Low-level lead exposure and cardiovascular disease: the roles of telomere shortening and lipid disturbance

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ABSTRACT — Lead exposure contributing to cardiovascular diseases is known and recognized widely. As the deleterious effects of low lead exposure attained increasing attention over the last decades, there have been numerous studies exploring the association of low levels of lead exposure and cardiovascular diseases. Moreover, it has been observed that lead exposure could cause telomere shortening and lipid disturbance, and that telomere shortening and lipid disturbance are closely related with cardiovascular diseases. Hence, telomere shortening and lipid disturbance might play an important role in the pathophysiological process of chronic low levels of lead exposure contributing to cardiovascular diseases. This review is intended to explore views of the rarely mentioned mechanism, telomere shortening and lipid disturbance, and the cardiovascular effects of low levels of lead exposure.

Key words: Lead exposure, Cardiovascular disease, Telomere damages, Lipid disturbances

INTRODUCTION

Lead is a ubiquitous toxin in the environment and certain professions, and exerts a harmful influence upon all organs and systems of the body, eventuating a wide variety of illnesses. Lead exposure has been considered a risk factor for cardiovascular disease (Kossowska et al., 2013; Zota et al., 2015; Silva et al., 2015) with great awareness. Lead's toxicity has led to its fading out for some uses gradually. However, lead was still in widespread use in the production of lead-acid batteries for its relative inertness, in the construction industry as an architectural metal, in sailboat keels as ballast for its high density and resistance to corrosion, in high voltage power cables as sheathing material and so on. On account of the widespread applications of lead, all humans have been exposed to lead from exogenous sources, through ingestion, inhalation or other ways. For example, contaminated water, even the dust in the air, can be crucial sources of lead in districts close to industrial sites or under certain occupational exposure. Furthermore, extensive soil contamination also forms a source of continued lead exposure in industrial societies. There are two forms of lead pollutants in the environment, organic lead and inorganic lead. The organic lead compounds that mainly exist as lead tetraethyl and lead tetramethyl, are volatile and tend to be diffused into air in a large portion, particularly with combustion of leaded gasoline. In addition, lead tetraethyl and lead tetramethyl are of high liposolubility, just parallel with the property of persistent organic pollutants which allows diffused permeability and entrance of the pollutants to the tissues and cells in bodies (Vallascas et al., 2013; Abadin et al., 2007). Probably because of their high liposolubility, the pollutants tend to accumulate in bodies. Although lead has been almost entirely removed from gasoline, paint, and other industrial or housing materials over the past 30 years in some countries (Lee et al., 2016), the general population’s exposure to lead still can scarcely be avoided. Even low lead levels below reference concentration can also produce toxicity causing disease (Kim et al., 2008).

Accumulating epidemiological and experimental studies have provided strong evidence that lead exposure increases the morbidity and mortality of cardiovascular diseases such as hypertension (Kossowska et al., 2013; Zota et al., 2015; Navas-Acien et al., 2007). Clinical and
epidemiological surveys have represented a clear correlation between the levels of blood lead and blood pressure (Poręba et al., 2011; Simões et al., 2011). The blood lead levels below the considered safe threshold for the harmful effects of lead are significantly associated with cardiovascular diseases, especially prehypertension (Lee et al., 2016). That is to say, lead exposure risks people’s health and brings about ill effects on the body all the time, although there was a decrease in human blood lead concentration over the two decades (Faramawi et al., 2015). Hence, never can we take lead exposure lightly, even at low levels, as it can easily accumulate in our bodies, especially storing in bones.

The telomere is a DNA-protein complex in eukaryotic cells located at the terminals of chromosomes. It is composed of repeated G-rich sequence (TTAGGG)ₙ, which together with telomere-binding proteins constitutes the shelterin complex, as called special “hat” structure (Lu et al., 2013). The absolute length of a telomere can shorten during cellular replication and the relative length of a telomere is generally measured in leukocytes (Buxton et al., 2014). Various environmental factors can affect the relative telomere length and one of the most important factors that can shorten telomere length is the classification of cardiovascular risk factors, especially lead exposure through functioning as heavy metals effects as well as its specific toxicity (Zota et al., 2015; Banfalvi et al., 2012). Relative telomere length is generally measured in DNA from leukocytes, due to its easy obtainment from blood. Since telomeres become shorter during each DNA replication cycle and along with biological aging, telomere shortening is regarded as a sign of biological aging and a contributor to cardiovascular diseases (Lu et al., 2013; Stewart et al., 2012).

As we all know, lipids are tightly related with atherosclerosis—one form of cardiovascular diseases. Lipid disturbances are considered detrimental factors for cardiovascular diseases (Poręba et al., 2011). During the past decades, mountainous evidence has confirmed that increased levels of total and low-density lipoprotein (LDL) cholesterol, and triglycerides are potentially risky for cardiovascular diseases. However, elevated levels of high-density lipoprotein (HDL) cholesterol are protective factors. Meanwhile, chronic lead exposure can alter lipid metabolism and cause lipid disturbance, according to several studies.

As there are diverse conventional mechanisms of lead exposure leading to cardiovascular diseases, in this review we will focus on the roles of telomere shortening and lipid disturbance, as well as the cardiovascular effects of low lead exposure.

**EFFECTS OF LOW LEAD EXPOSURE ON CARDIOVASCULAR DISEASE**

Lead exposure at low concentrations was shown to increase arterial pressure in animals (Simões et al., 2011; Fiorim et al., 2011). Both short-term and low lead exposure resulted in noteworthy elevation of blood pressure (Heydari et al., 2006), probably due to the pressure of vascular adrenergic system and nitric oxide pathway. Additionally, it was elucidated in animal experiments that chronic lead exposure at low levels brought about arterial hypertension that even continued long after the suspension of lead exposure (Chang et al., 2005), similarly causing elevated arterial blood pressure and impairment of the cardiovascular system in adults (Zota et al., 2013). Silveira et al. first demonstrated that a blood lead concentration of 12 μg/dL, below the WHO-established criteria, elevated systolic blood pressure and vascular reactivity apparently (Silveira et al., 2014). Most importantly, a recent population-based cohort study found that low-level lead exposure conspicuously contributed to cardiovascular disease (Lanphear et al., 2018), as a critically important but largely neglected risk factor. In fact, the half-life of lead in the blood, approximately 30 days, is rather short, whereas its habitation time in the bone (about 11-98 years) is comparatively long. As bone transformation increases with time, lead that has accumulated in bone over decades could enter the blood circulation again, consequently resulting in re-exposure to lead. Therefore, long-term and chronic lead exposure would be more likely measured by overall lead content rather than blood lead concentration (Vaziri and Khan, 2007). Accordingly, the lead load of bone indicates continuous lead exposure, while the blood lead content principally mirrors the degree of recent exposure to lead from external sources and the mobilization of reserved lead in the bones (Vaziri and Khan, 2007).

Nevertheless, many recent studies found that low levels of lead exposure, even below the threshold considered safe, could bring about potential harm and detrimental effects to cardiovascular systems (Silva et al., 2015; Fiorim et al., 2011), which posed a challenge to the established safe threshold as well as a caution for the world on the ubiquitous low levels of lead exposure. The safe threshold has varied dramatically, constantly going lower and lower over the past. In the early years, the safe threshold of lead exposure was established at levels of 60 μg/dL in 1960s, then reduced to 40 μg/dL, 30 μg/dL, 25 μg/dL and finally further reduced to 10 μg/dL in 1991 by the Centers for Disease Control in United States (Vorvolakos et al., 2016). Afterwards, while studies showed an association of the levels of blood lead low-
er than 10 μg/dL with cardiovascular disease mortality (Navas-Acien et al., 2007), cardiovascular disease was ever believed only apparently as lead concentrations not dropping below 5 μg/dL. More recently, a large population study demonstrated that lead levels lower than 5 μg/dL could similarly cause cardiovascular mortality, in which the mean blood lead concentration was 2.71 μg/dL (Lanphear et al., 2018). The established threshold again became far from useful as a safety criterion.

Undoubtedly, these findings possess immediate meaning and significance for public health around the world (Silva et al., 2015). Although environmental and occupational exposure to lead has declined in the past decades in Europe (Pawlas et al., 2013; Hrubá et al., 2012), the risk for damage to cardiovascular functions by short-term or low-concentration lead exposure should not be underestimated. More importantly, never should we ignore the fact that heavy exposure still exists in parts of the world where strict rules and regulations for environmental and occupational exposure are either unsuccessfully established or poorly implemented. For example, lead sostenuto put Argentina, Mexico, and Uruguay in a significant public health risk (Levallois et al., 2018). Besides, in the light of the yearly accumulation and stubborn residence of lead in the body, some seemingly humble sources of lead exposure, such as drinking water and breathing air, could inevitably do potential harm to public health. A recent study evaluated the potential impact of drinking water as a source and claimed that all sources of lead contamination should be reduced (Levallois et al., 2018). In a word, rules, regulations, and public health administration should be developed and imposed, and feasible measures and immediate steps should be taken to further prevent and better control lead exposure, so as to eliminate all possible lead-contaminated sources for the best, as no real, functioning safe threshold of lead exists. And the cardiovascular effects of lead should be considered in the social risk assessments and economic evaluation of lead exposure impact.

**TELOMERE SHORTENING**

Telomere shortening was widely studied in the context of chemical or organic pollutants. Subsequently, there emerged a new theory that telomere shortening might be involved in toxic effects of inorganic metals, such as lead and cadmium (Zota et al., 2015). Additionally, telomere attrition was presumably associated with cardiovascular diseases (Fyhrquist et al., 2013). Some recent studies revealed that telomere shortening may play a critically important role in the pathophysiological process of lead exposure promoting cardiovascular diseases, shedding new light on the mechanisms of cardiovascular effects with lead exposure.

Since telomeres function to protect chromosomes and the genome from damage through the maintenance of cellular stability and replication (Crabbe et al., 2012), telomere length most likely exert impacts on methylation levels of DNA sequences and genetic expression (Buxton et al., 2014). According to previous reports, there was a significant association between high levels of DNA breaks and occupational lead exposure, which was likely dependent on the duration and levels of human exposure to lead (Olewińska et al., 2010). Telomere shortening is hypothesized to contribute to organismal aging and trigger cellular senescence when telomeres reach a critically short length (Fyhrquist et al., 2013). And short telomere length in leukocytes appears to be a pernicious factor for cardiovascular diseases due to cardiovascular aging. That is to say, telomere shortening might obtain a potential participation in the pathological process of cardiovascular disease induced by lead exposure. As it is recognized that lead exposure contributes to cardiovascular diseases, relative telomere length was found to gradually shorten in response to increasing levels of lead exposure (Pawlas et al., 2016). Environmental and occupational exposure to lead appear to modify and shorten telomere length, especially occupational exposure. Table 1 shows the details of several studies about lead-induced telomere shortening. In a study on Chinese battery manufacturing plant workers occupationally exposed to high levels of lead (average 48.1 mg/dL), the peripheral white blood cell telomere length shortening was fastened apparently (Wu et al., 2012), which demonstrated occupational lead exposure and telomere shortening. Another study which included lead smelters and a control group of people unexposed to lead in their working environment (Pawlas et al., 2016), found that the relative telomere length of lead smelters with high blood lead levels of 33 μg/dL was significantly shorter than that of the control group, which had very low blood lead levels of 2.2 μg/dL (0.928 versus 1.126 relative units; p = 0.001). The study also showed dose-related changes, where increased lead exposure levels resulted in shorter relative telomere length. Furthermore, while many related studies examined adults and telomere length was considered as the biomarker of aging, a study measured relative telomere length in children environmentally exposed to lead at low-to-moderate levels (3.28 μg/dL) and observed apparently shorter telomeres, which indicated that lead exposure might contribute to telomere shortening and children were probably more vulnerable to low levels of lead exposure (Pawlas et al., 2015). Hence, all
that indicated a certain possibility that telomeric shortening could be an important mechanism for lead-induced cardiovascular diseases. But the exact explanation is ambiguous and inexplicit. There exist diverse possible mechanisms in association that lead exposure accelerates the process of telomere shortening, including richness in G-quadruplexes, DNA strand breaks, oxidative stress and systematic inflammation, as shown in Fig. 1. Because telomeres are rich in G-quadruplexes (Lu et al., 2013), it is most likely that lead ions displace physiological ions to generate a denser G-quadruplex formation, conversely resulting in telomere maintenance impairment and weakness during the replicating cycles (Pottier et al., 2013). Similarly, oxidative stress aggravates telomere shortening by high concentration guanine in telomere sequences and telomere is particularly sensitive to oxidative stress for damages (Zota et al., 2015). In addition, lead exposure was reported to probably induce DNA damage, including DNA double-strand breaks (Wong et al., 2014) and the deficiency of telomere DNA repair with single-strand breaks, which then result in telomere instability and attrition (Zota et al., 2015). But it was major depicted in lead-induced neurotoxicity. Moreover, systemic inflammation triggered by lead exposure is conspicuously related with diminished telomere length in peripheral leukocytes by augmenting degrees of cell turnover and caducity in cellular duplication (Liu et al., 2012; Wong et al., 2014), as inflammation can induce oxidative stress and DNA damage. Consequently, oxidative stress generally aggravates telomere shortening due to the fact that ROS damages DNA replication through complicated mechanisms in cells. Telomere length might also severe as biomarker of oxidative stress (Houben et al., 2008; Silins and Höberg, 2011). Meanwhile, mounting evidence indicates that lead exposure disrupts the balance of the antioxidative system and the oxidative system, thus increasing oxidative stress. Directly, there are several studies that have explicitly elucidated that oxidative stress is involved in the pot mech-

Fig. 1. Possible mechanism of lead-induced telomere shortening effects on cardiovascular diseases. Mechanism (1): lead replaces physiological ions, such as Ca²⁺, Na⁺, and Mg²⁺, producing more G-quadruplexes to decline the stabilities of telomere; Mechanism (2): lead exposure might cause DNA damage and impair the process of telomere DNA repair, accelerating the physiological shortening process of telomeres; Mechanism (3): the systematic inflammation caused by lead exposure induces oxidative stress, which could directly lead to an acceleration of telomere shortening as well as DNA damage and DNA repairing impairment, indirectly aggravating telomere shortening. Organismal aging and cellular senescence brought about by telomere shortening result in tissue and organism damage and manifest cardiovascular diseases in cardiovascular systems.
nism where lead exposure accelerates telomere shortening (Pawlas et al., 2016) and it seems to be closely connected with other possible mechanisms (Fig. 2). Perhaps, antioxidants may work well to block lead-induced telomere shortening. Additionally, lead, as a heavy metal, may disturb nucleic acid physiology through oxidative stress and inflammations, impairing nuclear membrane and disarranging the organization of chromatin (Banfalvi et al., 2012), which is essentially important to telomere stability (Crabbe et al., 2012).

As we can see in Table 1, telomere shortening bears a highly potential association with high lead exposure (Wu et al., 2012), and also obtain substantial functions in the pathophysiological process of low lead exposure leading to cardiovascular diseases (Wang and Jia, 2009; Pawlas et al., 2015), but more apparent shortening impacts in high levels of exposure. However, the specific mechanism of lead-induced telomere shortening remains poorly understood, and the explicit roles of telomere shortening in lead-induced cardiovascular effects require more evidence for confirmation. At least one recent study did not find any apparent impact of lead exposure (1.67 μg/dL) on telomere length in an adult population (Zota et al., 2015), which seems to be contradictory. Perhaps, the very low levels of lead exposure in that study are partly responsible for the negative results, as occupational exposure to lead always holds high levels and leads to significant telomere shortening (Pawlas et al., 2016), as seen in Table 1. At any rate, it brought us new insights into the mechanisms of lead-induced cardiovascular disease and encouraged us to engage in this field to acquire further understanding. Accordingly, more rigorous studies are required urgently to settle the controversy and obtain more significant evidence to demonstrate that telomere shortening is involved in the lead effects on cardiovascular diseases.

**LIPID DISTURBANCE**

In the light of the many studies in both humans and animals, lead exposure could change lipid metabolism to cause lipid disturbance eventually (Zhang et al., 2009; Kamal et al., 2011). Currently, it is exhibited that environmental and occupational exposure to lead are manifested lipid disturbances to induce pro-atherosclerotic effects, being risky for cardiovascular diseases (Poręba et al., 2011). Individuals with occupational exposure to lead show ascending levels of total cholesterol, LDL cholesterol and triglycerides, but descending concentrations of HDL cholesterol (Gatagonova, 1994; Kristal-Boneh et al., 1999). There is a positive linear relationship between serum LDL cholesterol levels and blood lead levels in occupational exposure to lead (Skoczyńska et al., 2007). The possible explanation behind elevated incidence of lipid disturbance brought about by chronic lead exposure presumptively is related to lead toxicity to the liver, where lipid metabolism is mainly processed. The molecular mechanisms might embrace the interference with fatty acid metabolism, facilitation of lipid profile peroxidation, restraint of antioxidant pathway and more activated lipid synthetase (Adegbesan and Adenuga, 2007; Kasperczyk et al., 2005). An epidemic study on populations in Abeokuta, Nigeria, has revealed that people occupationally exposed to lead have an augmented risk for cardiovascular disease.

**Table 1.** Studies of lead-induced telomere shortening.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Country</th>
<th>Year</th>
<th>Participants</th>
<th>Types of lead exposure</th>
<th>Mean blood lead level</th>
<th>Telomere length</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Wu et al., 2012)</td>
<td>China</td>
<td>2012</td>
<td>Battery plant workers</td>
<td>Occupational</td>
<td>48.1 μg/dL</td>
<td>Shortening significantly</td>
</tr>
<tr>
<td>(Pawlas et al., 2016)</td>
<td>Poland</td>
<td>2016</td>
<td>Lead smelters</td>
<td>Occupational</td>
<td>33 μg/dL</td>
<td>Shortening significantly</td>
</tr>
<tr>
<td>(Pawlas et al., 2015)</td>
<td>Poland</td>
<td>2015</td>
<td>Children</td>
<td>Environmental</td>
<td>3.28 μg/dL</td>
<td>Shortening significantly</td>
</tr>
<tr>
<td>(Zota et al., 2015)</td>
<td>USA</td>
<td>2015</td>
<td>Adults</td>
<td>Environmental</td>
<td>1.67 μg/dL</td>
<td>Not shortening apparently</td>
</tr>
</tbody>
</table>
of cardiovascular diseases as result of higher LDL/HDL cholesterol ratio, compared with controls (Ademuyiwa et al., 2005).

Moreover, peroxidation of cell membrane lipids is considered the major mechanism in lead toxicity eventuating lipid abnormalities (Kaczmarek-Wdowiak et al., 2004). While not inducing peroxidation immediately, lead indirectly contributes to peroxidation via oxidative stress, producing more lipid superoxides and generating more oxygen species (Kaczmarek-Wdowiak et al., 2004; Doroszko et al., 2008). Nevertheless, features of the study populations and coexistence of other perilous factors of cardiovascular diseases, might, to a certain extent, determine the effects of lead exposure on lipid mentalism in individuals (Doroszko et al., 2008; Skoczynska et al., 2007).

Lipid disturbance plays a great part in the cardiovascular effects of lead exposure (Kamal et al., 2011), even in low levels (Dursun et al., 2005). Yet, the clear mechanism of how lipid disturbance participates in the pathology of cardiovascular effects of lead exposure remains a bit indefinite, though it is described in broad outline based on existing studies. Maybe it was down to the mechanism of oxidative stress considering the close association between lipid disturbance and oxidative stress damage. At any rate, more prudent and precise studies are required to more explicitly explain the exact roles of lipid disturbance in the occurrence of lead-induced cardiovascular disease, especially with low-level lead exposure.

CONCLUSION

Today, lead continuously poses a major public health challenge to the whole world, by reason of its ubiquitous presence in our environment and the harmful effects of its established toxicity, even at low levels. In vivo and in vitro animal studies as well as population studies have shown that low lead exposure can also lead to cardiovascular diseases. Apart from some conventional mechanisms, it has been found that telomere shortening most likely plays an unignorable role in the cardiovascular effects of lead, and that lipid disturbance also plays an important part in the pathway whereby lead exposure contributes to cardiovascular diseases. However, both are closely related with conventional mechanisms. Nevertheless, clarification of the molecular mechanism of telomere shortening and lipid disturbance should be highly prioritized in this field. Conclusively, while the awareness of the deleterious effects of lead on cardiovascular diseases as risk factors, even below the threshold levels, should be greatly emphasized and highlighted occupationally and educationally, intensive, comprehensive measures to diminish all sources of lead exposure and further related studies about the novel mechanism of lead-induced cardiovascular diseases are extensively appealed and urgently required.

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Conflict of interest---- The authors declare that there is no conflict of interest.

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