to the sediments (Fakih *et al*., 2008; 2009 Mcheik *et al*., 2013). This repartition depends on the height of the sediment where it was shown that the re-adsorption was maximum at the surface and decreases with depth (Mcheik *et al*., 2013), and the rest of heavy metals infiltrate to arrive on the groundwater. Must population near the Al-ghadir pump water from well to use, that indicate the direct contact between population and the potential contaminated infiltrated water.

The heavy metals have been known to cause various diseases. Several studies showed a high correlation between the presence of heavy metals in blood and many diseases (Hassler *et al*., 1983, Cipriano *et al*., 2009). For example, the inhalation of Cr (VI) particles is strongly linked to respiratory cancers and short telomeres are associated with increased risk for lung cancer (Willeit *et al*., 2010). Moreover, telomere shortening in leukocytes was associated with the development of coronary artery and cerebrovascular disease, and shortening of the age-corrected telomere length was associated with a substantial additional risk of mortality from cardiovascular and infectious diseases (Brouilette *et al*., 2007, Cawthon *et al*., 2003, Sahin and Depinho, 2010).

Telomere length is considered as biomarker for aging (Harley *et al*., 1990; Zakian, 1995). Telomeres are DNA sequences and associated proteins that cap and stabilize the ends of linear chromosomes, thereby maintaining genome integrity and stability. Telomere length is not only related to the basic biology of aging as a trigger of cellular senescence but also reflects the balance between oxidative stress and antioxidant defense mechanisms (Matthews *et al*., 2006; Sherr and DeOinho, 2000). Thus, telomere attrition in circulating white blood cells has been proposed as a marker for cumulative oxidative stress and inflammation and, therefore, as an indicator of the pace of biological aging (Noureddine *et al*., 2011). More recently, another branch of telomere research has emerged linking ageing research with evolutionary ecology and the environmental statuses. Certain environmental factors can play a major role in accelerating the telomere shortening and thus the evolution of the cell to the state of replicative senescence. The Heavy metals exposure is one of these factors. It has recently been shown that there is a relationship between the telomere shortening and the zinc levels in patients with or without cardiovascular diseases (Cipriano *et al*., 2009).

In the present study, we measured telomere length in circulating leukocytes from 100 subjects living beside the polluted river and 100 age- and sex- matched control subjects. Our goal was to determine whether the exposure to heavy metals was associated with reduced telomere length independently from sex, age, and tobacco consumption. We also determined the plasma levels amount of various heavy metals. All these arguments lead us to consider whether these people exhibit exaggerated senescence compared to control subjects by measuring their telomere length, because of its critical role in maintaining the stability of DNA and cellular functions.

MATERIALS AND METHODS

Study population

We evaluated two groups of non smoker people. The first group consisted of 100 people (aged between 30-50 years) living along Al- Ghadir river. The second group consisted of 100 age-matched and sex-matched control subjects living in south Lebanon and theoretically using water of the Litani River which is not polluted by heavy metals.

DNA extraction and leukocytes telomere length (LTL) assay

Genomic DNA was extracted directly from blood samples by standard procedures, and stored long-term in TE (10mM Tris–HCl, 0.1mM EDTA, pH7.5) at 4°C. The concentration and purity of DNA extracts were determined by spectrophotometry.

Telomere length was assessed in a real-time quantitative polymerase chain reaction (PCR)-based assay (Cipriano *et al*., 2009). The telomere repeat copy number to single-gene copy number (T/S) ratio will be determined using an Applied Biosystems 7900HT thermocycler in a 96-well format, using the comparative Ct method (T/S = $2^{-\Delta\Delta Ct}$). Each sample will be run in triplicate, using the SYBR Green method (Sigma) and 30 ng of DNA. The sequences and final concentrations of the primers for the telomere and 36B4 (acidic ribosomal phosphoprotein PO, a single-copy gene for normalization) will be as follows: Tel F, 5’-CGGTTTGTTTGGGTTTGGGTTTGGGTTTGGGTTTGGGT T-3’, 300 nM; Tel R, 5’-GGCTTGCCTTACCCTTACCCTTACCCTTACCCTTACCC T-3’, 300 nM; 36B4F, 5’-CAGCAAGTGGGAAGGTGTAATCC-3’, 300 nM; and 36B4R, 5’-CCCATTCTATCATCAACGGGTA CAA-3’, 300 nM.

The Quantification Data given by the QPCR machine was the Cq value. We applied three steps in order to calculate the Δ Δ CT. At first we made standardization with respect to the reference gene: Ct = Ct target gene (Telomere) - the Ct reference gene (36B4). Then the standardization was compared to a calibrator that was added repeatedly in each well (In our case we chose the Control tube1C): ΔCT = Δ Ct each sample - Δ Ct of 1C. The third and final step was to get the Rq of each sample which is equal to $2^{-\Delta\Delta Ct}$. After identifying the Rq of each sample, we calculated the average mean and made a comparison between Al-Ghadir Subjects and the control subjects.

Evaluation of the Levels of Heavy Metals

The measurement of heavy metals in water is carried out according to the method used by Mcheik *et al*., 2015. Measurement of the rate of heavy metals in the blood of the samples shall be done at the end of the study in order to assure that heavy metals are the main cause of senescence in Al-Ghadir River Residents. This measurement is made in France Bioemco laboratory at the University Paris-Est Creteil using ICP-MS instrument.

The major heavy metals that can cause harm to the human body are arsenic, selenium, cadmium, mercury, thallium, chromium and lead. ICP-MS is sensitive enough to measure well into the parts per billion and even parts per trillion for certain elements. The instrument also has detection limits in the same range.

Literature has provided to major sample preparation methods for analysis of blood by ICP-MS. These methods, including simple with a diluents and microwave digestion, both have analytical benefits. The dilution and digestion procedures can minimize effects from dissolved solids in the blood samples. Additionally digestion can dissolve the carbon rich components often found in biological samples, eliminate a number of matrix effects, and limit contamination.

Microwave digestion

The microwave digestion samples were prepared for analysis by adding 0.75 mL aliquots of blood sample and 1.5 mL of concentrated HNO_3 to quartz insert. Next, Teflon digestion vessels are filled with 2 mL of concentrated hydrogen peroxide and 8 mL of deionized water. The peroxide permitted higher digestion temperature by reducing the nitric vapors. The quartz inserts were then lowered into the teflon vessels, capped and digested in an microwave digester following the steps showed on the table 1.

Table 1 parameters of the four steps used on microwave for the sample digestion

Step	Time	Power	Temp
1	2min	1000 W	85°C
2	3.3min	1000 W	135°C
3	4.3min	1000 W	230°C
4	15min	1000W	230°C

Following digestion, the vessels were cooled to the point where the inserts could be safely removed. The clear digest was then quantitatively transferred to a disposable centrifuge tube. The pigs blood digest was spiked with 0.75mL of calibrator and 0.75mL of diluents stock which contained the internal standards and brought up to 7.5 mL with deionized water. Quality control samples were prepared in an identical fashion to the standards using the quality control spike solutions.

Statistical analysis

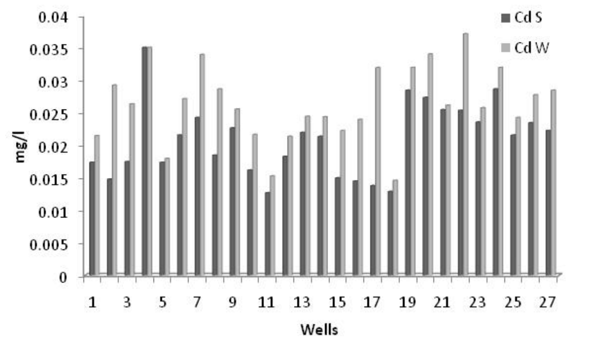
Analyses were conducted using SPSS statistical software. We used simple linear regression techniques to assess the relationship between LTL and each heavy metal. We also modeled heavy metals data as quartiles to allow for potential nonlinear associations. For quartiles, percent differences were estimated by comparing each of the upper 3 quartiles to the lowest quartile, and statistical tests for linear trends were conducted by modeling quartiles as an ordinal variable using integer values. All tests were two tailed; P values not greater than 0.1 were considered significant.

RESULTS AND DISCUSSIONS

Heavy Metal Analysis

Water Analysis

Figure 1 shows the total concentration of chemical elements in water of different wells of Al-ghadir river region. The results obtained in this study are fluctuated with the standard values of water quality given by WHO (2006) to categories the sites according to their characteristics and degree of pollution. Many pollutants are found in Al-ghadir river and present values higher than the WHO standard values, but in the present study, we selected only two heavy metals (Cd and Pb) because they have a relationship with Leukocytes Telomere Lengh (LTL) (Zota *et al*., 2015). The comparison between total concentrations of Cd and Pb in the water of the river taken from different wells distributed throughout the river between summer and winter is showed in figure 1. In this figure, we can see that the cadmium present values which vary from 2 to 5 times the standard values and lead presents values which vary from 10 to 15 times the standard values. These variations are due to the variation of season (Mcheik *et al*., 2015), the level of the heavy metals increases in summer and decreases in winter since the evaporation increases and the precipitation decreases during the summer. Moreover, the flow of water of Al-ghadir river decreases thirds between winter and summer which affect the infiltration and the dilution of groundwater.



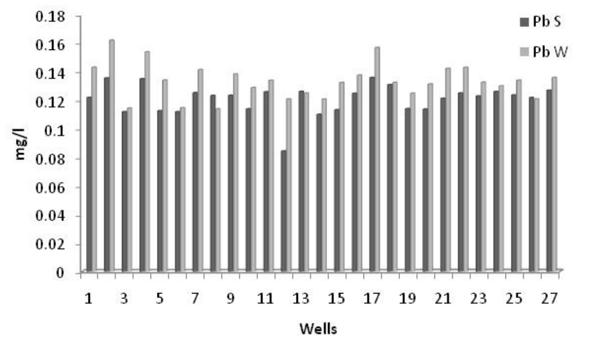


Figure 1 Comparison between the concentration of Cd and Pb in wells in the catchment area of Al-Ghadir river. (S) summer and (W) winter 2012. The standard values of water quality WHO (2006) are 0.005 ppm for Cd and 0.01 ppm for Pb.

Blood analysis

More than 206 volunteers have donated blood to make heavy metals analysis. 106 samples from peoples living near Al-Ghadir river and 100 control samples from peoples living near Litani river were analyzed by ICP-MS after a digestion by different steps as showed on materials and methods. The amounts of heavy metals were compared with the standards of heavy metals in blood published by ATSDR (ATSDR, 2015). The analysis of cadmium demonstrate that 21% of Al-Ghadir samples are higher than the standards values (15 ppb), and the lead analysis show that more than 90% of samples present a high values by comparing with different study concerning lead in bloods. Figure 2 shows the average of concentration and the standard deviation of cadmium and lead in all al-ghadir and all control samples. The Al-ghadir samples have higher levels of these heavy metals than the control ones. This difference is most probably due to water pollution of Al-ghadir river. The differences between the values in all Al-ghadir samples are very high as demonstrated by the standard deviation (figure 2). In order to better discuss the results and to reduce the standard deviation, some samples that present low values of heavy metals are eliminated from this work. Selected samples of Al-ghadir (figure 2) represent the samples with high values of heavy metals, the standard deviation of selected samples decreases than that of all samples.

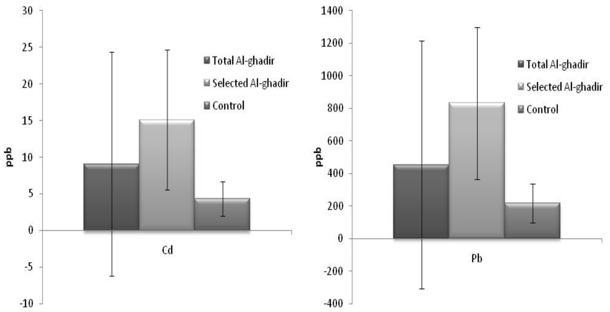


Figure 2 Average of concentrations of Cd and Pb in all and selected Al-ghadir samples and control samples.

Relationship between amounts of heavy metals in blood and in river water

Different sources of heavy metals in blood are cited in literature (ATSDR 2015, CDC 2013), drinking water, food, inhaled air, hand-to-mouth activities in children, etc. In Al-ghadir river regions, all these sources are exposed to population since the poverty and the presence of solid waste leached directly in the river without any treatment. This explains the presence of high concentration of heavy metals in the river. However, the population near Al-ghadir river presents a high values of heavy metals in blood, we can suggest that the presence of heavy metals in blood is due to the long contact of population with these sources (figure 3). In this study, the age of blood donors is 45 years approximately, which indicate that the contact time with all these sources is at least 40 years.

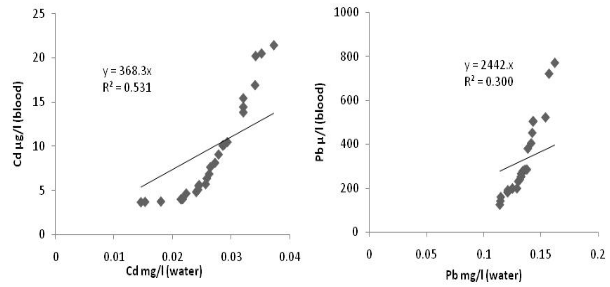


Figure 3 Correlation between the blood and water amounts of cadmium (r= 0.53) and lead (r=0.3) in Al- ghadir samples.

Figure 3 shows a moderate correlation between blood cadmium and lead and water cadmium and lead. The linear correlation coefficients are respectively 0.531 and 0.3. This moderate correlation could be explained by an indirect recent exposure of people to the polluted water. In fact, people living beside Al-Ghadir river do not use directly the water of the river for drinking but this water is used for domestic use and watering vegetables.

Leukocytes Telomere Length (LTL) in subjects living beside the polluted river and in Control Subjects

Telomere length ratios were significantly lower for the Al-Ghadir samples (1.16) than in the overall control population (2.9) (Figure 4a). To be more accurate in our analysis, we have compared each Al-Ghadir Samples to a control age- sex matched. We have compared the Rq value of each sample to a control sex age matched. We noticed the great difference between the two subjects being compared and the average mean of the control subjects (4.391) is greater than that of Al-Ghadir samples (2.158). (figure 4b). The means were 4.391 (90% Confidence Interval CI: [2.94, 5.83]) for Rq control, and 2.158 µg/L (90% CI: [1.81, 2.502]) for Rq Al-ghadir.

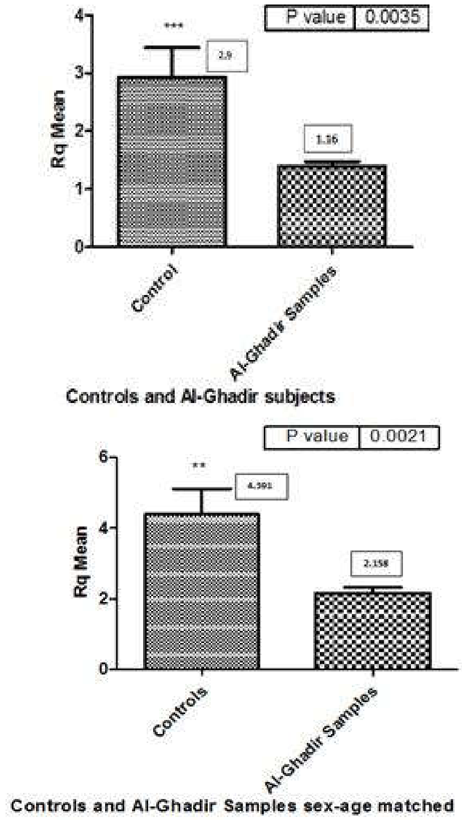


Figure 4 (a) the Rq means of control and Al-Ghadir subjects in addition to the significance of the variances (***), the error bar and the P-value=0.003. (b) the Rq means of control and Al-Ghadir subjects sex age matched in addition to the significance of the variances(**), the error bar and the P-value=0.0021

We also modeled Rq control and Rq Al-Ghadir data as quartiles. Q1, Q2 and Q3 are respectively the lowest Rq values (25%), the median Rq values (50%) and the highest Rq values (75%).

Table 2 Rq means and percentiles of the control and Al-ghadir subjects.

		Rq Control	Rq Alghadir
N	Valid	43	43
	Missing	0	0
Mean		4.39100	2.158077
Median		3.20400	2.013000
Std. Deviation		4.687210	1.1180688
Percentiles	25	1.62400	1.310300
	50	3.20400	2.013000
	75	5.10000	2.900000

According to this, we divided Rq values into 4 groups: less than Q1, between Q1 and median, between median and Q3 and more than Q3. (Table 2)

Relationship between telomere length and amounts of heavy metals

In order to understand the consequence of the exposure to heavy metals on telomere length, we selected some Al-Ghadir samples that present a high concentration of heavy metals and the correspondent values of Rq and the values of Rq for age and sex matched control samples. (Table 3)

Table 3 Rq values and concentrations of Cd, Cr and Pb in blood of 34 selected samples of Al-Ghadir samples with sex-age matched controls.

Al-Ghadir Samples	Rq contorls	Rq Al-ghadir sample	Cd µg/l	Pb µg/l	Al-Ghadir Samples	Rq contorls	Rq Al-ghadir sample	Cd µg/l	Pb µg/l
4	1.148	0.3186	8.1	405.4	43	1.516	0.4897	32.0	1599.9
5	2.0849	1.803	10.1	506.5	45	4.235	1.9851	24.8	1241.4
6	2.751	1.03	20.2	1010.7	46	2.614	1.982	10.1	503.4
7	4.23	3.1338	16.9	845.7	47	2.67	1.988	5.5	275.2
8	3.204	2.9	15.4	771.3	48	2.57	1.8955	4.0	199.6
9	2.73	1.9	10.5	523.1	49	5.91	2.866	3.7	183.8
11	2.028	1.474	4.0	199.4	51	3.7	1.835	13.8	191.6
12	7.013	2.828	5.7	284.5	54	8.34	1.9695	3.5	276.3
13	2.989	1.26	7.6	380.8	70	4.4	1.9607	3.6	181.6
14	4.723	4.23	21.4	1072.1	72	7.313	2.647	4.6	231.2
16	1.624	1.4379	5.0	252.4	76	12.934	4.943	6.3	266.6
18	5.1	1.4103	4.8	240.1	84	6.934	2.914	6.8	142.2
21	6.23	3.114	9.1	452.5	86	6.2193	3.901	2.3	116.5
26	6.974	2.4116	5.6	279.1	92	3.846	1.894	3.7	285.8
32	2.6	2.0016	14.4	721.8	95	3.6123	2.019	3.2	160.4
33	5.362	2.014	4.0	199.0	96	4.91	1.827	33.1	253.4
38	3.4	1.602	36.1	1804.3	99	3.4	1.3993	20.5	125.0

For each group, we calculated the means of cadmium and lead concentration. In the first group (Rq less than Q1), the means were 12.77 (90% CI: [5.915, 19.635]) for cadmium, and 526.71 (90% CI: [182.556, 870.869]) for lead. In this group, blood lead was inversely correlated with LTL represented by Rq values**.** The simple linear equation is given: Rq= 1.399-0.001*[pb]. In the second group (Rq between Q1 and median), the means were (90% CI: [5.258, 21.053]) for cadmium, and 469.13 (90% CI: [148.795, 789.472]) for lead. In this group also, blood lead was moderately inversely correlated with LTL. The simple linear equation is given: Rq= 1.941-0.0001*[pb]. For these two groups, we can conclude that leukocytes telomeres were shorter in subjects who have high concentration of blood lead.

In the third group (Rq between median and Q3), the means were 8.65 (90% CI: [4.319, 12.993]) for cadmium, and 432.88 (90% CI: [215.687, 650.091]) for lead. Finally, for the fourth group (Rq more than Q3), means were 10.23 23 (90% CI: [5.638, 14.837]) for cadmium, and 481.33 (90% CI: 234.648, 728.027) for lead. For these two groups, no correlation was found between blood cadmium or lead and LTL and thus there is no evidence that cadmium and lead concentrations have an influence on the leukocytes telomere length of the subjects who have high Rq values.

DISCUSSION

It is critical to identify factors that lead to accelerated telomere shortening and thus cell senescence. There has been a large focus on genetics and health behaviors, but minimal attention has been paid to environmental exposures. In our study, we found that the indirect exposure to heavy metals through polluted water is inversely associated with LTL. The higher the RQ which correspond to the length of the telomeres, the more is the length of the telomere and though the less is the biological age.

So we were able to notice that the control subjects have less biological age than Al-Ghadir Samples. The Al-Ghadir residents were proved to have primary shortening of the telomere length of the circulating leukocytes thus they have accelerated aging compared to control subjects.

Telomere shortening has been linked to the processes of both aging and cancer (Sahin and Depinho, 2010) and individuals with shorter telomeres might be more susceptible to age-related diseases than can be expected by their chronological age. Considering telomeres in white blood cells as a marker of accumulated oxidative stress and of the aging process, the long-term consequences of pollution could have an influence on telomere integrity. The findings on decreased telomere length in the present study agreed with previous reports on the relationship between long-term pollution exposure, especially heavy metals, and the telomere length. In 2009, Cipriano *et al.* showed a relationship between the critical shortening of telomeres, responsible for senescence, and zinc levels in patients with or without cardiovascular diseases. Hoxha *et al.*, (2009) noted that blood telomere length was shorter in police officer with long-term exposure to traffic pollutants compared with office workers. McCracken *et al.,* (2010) have reported an inverse association between 1-year exposure levels to black carbon and blood telomere length in a cohort of individuals in Eastern Massachusetts. In March 2012 De Felice *et al.*, have noticed telomere shortening in women residents close to waste landfill sites. In April 2012 Wu *et al.*, suggested that the Lead exposure, particularly long-term exposure, significantly results in telomere length shortening in Chinese battery plant workers. And recently Zota *et al*., (2015) showed an inverse correlation between LTL and blood lead and cadmium, and urine cadmium, in a representative sample of US adults.

Al-Ghadir River contains many sources of pollution that might have contributed in this telomere shortening. But the most dangerous one is the heavy metals pollution that is founds in its surface water and sediments. We observed a high association of LTL with blood cadmium and lead. Despite that some studies suggested that urine heavy metals is a better surrogate for cumulative exposure because it reflects heavy metals accumulated in the kidneys and other tissues (Börjesson *et al*., 1997; Lauwerys *et al*., 1979), a recent study demonstrated that there was noticeable overlap between the 2 biomarkers and that blood cadmium concentration can also partly explained by longer-term exposures (Adams and Newcomb, 2014). LTL in blood may not accurately reflect cellular aging of different tissues (Auber and Lansdorp, 2008); thus, associations between urine heavy metals and LTL in other tissues, such as the kidneys, might be stronger than those found in our study.

CONCLUSION

We have proved that Al-Ghadir River is a catastrophic problem on the health of its residents. There is a relationship between the heavy metal pollution found in the river and the senescence of its residents. Metal pollution is assumed to cause biological aging. These findings suggest that environmental toxicants may influence LTL in ways that are comparable to other lifestyle and behavioral factors, such as smoking. This project constitutes a first in this field in Lebanon studying the effect of metal pollution on biological aging. It should be expanded to other study sites and other types of pollution. It is a first step for others who will then perform on other sites in Lebanon to show the effect of this kind of pollution and other public health problems in terms of biological aging. These results must also encourage people not to use the polluted water and the state to find a solution to this major catastrophe that possesses a real threat on the health of the population.

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