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Review

Environmental contaminants acting as endocrine disruptors modulate atherogenic processes: new risk factors for cardiovascular diseases in women?

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Abstract: The number of aged individuals is increasing worldwide, rendering essential the comprehension of pathophysiological mechanisms of age-related alterations, that could facilitate the development of interventions contributing to "successful aging" and improvement of quality of life. Cardiovascular diseases (CVD) include pathologies affecting heart or blood vessels, such as hypertension, peripheral artery disease and coronary heart disease. Indeed, age-associated modifications in body composition, hormonal, nutritional and metabolic factors, as well as a decline in physical activity are all involved in the increased risk of developing atherogenic alterations raising the risk of CVD development. Several factors have been claimed to play a role in the alterations observed in muscle and endothelial cells and leading to increased CVD, such as genetic pattern, smoking, unhealthy lifestyle. Moreover, a difference in the risk of these diseases in women and men has been reported. Interestingly, in the last decades attention has been focused on a potential role of several pollutants which disrupt human health by interfering with hormonal pathways, and more specifically in non-communicable diseases such as obesity, diabetes and CVD.

This review will focus on the potential alteration induced by Endocrine Disruptors (Eds) in the attempt to characterize a potential role in the cellular and molecular mechanisms involved in the atheromatic process and CVD progression.

Keywords: Endocrine disruptors, gender, female, atherosclerosis, Cadmium, Bisphenol A, inflammatory cytokines, cardiovascular diseases

1.Introduction

As the number of older individuals continues to increase, it is important to understand the pathophysiological mechanisms of age-related pathologies in order to develop interventions that can be easily implemented and contribute to "successful aging" and prevention of chronic diseases.

Age-related changes in body composition, metabolic factors, and hormonal levels, accompanied by a decline in physical activity, might all provide mechanisms responsible for the tendency to lose muscle mass, gain fat mass and develop cardiovascular diseases [1]. Indeed, cardiovascular diseases (CVD) are important widespread health problems,

which lead to high prevalence of both mortality and morbidity, and during the last decades have become a major health threat around the world[1-3].

Ageing also increases the risk of muscle mass reduction with a corresponding increase of fat mass and inflammation status which, in association with hormonal imbalance and altered nutritional pattern[4], might synergistically increase CVD[3,5]. Of note, these age-related alterations are often sex-related as well[6-8].

Obesity, caused by an imbalance in which energy intake exceeds energy expenditure over a prolonged period, has always been recognized as a risk factor for metabolic disorders and CVD[9]. In particular, obese postmenopausal women are often affected by hypertension, dyslipidemia, diabetes mellitus, and CVD presenting a risk even higher than men[10].

In men, the condition of late-onset hypogonadism, frequently observed in the elderly, correlates with changes in body composition and increased cardiovascular risk [6,8,11,12]. Furthermore, recent epidemiological studies indicate that reduced androgen levels are correlated with high blood pressure, left ventricular mass, and increased cardiovascular mortality in men[13].

Moreover, recent data have indicated that some environmental pollutants, such as Cadmium (Cd) and Bisphenol A (BPA), which are widespread in the environment and can be introduced in the human organism in different ways, can cause significant alterations on human health, acting as endocrine disruptors (Eds). In particular, recent data suggest that the cardiovascular system might be a target of both pollutants Cd and BPA[14].

Thus, aim of this review is to evaluate data on Eds focusing on mechanisms of endothelial cell homeostasis disruption potentially leading to an increased risk of cardiovascular diseases, addressing, when possible, sex-dependent differences.

2. Atherosclerotic plaque formation

Atheroma, better known as atherosclerotic plaque, can be defined as a degeneration of the arterial walls due to the deposit of plaques essentially formed of fat and fibrotic tissue. Atherosclerotic plaque can be considered expression of a chronic inflammatory disease which can be defined atherosclerosis, the main cause of CVD and the first cause of death among the population in industrialized countries.

The atherosclerotic process starts from the endothelial cells, which are capable of processing many active substances and modulating the biological activity of the various vessel wall structures, blood cells, and proteins of the coagulation system, normally in contact with the surface of the endothelium[15]. Indeed, the endothelium is a critical regulator of vascular homeostasis by controlling barrier integrity as well acting as a crucial signal transducer. When endothelium homeostasis is compromised and endothelial cells are stimulated, this event leads to upregulation of adhesion molecules, secretion of cytokines and chemokines, alteration of adhesion molecules [15]. This process is triggered by well-established cardiovascular risk factors, such as smoking, hypertension, obesity, diabetes, and environmental stressors[16]. In arteries, where endothelial cell alterations have started, low-density lipoproteins (LDL) are accumulated in the subendothelial space and altered by oxidative processes leading to formation of oxidized low density lipoprotein (oxLDL), that induces an inflammatory response of stromal cells, triggering its uptake by tissue-resident macrophages and, in turn starting a pro-inflammatory cellular immune response [17]. These data describe how inflammation is one of the important drivers of atherosclerosis, adverse cardiac remodelling and CVD[16]. In this critical process, alteration of proinflammatory cytokine levels can play a fundamental role in triggering and maintaining the local and systemic inflammation process.

3. Pro-inflammatory cytokines effects on cardiovascular system

Pro-inflammatory cytokines, which include several adipokines, are involved in many pathological processes, including inflammation, endothelial damage, atherosclerosis, hypertension. Their dysregulation is a strong contributing factor of the low-grade inflammatory state, which leads to a cascade of metabolic alterations inducing an increased risk of cardiovascular complications[18,19].

Tumor necrosis factor-alpha(TNF-α) is a pro-inflammatory cytokine, which plays important regulatory effects on lipid metabolism, adipocyte function and insulin signaling[20]. In obese rats, TNF-α produced by periarteriolar fat alters endothelium-dependent vasodilatation likely by inhibiting the insulin-mediated release of nitric oxide (NO)[21].Moreover, recent results indicate that TNF-α upregulates the release of the adhesion molecules intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1) in endothelial cells, facilitating leukocytes adhesion to vessel walls[22]. Thus, TNF-α may play an important role in vascular disease, confirming a pivotal role of this pro-inflammatory cytokine in the pathogenesis of atherosclerosis, endothelial damage and heart cell remodelling toward higher disease severity[23].

Interleukin-6 (IL-6) is a cytokine, which has a wide range of actions, including promotion of coagulation and immune/inflammatory reaction[24]. This cytokine is produced by different cell types, including fibroblasts, cardiac and endothelial cells; its levels can significantly increase, for instance, after menopause and with the decades of life, determining, along with increased levels of other cytokines, a subclinical chronic inflammatory status[25-27]. Interestingly, IL-6 has also been demonstrated to be an important correlation factor between inflammation and atherosclerosis. Indeed, it has been demonstrated that TNF-α, can stimulate IL-6, which in turn can modulate C-reactive protein (CRP, an inflammatory biomarker of cardiovascular risk) production in smooth muscle cells, negatively affecting the expression of adhesion molecules and endothelial function[28].Moreover, cohort studies have shown that increasing levels of this pro-inflammatory cytokine appear to be correlated to an increased risk (two-fold) of cardiovascular and all-cause mortality in healthy aged people, also having a significant prognostic value in subjects affected by unstable angina[29].

Angiotensin (AT), predominantly produced by the liver and adipose tissue, is the precursor of the vasoactive peptide angiotensin II and it appears correlated to higher blood pressure[30].

Plasminogen activating inhibitor (PAI-1), produced by liver and adipose tissue, inhibits the activity of tissue-plasminogen activator favouring thrombus formation over ruptured atherosclerotic plaques. PAI-1 expression is elevated in visceral obesity, insulin resistance (IR) and hypertriglyceridemia, and its levels appears to predict risk for future development of both type 2 diabetes (T2D) and CVD[31].

Leptin, the first identified adipose tissue-derived factor, is secreted by adipocytes in proportion to body fat tissue. Interestingly, hyperleptinemia, often present in subjects affected by overweight or obesity, has been widely recognized as an independent cardiovascular risk factor[32,33]. Several data suggest that hyperleptinemia might play a pivotal role in the pathogenesis of endothelial dysfunction and atherogenesis, likely stimulating the release of oxygen reactive species (ROS) as well as the recruitment of monocytes[33].Leptin induces macrophage cholesterol ester synthesis, contributing to foam cell formation *in vitro*[34]with high glucose levels, also inducing the expression of CRP[35].

Resistin is produced by macrophages and visceral adipocytes, and its name derives from the induction of IR[36]. Resistin modulates insulin sensitivity in both skeletal muscle and liver and positively correlates with IR and glucose tolerance in both human and animal models[37]. Interestingly, resistin is believed to be a marker of inflammation, contributing to atherogenesis. Indeed, in vitro data obtained in human endothelial cells show that resistin induces a dose-dependent proliferation of smooth muscle cells, increases endothelin-I release, VCAM and ICAM-1[38,39]. In addition, resistin appears to be a good predictor marker of coronary artery calcification[40], being also associated with

arterial stiffness[41], while it seems inversely associated to left ventricular fractional shortening, biomarker of left ventricular systolic function[42]. Several recent evidences indicate how resistin is independently linked with an increase in the risk of both myocardial infarction and ischemic stroke[43].

4. Endocrine disruptors

The term endocrine disruptors (Eds) implies several chemicals, with a particular effect on the endocrine system, since they interfere with specific receptor-mediated hormone activity[44]. Due to this characteristic, Eds can alter cellular metabolism with potential long-term and harmful effects. Eds are molecules of either natural origin or man-made products, which include over 300 synthetic compounds such chemicals as the plasticizers polybrominateddiphenyl ethers (PBDEs) and polychlorinated biphenyl (PCB), as insecticides (i.e. dichlorodiphenyltrichloroethane DDT and metabolites, pyrethroids), herbicides (i.e. atrazine, nitrofen), fungicides (i.e. zineb, ziram), pharmacological agents [i.e., bisphenol A –(BPA)] [45-50], dioxins, dioxin-like compounds, phthalates and heavy metals as lead, mercury and Cadmium (Cd)[45]. Due to this distinctiveness, there is rising concern about effect on the endocrine or cardiovascular systems by Eds, such as Cd or BPA, since it has been demonstrated that these molecules might mimic the activity of natural hormones such as estrogens and androgens leading to the activation of specific signaling pathways [51]. Of note, Eds can block the interaction of these hormones with their natural receptors [52,53] or enhance the levels of proinflammatory cytokines [54].

5. Endocrine disruptors and cardiovascular system

As already mentioned above, CVD are disorders that affect blood vessels and heart, representing one of the leading causes of both morbidity and mortality worldwide. Risk factors for CVD include, unhealthy diet[11], sedentary life-style, alcohol abuse, smoke and pollution [55]. For instance, some pollutants acting as Eds, have been correlated to an increased risk of developing CVD due to a direct and specific alteration in pro-inflammatory cytokines levels and endothelium damage, leading to atherosclerotic lesions. Cd and BPA, two Eds which have been highly correlated with CVD will be further described.

5.1.Cadmium and cardiovascular effect

Cd is a toxic heavy metal, found in soil, contaminated water and food,that is used in various industrial activities while a non-occupational source is represented by cigarette smoking, as Cd accumulates in tobacco leaves. Several studies indicate a negative effect of this ED on CVD. The molecular mechanisms by which Cd exerts the negative effects on the cardiovascular tissues are linked to the induction of oxidative stress, sinceitmightdisrupt endogenous antioxidant defense such as glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD). In addition, Cd induces ROS generation[56], harms the mitochondrial electron chain transport, and decreasesthe antioxidant scavengers such as glutathione (GSH), leading to an unbalance in the cellular redox state,and, so far, triggering the production of ROS[57-59].

5.1.1. Clinical studies

Clinical studies have indicated that this heavy metal acts as a pro-atherogenic factor since its presence has been identified in carotid plaques leading to a significant increase in vulnerability of the plaques compared to plaques that do not fissure and rupture [60-62]. Epidemiological studies showed that high serum level of Cd was linked with CVD mortality and carotid plaques prevalence in a Swedish population and, also, correlated with an increase in CVD risk in Korean male population[63,64]. Moreover, a follow up study performed for almost 20 years on a Swedish population-based cohort of over

4000 middle-aged subjects of both sexes, demonstrated that Cd might play a pivotal role in smoking-induced CVDs, by measuring the level of Cd in the blood[65].

Another interesting study has demonstrated a correlation between high urine and blood concentration of Cd and plaques formation in a female and male population over sixty years of age[66], indicating that even if Cd likely acts by disrupting the estrogen receptor pathway, both genders are affected by the pollutants' negative action on cardiovascular health.

Interestingly, several studies demonstrated that Cd accumulation correlates with increased macrophages presence, a recognized hallmark of symptomatic and vulnerable carotid plaques [67,68]. In detail, recently published data obtained from a Canadian population indicated a correlation between pollutants and carotid intima-media thickness (CIMT)[69]. The hypothesis that Cd triggers the vulnerability of carotid plaques, likely by increasing the risk of rupture and ischemic stroke was supported by a recent study which showed that Cd accumulation was linked to the incidence of ischemic stroke [62].

It is well known that cigarette smoke is a significant risk factor for CVD and a main source of Cd, thus leading several studies to attempt to characterize the molecular mechanism(s) of the increased Cd-related CVD incidence [70-72]. Indeed, cigarette smoke, therefore Cd as well, induces vascular damage by stimulating vascular plaque inflammation and vasomotor dysfunction[73]. Five cross-sectional studies, recently realized by the National Health and Nutrition Examination Survey (NHANES), involving US population, confirms that subjects with higher levels of either blood or urinary Cd had increased risks of peripheral artery disease, hypertension, heart failure, myocardial infarction, and stroke[74-77].

5.1.2. *In vitro* studies

It is well known that the genesis of atheromatic plaque is a complex mechanism, which has determined several players including endothelium permeability. Indeed, *in vitro* studies have characterized Cd as a pro-atherogenic factor with a cytotoxic effect in macrophages. In particular, our research group has published data demonstrating that Cd exposure can alter androgen receptor levels in Human Umbilical Vein Endothelial Cells (HUVECs) and, even more importantly stimulate pro-inflammatory signaling, strongly indicating a role for Cd in cell injury linked to endothelial damage and CVD[78]. Moreover, Cd can also cause endothelial cells dysfunction, since it alters vascular endothelial cells permeability, decreases nitric oxide (NO) production, inhibits endothelial cell proliferation, induces upregulation of adhesion molecules such as VCAM-1 expression level, triggers endothelial cells apoptosis and alters proinflammatory cytokines levels[79].

5.2.BPA and cardiovascular effect

Bisphenol A (BPA),is a synthetic organic compound with two phenolic groups. Since the sixties of the last century, it is largely used for the production of polycarbonate plastics (popular for their properties including transparency and thermal and mechanical resistance), for preparation of food containers, and for epoxy resins employedfor internal protective coating of food and beverage cans.It is one of the highest volume chemicals produced worldwide. Studies of the last two decades have however revealed that BPA acts as an ED, interfering as other molecules and pollutants with hormonal pathways.

5.2.1 Clinical studies

Epidemiological studies documented an increased risk of coronary artery disease in healthy population exposed to BPA[80-82]. Further, urinary BPA levels significantly correlated with peripheral arterial alterations,independently of other known CVD risk factors[83]. An interesting meta-analysis reported that urinary levels of BPA normally

found in thegeneral population correlated with increased prevalence ofhypertension, diabetes, obesity[84]. NHANES in 2003 and 2004[80], documented that higher concentration of urinary BPA was linked to an increased risk of self-reported CVD (myocardialinfarction, angina, or coronary heart disease), but not of stroke. While similar data were subsequently reported by other authors who demonstrated similar associations[85] and Casey et al showed significant correlation between urinary BPA and coronary heart disease in another survey, results were not confirmed in subsequent evaluations[86]. Moreover, the prospectivestudy within the EPIC-Norfolk cohort, depicteda positive correlation between urinary BPA concentrations and occurrence of coronary artery disease[81]. These data demonstrated that several cross-sectional epidemiological studies found positive correlation between levels of urinary BPA and CVD risk factors, such as hypertension, hypercholesterolemia[87]. On the other hand, a recently published study[88] performed in a sub-cohort of the Spanish European ProspectiveInvestigation into Cancer and Nutrition (EPIC) did not find a significant correlation between urinary BPA levels and the risk of incident ischemic heart diseases (IHD). The apparent contradictory results of these studies and surveys might be due most likely to different experimental designs, timing of exposure, and other bias, as they might be uncontrolled or residual confounding factors, such as route of administration of these pollutants, degradation time of BPA or different exposure doses evaluated in the studies[89-91].

Finally, several epidemiologic studies indicated positive associations of urinary BPA level with serum IL-6 levels in both pregnant women and adult males[92,93]. Moreover, several in vivo studies showed that BPA exposure increases pro-inflammatory cytokines TNF-α and IL-6, while decreases the anti-inflammatory cytokines IL-10 and transforming growth factor-β (TGF-β) in human macrophages, strongly suggesting that BPA can trigger inflammation status likely increasing the risk of CVD.

5.2.2 *In vitro* studies

A rising number of studies indicate that exposure to environmentally significant levels of BPA might increase the susceptibility for cancer in the reproductive organs, increase body weight[94,95], but also, as mentioned earlier, increase the risk of CVD[80,85]. Thus several *in vitro* studies focused on the characterization of the mechanism(s) by which this molecule could affect endothelial cells. One of the first studies performed to evaluate the potential mechanism of action of BPA on endothelial cells was conducted by Andersson and colleagues demonstrating that BPA increased mRNA expression of vascular endothelial growth factor receptor 2 (VEGFR-2), vascular endothelial growth factor A (VEGF-A), endothelial nitric-oxide synthase (eNOS), connexin 43 (Cx43), and also stimulated NO production in HUVEC cells, a well-known human *in vitro* model of endothelial cells[96]. Furthermore, they demonstrated that BPA also stimulated expression of phosphorylated eNOS and endothelial tube formation in HUVEC, suggesting that relevant levelsof BPA might lead to proangiogenic effects in human primary endothelial cells[96].

Another study attempted to further characterize the molecular alterations induced by BPA exposure *in vitro*[97]. The authors evaluated markers of cellular oxidative stress in an experimental *in vitro* model of hypothalamic neurons exposed to BPA, demonstrating that BPA increased, in a time- and dose-dependent manner, the production of intracellular peroxides and mitochondrial superoxide[97]. The results of this study confirmed emerging evidence indicating that non-institutionalized human population have higher levels of urinary BPA and high levels of oxidative stress markers leading to higher risk of CVD, as well as other metabolic chronic diseases.

To further demonstrate an enhancement of inflammation induced by BPA, Song et al demonstrated in two different experimental cellular modelss that BPA induced COX-2 mRNA expression, along with induction of promoter activity, suggesting a direct effect

on increased transcription. Moreover, BPA treatment also increased mRNA levels of the pro-inflammatory cytokines TNF-α and IL-6 [98].

Since clinical findings suggested that BPA might increase the risk of ischemic heart attack and also heart function alterations, another interesting experimental study evaluated the potential effect of BPA on electrical conduction in excised hearts. Results showed that acute BPA exposure slowed electrical conduction, highlighting a potential interfering role of BPA in heart electrophysiology, and, therefore, suggesting that an in vivo exposure could cause or exacerbate conduction abnormalities in high-risk subjects [99].

6. Conclusions

In conclusion, the published studies reviewed here strongly indicate that EDs can trigger human health by interfering with hormonal pathways, inflammatory status, immune responses in both sexes. Since it is known that sex hormones might significantly alter the immune and inflammatory responses during atherosclerosis process, causing different disease phenotypes according to sex, present data lead to the hypothesis that EDs might interfere with cardiovascular homeostasis by interfering with these processes (see Fig. 1). For instance, women respond to infection and damage by an increase in both antibody and autoantibody responses, while men respond by an increase in innate immune activation, suggesting that in spite of a well-known sexual dimorphism in the incidence and complications of atherosclerosis, there are few data explaining the potential mechanisms underlying gender difference as a biological variable in the CVD.

Interestingly, the underlying molecular and cellular mechanisms of the complex relationship among EDs, such as Cd and BPA, and clinical conditions such as CVD are starting to be clarified, apparently indicating that these molecules can play a role as factor risk in a gender-independent manner. Further research is however needed to develop valuable and beneficial intervention for preventing ageing processes often accelerated by stress factors such as pollutants and specifically EDs. New studies are required to fully characterize all the mechanism(s) involved in the process in both genders in order to attempt proper prevention strategy in a sex-dependent manner.

Figure 1: Risk factors for CVD. As the main risk factors related to CVD development exhibit sexdimorphism, sex-dependent effects of EDs are conceivable as well.

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