Review article

Cadmium and atherosclerosis: A review of toxicological mechanisms and a meta-analysis of epidemiologic studies

Alexey A. Tinkov[a,b,c,*,1], Tommaso Filippini[d,1], Olga P. Ajsuvakova[e], Margarita G. Skalnaya[b], Jan Aaseth[f,g], Geir Bjørklund[h], Eugenia R. Gatiatulina[i], Elizaveta V. Popova[j], Olga N. Nemereshina[i], Pai-Tsang Huang[k], Marco Vinceti[d], Anatoly V. Skalny[a,b,l,m]

[a] Yaroslavl State University, Yaroslavl, Russia
[b] Peoples' Friendship University of Russia (RUDN University), Moscow, Russia
[c] Institute of Cellular and Intracellular Symbiosis, Russian Academy of Sciences, Orenburg, Russia
[d] CREAGEN, Environmental, Genetic and Nutritional Epidemiology Research Center, University of Modena and Reggio Emilia, Modena, Italy
[e] All-Russian Research Institute of Phytopathology, Odintsovo, Moscow Region, Russia
[f] Faculty of Public Health, Inland Norway University of Applied Sciences, Elverum, Norway
[g] Research Department, Innlandet Hospital Trust, Brumunddal, Norway
[h] Council for Nutritional and Environmental Medicine, Mo i Rana, Norway
[i] South-Ural State Medical University, Chelyabinsk, Russia
[j] St. Joseph University in Tanzania, St. Joseph College of Health Sciences, Dar es Salaam, Tanzania
[k] Wan Fang Medical Center, Taipei, Taiwan, ROC
[l] Orenburg State University, Orenburg, Russia
[m] Trace Element Institute for UNESCO, Lyon, France

ARTICLE INFO

ABSTRACT

Cadmium has been proposed to be the one of the factors of atherosclerosis development, although the existing data are still controversial. The primary objective of the present study is the review and the meta-analysis of studies demonstrating the association between Cd exposure and atherosclerosis as well as review of the potential mechanisms of such association. We performed a systematic search in the PubMed-Medline database using the MeSH terms cadmium, cardiovascular disease, atherosclerosis, coronary artery disease, myocardial infarction, stroke, mortality and humans up through December 20, 2017. Elevated urinary Cd levels were associated with increased mortality for cardiovascular disease (HR = 1.34, 95% CI: 1.07–1.67) as well as elevated blood Cd levels (HR = 1.78, 95% CI: 1.24–2.56). Analysis restricted to never smokers showed similar, though more imprecise, results. Consistently, we also observed an association between Cd exposure markers (blood and urine) and coronary heart disease, stroke, and peripheral artery disease. Moreover, Cd exposure was associated with atherogenic changes in lipid profile. High Cd exposure was associated with higher TC levels (OR = 1.48, 95% CI: 1.10–2.01), higher LDL-C levels (OR = 1.31, 95% CI 0.99–1.73) and lower HDL-C levels (OR = 1.96, 95% CI: 1.09–3.55). The mechanisms of atherogenic effect of cadmium may involve oxidative stress, inflammation, endothelial dysfunction, enhanced lipid synthesis, up-regulation of adhesion molecules, prostanoid dysbalance, as well as altered glycosaminoglycan synthesis.

1. Introduction

Cardiovascular diseases (CVD) are the leading cause of death in the US (Benjamin et al., 2017) and European countries (Wilkins et al., 2017) accounting for 31% of all world-wide deaths or 17.7 million in 2016 (WHO, 2017) and 45% of all deaths or 3.9 million in Europe (Wilkins et al., 2017). Of these, about 50% were attributed to coronary heart disease (CHD), followed closely by stroke (Feigin et al., 2017), while peripheral vascular disease (PVD) contributed only 1–2% (Criqui and Aboyans, 2015). At the same time, the trends have been different between high-income countries and low-, medium-income countries. In particular, Western Europe, USA, and Australia show a dramatic decline in both CHD and stroke. Studies from Eastern Europe and Asia also report a decline in stroke mortality, whereas CHD mortality remains

---

variable (Kelly and Fuster, 2010). In addition, American Heart Association reported that 92.1 million adults in USA have CVD. It was proposed that approximately 43.9% of the US people will have CVD by 2030 (Benjamin et al., 2017). Prevalence of CVD from European Social Survey 2014–2015 in for all European countries was 9.2% (ESS, 2015). According to WHO Mortality Database for global burden of disease estimates 2000–2011, the number of deaths from CVD vary from 40% for men (with 19% of CHD, 9% of stroke and 12% of the other CVD) to 49% (with 20% of CHD, 14% of stroke and 15% of the other CVD) for women (WHO, 2013).

Recent studies have demonstrated that environmental pollution plays a significant role in CVD (Pope et al., 2004) and atherosclerosis in particular (Lawal, 2017). Moreover, it has been shown that an interaction between genetic and environmental factors may significantly contribute to atherosclerosis (Org et al., 2015). The mechanisms linking environmental pollution and atherosclerosis include oxidative stress, inflammation (Araujo, 2011), platelet activation (Poursafa and Kelishadi, 2010), and other pathways (Campen et al., 2012). Of organic pollutants, the most significant association with atherosclerosis was revealed for bisphenol A, phthalates (Lind and Lind, 2011), polychlorinated biphenyls, pesticides, dioxin (Lind et al., 2012a, 2012b). In turn, heavy metal ions as the major inorganic pollutants are also known to promote CVD and atherosclerosis (Prozialeck et al., 2007). In particular, an association between the incidence and mechanisms of atherosclerosis was demonstrated for arsenic (Simeonova and Luster, 2004). Cadmium was also proposed to be the one of the potential factors of atherosclerosis development (Messner et al., 2009). However, the existing data are still controversial (Santos-Gallego and Jialal, 2016).

Although cadmium levels in the environment have been decreasing for the last 50 years due to improved emission control for fossil fuel combustion and improved technology for the production, use and disposal of cadmium and cadmium-containing products (Crea et al., 2013), the rate of Cd exposure is still high. In non-smoking and non-occupationally exposed population, the main source of Cd exposure is diet, with additional relevant contribution from air pollution (Vilavert et al., 2012; Filippini et al., 2016; Coudon et al., 2017). In particular, a more restrictive dietary intake guideline for Cd have been suggested in order to enhance the health protection (Satarug et al., 2017). Nevertheless, the estimated mean weekly intake of Cd in European population ranges from 1.9 to 3.0 µg/kg, in such cases exceeding the limit of 2.5 µg/kg suggested by the European Food Safety Authority (Nawrot et al., 2010; EFSA, 2012). Moreover, even low-dose Cd exposure is associated with increased mortality, as demonstrated in the recent meta-analysis (Larsson and Wolk, 2016). Therefore, the assessment of the toxicological effects of Cd exposure in general (Tinkov et al., 2017), including its role in atherosclerosis development, is of particular interest.

The primary objective of the present study is to review the epidemiologic studies examining the association between Cd exposure and atherosclerosis, also addressing the biological plausibility of this possible association.

2. Materials and methods

We performed a systematic search in the PubMed-Medline database using the MeSH terms cadmium, cardiovascular disease, atherosclerosis, coronary artery disease, myocardial infarction, stroke, mortality and humans up through 20 December 2017. We performed a meta-analysis of retrieved observational studies assessing the incidence or mortality (cohort studies) or prevalence (cross-sectional studies) of cardiovascular outcome (i.e. cardiovascular diseases, coronary heart disease, and stroke) or cardiovascular risk factors (i.e. peripheral arterial disease and abnormalities in lipid profile) (Fig. 1). Generally, we compared the higher versus the lowest categories of Cd exposure using a methodology already specified in detail (Vinceti et al., 2016). The extracted data for meta-analysis included study design (i.e. cross-sectional or cohort), number, sex and country of participants, type of Cd
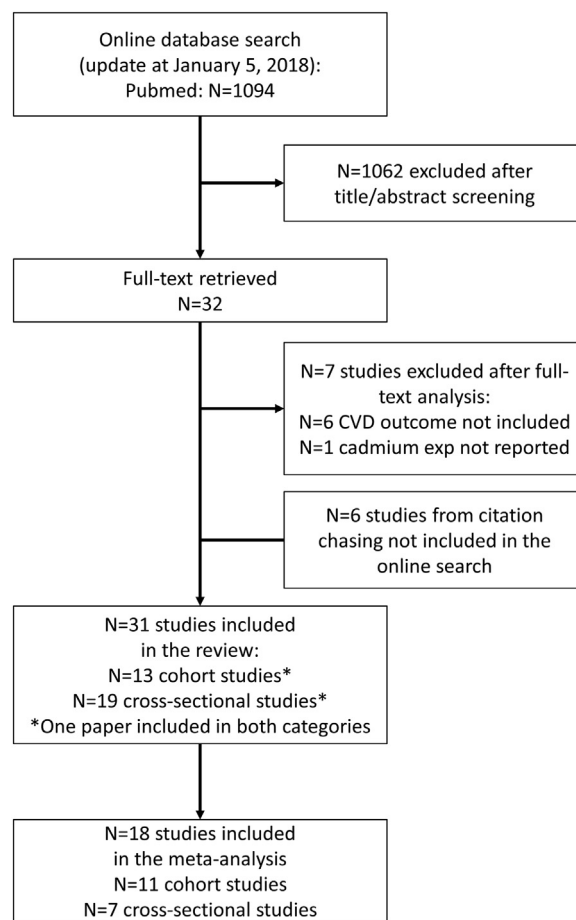

Fig. 1. Flow-chart of online search and selection.

exposure assessment (blood, urine or intake), the covariates adjusted for in the multivariable analysis, and eventually the odds ratios (OR), risk ratios (RR) or hazard ratios (HR) estimates and their 95% CI for the most adjusted model reported (Table 1 and 2). We used a random-effect model to account for heterogeneity (I^2) in study-specific results. We performed stratified analysis according to Cd assessment methods and restricting to never smoker participants.

In order to review the Cd-induced mechanisms of atherosclerosis we performed a search in PubMed-Medline database using the MeSH terms cadmium, atherosclerosis, lipid profile, lipoprotein, adhesion molecules, endothelial dysfunction, vascular inflammation. The latest search was dated as 20 December 2017.

3. Cadmium, cardiovascular diseases and coronary heart disease

3.1. Cross sectional studies

Examination of 948 men and 960 women (NHANES 2005) demonstrated that increased blood Cd levels were associated with a nearly 2-fold higher prevalence of ischemic heart disease in a general cohort. The observed association was especially tight in women (OR = 2.28, 95% CI: 1.26–4.15) than in men (OR = 1.88, 95% CI: 0.96–3.69) (Lee et al., 2011). Correspondingly, a 50% increase in urine and especially blood Cd levels is associated with elevated prevalence of myocardial infarction and heart failure. After adjustment for smoking status (never smokers only) the association between heart failure and blood (OR = 1.10, 95% CI: 0.96–1.27) and urinary (OR = 1.02, 95% CI: 0.88–1.18) Cd concentration was found to be weaker (Peters et al., 2010). Higher urinary and blood Cd levels was also associated with increased prevalence rate (PR) of myocardial infarction in NHANES 2003–2012