Medical Hypotheses 122 (2019) 106–110

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Early-life inflammation pathways trigger a cascade leading to development of atherosclerotic plaque through the "butterfly effect" – An hypothesis

M. Kowara[a,b], K. Kasarełło[a], K. Czarzasta[a], G. Opolski[b], A. Cudnoch-Jędrzejewska[a,*]

[a] Department of Experimental and Clinical Physiology, Laboratory of Centre for Preclinical Research, Medical University of Warsaw, Poland
[b] 1st Department of Cardiology, Medical University of Warsaw, Poland

A B S T R A C T

Atherosclerosis is a common disease whose complications, such as myocardial infarction, are a leading cause of mortality worldwide. Therefore, ideas which try to explain the circumstances of atherosclerotic plaque initiation and progression are warranted. We hypothesize that low-grade inflammation in early life (especially an imbalance between pro- and anti-inflammatory macrophages) triggers a "butterfly effect" within the arterial wall by initiating a sequence of processes that finally leads to atherosclerotic plaque development and progression. Therefore, pharmacological and non-pharmacological interventions aimed to prevent atherosclerosis development should be applied not only in the adult population over 40 years old (according to current American and European guidelines) but should start in early life.

Introduction

Atherosclerosis is a systemic disease that affects arterial vasculature, leading to vessel narrowing and obstruction. Although atherosclerosis is localized in many areas of the body, the result is the same – insufficient oxygen supplied to tissues. This causes tissue dysfunction and even necrosis, especially in the case of a sudden obstruction of a culprit artery (e.g., by a thrombus generated upon a ruptured atherosclerotic plaque). This pathological process manifests as different diseases – coronary artery disease (CAD), peripheral artery disease (PAD) and cerebrovascular disease (CVD) [1,2]. According to the FRENA study, patients with symptomatic atherosclerotic diseases (CAD, PAD, CVD) are prone to subsequent ischemic stroke and myocardial infarction [3]. The World Health Organization and United Nations statistics show that ischemic heart disease is a leading cause of death worldwide (circa 380,000 annual deaths in the United States and 600,000 in the Russian Federation due to ischemic heart disease in 2010) [4]. The initiation of atherosclerotic plaque and its progression leading to destabilization and rupture depends on different molecular pathways, i.e., inflammation, extracellular matrix (ECM) accumulation and remodeling, immune cell infiltration and cellular death (apoptosis, necrosis and autophagy) [5,6]. The areas of the arteries in which atherosclerotic plaque initiates depends on irregular shear stress values and patterns and can also be attributed to circumferential stress [7,8]. Emerging evidence supports a pivotal role of low-grade inflammation in the development of plaque [9]. The plaque originates from oxidized low-density lipoprotein (oxLDL) storage within the subendothelial region, which triggers maladaptive immune reactions mediated by different transcription factor families, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), hypoxia-inducible factor 1 (HIF-1), signal transducer and activator of transcription 1 and 3 (STAT1, STAT3), activator protein 1 (AP-1) and nuclear factor of activated T-cells (NFAT) [10]. As a consequence, immune cells infiltrate the region of newly-developed plaque and enhance local inflammation, leading to residual cell apoptosis and ECM remodeling. The crucial immune cells within the atherosclerotic plaque are macrophages, which not only sustain and control the inflammatory reaction by cytokine secretion (especially IL-1β by inflammasome in the initial phase of the development of plaque), but also affects the ECM microenvironment by secretion of metalloproteinases such as matrix metalloproteinase-1 (MMP-1), matrix metalloproteinase-8 (MMP-8) and matrix metalloproteinase-13 (MMP-13) [11,12]. These processes lead to plaque progression, which can turn either into a stable plaque (a basis of stable atherosclerotic diseases, such as stable coronary artery disease, characterized by a thick fibrous cap and decreased infiltration of inflammatory cells) or into a vulnerable plaque (a basis of unstable atherosclerotic diseases, such as myocardial infarction or ischemic stroke, characterized by a thin fibrous cap and increased infiltration of inflammatory cells) [13]. However, the question is: at which point in time is the artery "programmed" towards atherosclerotic plaque development? In early life or in later life? Is it irreversible? Currently, it is assumed that atherosclerosis is associated with vascular aging as a result of permanent and progressive inflammation (the theory of inflamm-aging). The crucial cell in this process is the macrophage, because it integrates pro- and anti-

* Corresponding author at: 1b, Banacha Str., 02-097 Warsaw, Poland.
E-mail address: agnieszka.cudnoch@wum.edu.pl (A. Cudnoch-Jędrzejewska).

https://doi.org/10.1016/j.mehy.2018.10.026
Received 24 July 2018; Accepted 29 October 2018

inflammatory signals and its chronic age-related stimulation reflects increased pro-inflammatory status at an organismal level (the concept of macroph-aging). The entire process of vascular inflamm-aging is controlled by the anti-aging cellular defense network, whose efficacy decreases with age. As a consequence, atherosclerosis seems to be a result of progressively increasing inflammation in arteries of elderly people, in whom atherogenesis overwhelms the protective anti-aging cellular defense network [14]. Therefore, atherosclerosis is considered to be a disease related to senescence and the population "at risk" are those over 40 years old [15,16]. In that population, more or less accelerated plaque progression is related to risk factors (i.e., smoking, hypertension and high LDL serum level) [17]. However, some individuals are more predisposed to atherosclerotic plaque progression and its clinical manifestation. This phenomenon is caused by individual genomic and epigenomic programming. The epigenomic programming is expressed by Barker's Hypothesis of the "Developmental Origins of Health and Disease" (DOHaD), which postulates a crucial role of the influence of environmental factors in very early development (embryonal and fetal). Factors, such as a high fat diet, undernutrition, alcohol intake, acting upon embryonic cells can alter their epigenome by affecting DNA methylation or histone modification, which further causes permanent changes in the physiology of the cell and its progeny resulting in alteration of different physiological processes in later life and predisposition to age-related diseases [18]. In conclusion, it is currently presumed that development of atherosclerotic plaque occurs mainly in later life as the result of increased pro-inflammatory status in the organism (the concept of inflamm-aging) and predisposition to atherosclerosis programmed by genetic and epigenetic factors (illustrated in Fig. 1A).

However, low-grade inflammation also occurs within the arterial tissue in early life. It can cause irreversible damage to cellular membranes, DNA and other cellular structures and such changes might trigger a sequence of reactions that finally bring long-lasting deleterious effects in later life [19,20]. This means that the early-life period might potentially be crucial for the development of atherosclerotic plaque in later life.

The hypothesis

We hypothesize that:

1. initial processes which trigger pathways promoting atherosclerotic plaque development occurs in early life. Although anti-aging cellular networks are efficient in that period of life, initial changes related to increased low-grade inflammation, especially an imbalance between pro- and anti-inflammatory macrophages (M1 macrophages superiority over M2 macrophages), trigger cascades of further reactions that finally lead to accelerated atherosclerotic plaque development in later life in adults and the elderly (Fig. 1B); and
2. additional interventions aimed to decrease low-grade vascular inflammation on a cellular level applied in early life (childhood and adolescence) results in atherosclerotic plaque progression attenuation in later life. These interventions could be lifestyle and dietary modifications or even pharmacotherapy (with the use of specific anti-inflammatory agents, e.g., antibodies).

Evaluation of the hypothesis

The macrophages in the subendothelial region of arteries exert a long-lasting influence upon the cellular microenvironment [21]. They are partly derived from circulating monocytes and also from resident macrophages, which are established in a pre-natal period and persist through to adulthood (due to their longevity and self-renewal) [22,23]. Macrophages, according to their activity, are divided into two main subpopulations – M1 and M2 [24]. The M1 subpopulation exerts a pro-inflammatory activity, whereas M2 – an anti-inflammatory activity (especially the M2a subgroup). M1 macrophages are polarized by lipopolysaccharide (LPS) together with Th1-dependent cytokines, i.e., interferon-γ (IFN-γ) and granulocyte-monocyte colony stimulating factor (GM-CSF) and secrete pro-inflammatory cytokines – interleukins (IL): IL-1β, IL-6, IL-12, IL-23 and tumor necrosis factor-α (TNF-α), whereas M2 macrophages are polarized by Th2-dependent cytokines (IL-4, IL-13) and secrete anti-inflammatory cytokines, i.e., transforming growth factor-β (TGF-β) and IL-10 [25]. The profile and the quantity of cytokines within the subendothelial region depends on the M1/M2 macrophage balance [26]. We assume that a dysregulated balance towards a pro-inflammatory M1 phenotype within the subendothelial vascular region at a young age provides long-lasting changes in the local microenvironment and in a longer perspective will initiate and accelerate atherosclerotic plaque progression, finally leading to an increased risk of its instability (Fig. 2).

For example, M1 macrophage inflammasome – NACHT, LRR and PYD domains containing protein 3 (NLRP3) and NF-κB activation by oxLDL causes expression and secretion of IL-1β cytokine which activates other immune cells, induces endothelial expression of adhesion molecule ligands and maintains the immune reaction within the subendothelial microenvironment [25,27,28]. While all of these processes might lead to atherosclerotic plaque development, IL-1β is considered an important factor in the early stages of atherogenesis [29]. As a consequence, IL-1β inhibition by canakinumab (an antibody against IL-1β) decreases the pro-inflammatory response and can also be an inducer of long-lasting atheroprotection [30–33]. Additionally, the miR-195 particle turned out to be an inhibitor of the M1 phenotype, which could affect the development of plaque [34]. However, macrophage activation and the immune reaction within the subendothelial region is

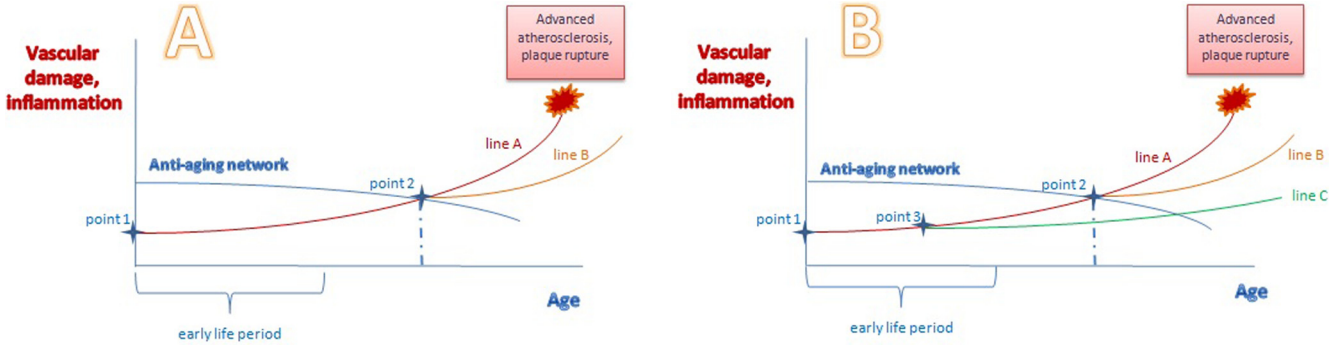

Fig. 1. Classical (A) and hypothesized (B) views of atherosclerotic plaque progression regulation. Point 1 – programming via genetic and epigenetic (DOHaD hypothesis) factors; point 2 – current primary prevention, reduction of risk factors; point 3 – proposed preventive intervention in early life; line A – vascular aging and atherosclerotic plaque progression; line B – vascular aging and atherosclerotic plaque progression after primary prevention; line C – hypothesized vascular aging and atherosclerotic plaque progression after early-life prevention strategy.

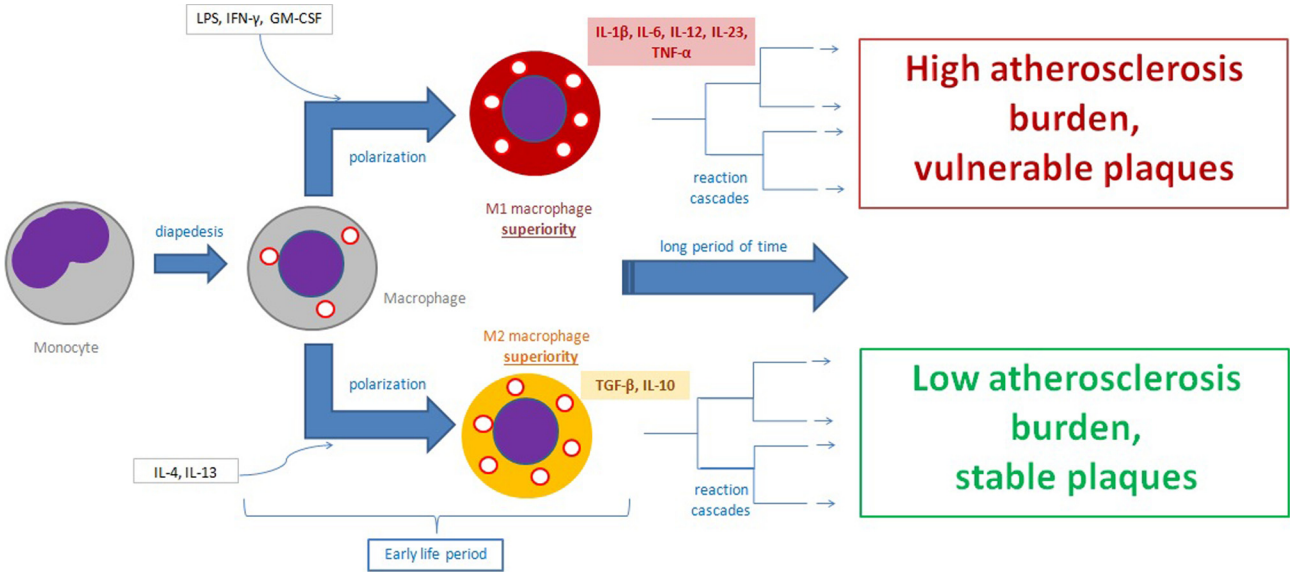

Fig. 2. Potential long-lasting effects of macrophage polarization in early life upon atherosclerosis in later life.

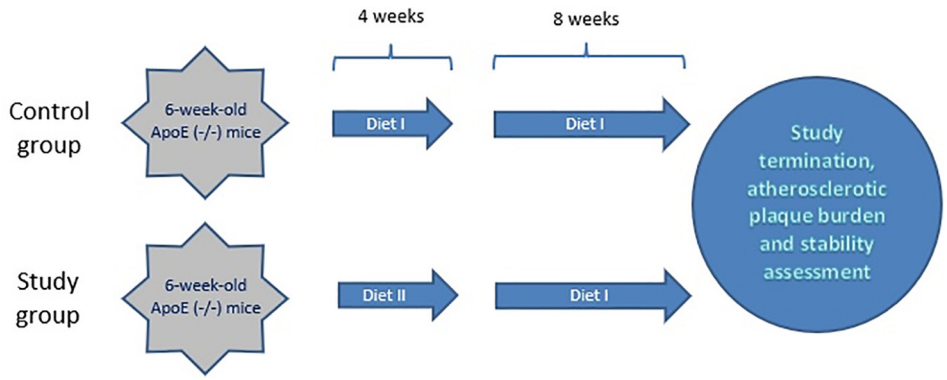

Fig. 3. A hypothetical design of pre-clinical study verifying the hypothesis of ELPHaD (Early Life Programming of Health and Disease). Diet I – a high fat diet with cholesterol, Diet II – a high fat diet with cholesterol with ω-3 fatty acid.

very complex and depends on many different interfering cellular pathways. Therefore, the inhibition of one single pathway could bring misleading results [35]. For example, a knockdown of pro-inflammatory NF-κB in low-density lipoprotein receptor knock-out [LDLR (−/−)] mice resulted in increased atherosclerotic plaque burden, while this factor also downregulates expression of IL-10, an anti-inflammatory cytokine [36]. Interventions, aimed to switch macrophage polarization towards M2 and inhibit M1 differentiation at an early stage of life, might potentially bring protection against atherosclerosis in later life. However, we hypothesize that this not only concerns the specific issue of macrophage polarization but provides more comprehensive implications. In general, agents presenting pleiotropic anti-inflammatory properties exert an atheroprotective potential. For example, eicosapentaenoic acid (EPA) inhibits pro-inflammatory cytokine (IL-1β, IL-6, TNF-α) production by activated monocytes via NF-κB inhibition [37]. Different studies on the apolipoprotein E knockout [ApoE (−/−)] and [LDLR (−/−)] mice models have revealed that ω-3 polyunsaturated fatty acids added to a high fat diet resulted in decreased atherosclerotic plaque burden and increased plaque stability [38]. Similarly, a glucose-lowering agent metformin attenuates atherosclerosis and vascular senescence in pre-clinical mice model, whereas in clinical model it decreases mortality in diabetic patients with atherothrombosis according to REACH study [39,40]. We suggest that anti-inflammatory strategies, such as ω-3 fatty acid or a flavonoid-rich diet, as well as lipid profile and metabolic management (for example by statins or aforementioned metformin) introduced in early life, can disrupt pro-atherogenic pathways and create long-lasting protection from atherosclerotic plaque development, which partially prevents atherosclerosis in later life [41,42]. We called this hypothesis ELPHaD (Early Life Programming of Health and Disease), similar to Barkers' Hypothesis DOHaD (Developmental Origins of Health and Disease). We emphasize that atherosclerotic plaque progression in adulthood and in the elderly depends on a disequilibrium between pro-inflammatory and anti-inflammatory transcription factors and cellular pathways in early life (infancy, childhood and adolescence) and specific inhibition of pro-inflammatory transcription factors and cellular pathways in early life protects from atherosclerosis in later life. Pre-clinical studies aiming to investigate anti-inflammatory interventions exclusively in early life and their impact upon atherosclerotic plaque burden and stability in adult animals would be valuable. For instance, a study in which 6-week-old [ApoE (−/−)] from control group is fed high fat diet with cholesterol for the entire period of study (12 weeks), whereas in mice from study group an additional component of ω-3 polyunsaturated fatty acid is given exclusively for 4 weeks during their adolescence, while for remaining 8 weeks these animals obtain high fat diet with cholesterol (Fig. 3).

Consequences of the hypothesis and discussion

Our hypothesis reflects a more general assumption, i.e., a change at

one point of time can provide long-range effects. It is a “butterfly effect” applied to biological systems. The “butterfly effect” in human biology has been mentioned in the theory of carcinogenesis – one single mutation might initiate a sequence of changes that finally leads to cancer [43]. Another field in which the “butterfly effect” is discussed is the world of microRNA. If a certain microRNA which regulates transcription of hundreds of genes becomes deactivated by mutation, the effects could resonate [44]. Clinical studies which show a distinct association between stressful experiences in childhood (such as physical abuse or household substance abuse) and increased risk of chronic diseases in adulthood tend to confirm the “butterfly effect” in health and disease [45]. In our hypothesis, we postulate a similar effect in atherogenesis. It is known that atherosclerotic plaque development is a long-lasting effect, while lesions specific for the initiation of atherosclerotic plaque have been observed even in late fetal stillborns and infants who died of Sudden Infant Death Syndrome (SIDS) [46]. The idea that different factors acting in early life influence future atherosclerotic plaque development and result in an altered burden of atherosclerotic disease in later life is supported by clinical studies. For example, the study based upon the Boyd Orr cohort, whose follow-up period was 59 years, showed that increased cardiovascular mortality was linked with higher childhood body mass index (BMI) [47]. A more contemporary study – the Cardiovascular Risk in Young Finns Study performed by West et al. has revealed that children of smoking parents are more prone to developing carotid atherosclerotic plaque in adulthood [48]. The meta-analysis of 4 prospective studies (n = 4380 patients) investigating the association between childhood exposure and adult atherosclerosis (Cardiovascular Risk in Young Finns Study from Finland, Childhood Determinants of Adult Health Study from Australia, Bogalusa Heart Study and Muscatine Heart Study, both from the USA) has demonstrated that elevated body mass index, blood pressure, total cholesterol and triglycerides in childhood correlated significantly with intima-media thickness (IMT) measured in adulthood (20–24 years old) [49]. The ARIC (Atherosclerosis Risk in Communities) study has shown that increased BMI at the age of 25 resulted in increased all-cause mortality in later life, irrespective of the ethnic group (African American or White) to which an individual belongs [50]. This correlation remains even after adjustment for weight change between the age of 25 and the age of the first visit (45–64). In addition, the Aboriginal Birth Control Study upon 351 children from the population of Australian Aborigines has shown, that metabolic syndrome in childhood (age between 9 and 13 years old) is associated with the presence of subclinical atherosclerosis (increased intima-media thickness) after 6 years of follow-up [51]. It is clear that risk factors, such as the aforementioned increased BMI or metabolic syndrome enhances low-grade inflammation within the arterial wall and this mechanism might potentially explain their long-range effect upon atherosclerotic plaque [52]. However, there is more direct evidence linking atherosclerosis with earlier inflammation. For example, severe infection in childhood results in an increased risk of acute coronary syndrome at a relatively young age (before the age of 56 years) [53]. This phenomenon could be associated with long-lasting effects of altered immune cell phenotype caused by the earlier infection. The immune cells that integrate pro- and anti-inflammatory signals and regulate local inflammation are macrophages. Their presence within the atherosclerotic plaque at different stages of development has been well documented and their quantity (both the pro-inflammatory M1 subpopulation and the anti-inflammatory M2 subpopulation) increases during plaque progression. Moreover, an increased M1/M2 ratio characterizes vulnerable plaques, prone to rupture [54]. Therefore, macrophages tend to be crucial immune cells that orchestrate reactions sustaining a local inflammatory state and their regulation in early life (e.g., by promoting the M1/M2 ratio towards anti-inflammatory M2) could potentially resonate, especially since a single macrophage established within the arterial wall intima in early life can persist for even more than a decade, as mentioned above [22,23]. It is noteworthy that monocytes obtained from obese children and adults at risk of ischemic heart disease present a similar gene expression profile, suggesting that their similar pro-inflammatory activity facilitates plaque development [55]. However, there is evidence that challenges our hypothesis. An interesting study by Gonçalves et al., in which carotid atherosclerotic plaques dissected from 10 patients undergoing carotid surgery (aged from 46 to 80 years) were analyzed for 14C content using mass spectrometry, revealed that the mean biological age of the plaques was from 6.4 to 12.9 years (according to the plaque anatomical areas). This means that the plaque progression could be attenuated in the early phase by efficient cellular anti-aging networks, which effectively compensates even for the irreversible changes caused by pro-atherogenic and pro-inflammatory factors in early life [56]. In elderly people, the balance between pro-inflammatory and anti-inflammatory cells and cytokines shifts towards pro-inflammatory and these changes predispose elderly individuals to cardiovascular diseases [57,58]. Additionally, an animal study demonstrates that immune cells derived from old mice present a more pro-atherogenic cytokine profile compared with young mice [59]. Therefore, it can be hypothesized that a superiority of pro-inflammatory factors would be necessary for the triggering and maintenance of atherosclerotic plaque progression. According to that theory, the effective anti-inflammatory and anti-aging cellular network is sufficient for atherosclerotic plaque attenuation in early life and the goal in atherosclerosis prevention is extending this effectiveness towards senescence. Janic et al postulate, that low-dose treatment by angiotensin converting enzyme inhibitors (ACE-I) and statins in middle-aged subjects (i.e. from 30 to 55 years old) even for 1 month followed by 6–12 months without treatment would be sufficient to attenuate arterial wall ageing and atherosclerotic plaque progression [60]. This effect would depend on pleiotropic activity of both ACE-I and statins, that favors the plaque stabilization [61,62]. Nevertheless, atherosclerotic plaque initiates in earlier life, before 30 years old. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study performed upon approximately 3000 individuals aged 15–34 years, who died as a result of accidental injury, homicide or suicide, and were autopsied within 48 h of death revealed the presence of fatty streak and raised lesions (i.e., plaques with fibrous caps, calcification or ulceration). The study also presented the spatio-temporal correlation between the fatty streaks and raised lesions as well as the correlations in this population between lesion abundance and risk factors, such as smoking, lipoprotein cholesterol serum concentrations, BMI, glycosylated hemoglobin and hypertension [63,64]. Therefore, additional studies are warranted to answer the question of which hypothesis reflects reality better. If our concept (ELPHaD) is more accurate, then it follows that we should:

1. concentrate upon lifestyle promotion, risk factor reduction and infective disease prevention (by hygiene and vaccination programs) in children and young adults as a prevention of anticipated atherosclerotic diseases; and
2. undertake studies on specific interventions (e.g., anti-inflammatory antibody, active compounds promoting M2 macrophage differentiation) exclusively in early life as a protection from atherosclerotic diseases in later life.

It is necessary to emphasize that if the hypothesis turns out to be true then the programs proposed as a consequence of the ELPHaD hypothesis should be additional to and not substitutional to current atherosclerosis prevention and therapy guidelines.

Conflict of interest

None.

References

[1] Meves SH, Hummel T, Endres HG, et al. Effectiveness of antiplatelet therapy in

atherosclerotic disease: comparing the ASA low-response prevalence in CVD, CAD and PAD. J Thromb Thrombolysis 2014;37:190–201.
[2] Gutstein DE, Fuster V. Pathophysiology and clinical significance of atherosclerotic plaque rupture. Cardiovasc Res 1999;41:323–33.
[3] Aguilar E, Garcia-Diaz AM, Sanchez Munoz-Torrero JF, et al. Clinical outcome of stable outpatients with coronary, cerebrovascular or peripheral artery disease, and atrial fibrillation. Thromb Res 2012;130:390–5.
[4] Nowbar AN, Howard JP, Finegold JA, Asaria P, Francis DP. 2014 global geographic analysis of mortality from ischaemic heart disease by country, age and income: statistics from World Health Organisation and United Nations. Int J Cardiol 2014;174:293–8.
[5] Grootaert MOJ, Moulis M, Roth L, et al. Vascular smooth muscle cell death, autophagy and senescence in atherosclerosis. Cardiovasc Res 2018;114:622–34.
[6] Silvestre-Roig C, de Winther MP, Weber C, Daemen MJ, Lutgens E, Soehnlein O. Atherosclerotic plaque destabilization: mechanisms, models, and therapeutic strategies. Circ Res 2014;114:214–26.
[7] Anssari-Benam A, Korakianitis T. Atherosclerotic plaques: is endothelial shear stress the only factor? Med Hypotheses 2013;81:235–9.
[8] Papaioannou TG, Karatzis EN, Vavuranakis M, Lekakis JP, Stefanadis C. Assessment of vascular wall shear stress and implications for atherosclerotic disease. Int J Cardiol 2006;113:12–8.
[9] Golia E, Limongelli G, Natale F, et al. Inflammation and cardiovascular disease: from pathogenesis to therapeutic target. Curr Atheroscler Rep 2014;16:435.
[10] Tabas I, Bornfeldt KE. Macrophage phenotype and function in different stages of atherosclerosis. Circ Res 2016;118:653–67.
[11] Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol 2012;32:2045–51.
[12] Maziere C, Maziere JC. Activation of transcription factors and gene expression by oxidized low-density lipoprotein. Free Radic Biol Med 2009;46:127–37.
[13] Mauriello A, Sangiorgi G, Fratoni S, et al. Diffuse and active inflammation occurs in both vulnerable and stable plaques of the entire coronary tree: a histopathologic study of patients dying of acute myocardial infarction. J Am Coll Cardiol 2005;45:1585–93.
[14] Franceschi C, Bonafe M, Valensin S, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci 2000;908:244–54.
[15] Karmali KN, Goff Jr. DC, Ning H, Lloyd-Jones DM. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. J Am Coll Cardiol 2014;64:959–68.
[16] Piepoli MF, Hoes AW, Agewall S, et al. European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315–81.
[17] Rudolf J, Lewandrowski KB. Cholesterol, lipoproteins, high-sensitivity c-reactive protein, and other risk factors for atherosclerosis. Clin Lab Med 2014;34. 113-27, vii.
[18] Lee HS. Impact of maternal diet on the epigenome during in utero life and the developmental programming of diseases in childhood and adulthood. Nutrients 2015;7:9492–507.
[19] El Assar M, Angulo J, Rodriguez-Manas L. Oxidative stress and vascular inflammation in aging. Free Radic Biol Med 2013;65:380–401.
[20] Farias JG, Herrera EA, Carrasco-Pozo C, et al. Pharmacological models and approaches for pathophysiological conditions associated with hypoxia and oxidative stress. Pharmacol Ther 2016;158:1–23.
[21] Ginhoux F, Guilliams M. Tissue-resident macrophage ontogeny and homeostasis. Immunity 2016;44:439–49.
[22] Gentek R, Molawi K, Sieweke MH. Tissue macrophage identity and self-renewal. Immunol Rev 2014;262:56–73.
[23] Varol C, Mildner A, Jung S. Macrophages: development and tissue specialization. Annu Rev Immunol 2015;33:643–75.
[24] Bobryshev YV, Ivanova EA, Chistiakov DA, Nikiforov NG, Orekhov AN. Macrophages and their role in atherosclerosis: pathophysiology and transcriptome analysis. Biomed Res Int 2016;2016:9582430.
[25] Shapouri-Moghaddam A, Mohammadian S, Vazini H, et al. Macrophage plasticity, polarization, and function in health and disease. J Cell Physiol 2018;233:6425–40.
[26] Moore KJ, Sheedy FJ, Fisher EA. Macrophages in atherosclerosis: a dynamic balance. Nat Rev Immunol 2013;13:709–21.
[27] Liu W, Yin Y, Zhou Z, He M, Dai Y. OxLDL-induced IL-1 beta secretion promoting foam cells formation was mainly via CD36 mediated ROS production leading to NLRP3 inflammasome activation. Inflamm Res 2014;63:33–43.
[28] Lu X, Kakkar V. Inflammasome and atherogenesis. Curr Pharm Des 2014;20:108–24.
[29] Tabas I, Garcia-Cardena G, Owens GK. Recent insights into the cellular biology of atherosclerosis. J Cell Biol 2015;209:13–22.
[30] Cheng CC, Hsueh CM, Liang KW, Ting CT, Wen CL, Hsu SL. Role of JNK and c-Jun signaling pathway in regulation of human serum paraoxonase 1 gene transcription by berberine in human HepG2 cells. Eur J Pharmacol 2011;650:519–25.
[31] Khambhati J, Engels M, Allard-Ratick M, Sandesara PB, Quyyumi AA, Sperling L. Immunotherapy for the prevention of atherosclerotic cardiovascular disease: promise and possibilities. Atherosclerosis 2018;276:1–9.
[32] Kotla S, Singh NK, Rao GN. ROS via BTK-p300-STAT1-PPARgamma signaling activation mediates cholesterol crystals-induced CD36 expression and foam cell formation. Redox Biol 2017;11:350–64.
[33] Martinez-Martinez E, Buonafine M, Boukhalfa I, et al. Aldosterone target NGAL (neutrophil gelatinase-associated lipocalin) is involved in cardiac remodeling after myocardial infarction through NFkappaB pathway. Hypertension 2017;70:1148–56.
[34] Bras JP, Silva AM, Calin GA, Barbosa MA, Santos SG, Almeida MI. miR-195 inhibits macrophages pro-inflammatory profile and impacts the crosstalk with smooth muscle cells. PLoS ONE 2017;12:e0188530.
[35] Randolph GJ. Mechanisms that regulate macrophage burden in atherosclerosis. Circ Res 2014;114:1757–71.
[36] Kanters E, Pasparakis M, Gijbels MJ, et al. Inhibition of NF-kappaB activation in macrophages increases atherosclerosis in LDL receptor-deficient mice. J Clin Invest 2003;112:1176–85.
[37] Morin C, Charbonneau L, Ouellet N, et al. Eicosapentaenoic acid monoglyceride resolves inflammation in an ex vivo model of human peripheral blood mononuclear cell. Eur J Pharmacol 2017;807:205–11.
[38] Le Goff W. A new piece in the puzzling effect of n-3 fatty acids on atherosclerosis? Atherosclerosis 2014;235:358–62.
[39] Forouzandeh F, Salazar G, Patrushev N, et al. Metformin beyond diabetes: pleiotropic benefits of metformin in attenuation of atherosclerosis. J Am Heart Assoc 2014;3:e001202.
[40] Roussel R, Travert F, Pasquet B, et al. Metformin use and mortality among patients with diabetes and atherothrombosis. Arch Intern Med 2010;170:1892–9.
[41] Gonzalez-Gallego J, Garcia-Mediavilla MV, Sanchez-Campos S, Tunon MJ. Fruit polyphenols, immunity and inflammation. Br J Nutr 2010;104(Suppl. 3):S15–27.
[42] Skilton MR. omega-3 fatty acids, impaired fetal growth, and cardiovascular risk: nutrition as precision medicine. Adv Nutr 2018;9:99–104.
[43] Vogt PK, Hart JR, Yates 3rd. JR. A butterfly effect in cancer. Mol Cell Oncol 2016;3:e1029063.
[44] Lee HC, Yang CW, Chen CY, Au LC. Single point mutation of microRNA may cause butterfly effect on alteration of global gene expression. Biochem Biophys Res Commun 2011;404:1065–9.
[45] Kivimaki M, Steptoe A. Effects of stress on the development and progression of cardiovascular disease. Nat Rev Cardiol 2018;15:215–29.
[46] Milei J, Ottaviani G, Lavezzi AM, Grana DR, Stella I, Matturri L. Perinatal and infant early atherosclerotic coronary lesions. Can J Cardiol 2008;24:137–41.
[47] Gunnell DJ, Frankel SJ, Nanchahal K, Peters TJ, Davey Smith G. Childhood obesity and adult cardiovascular mortality: a 57-y follow-up study based on the Boyd Orr cohort. Am J Clin Nutr 1998;67:1111–8.
[48] West HW, Juonala M, Gall SL, et al. Exposure to parental smoking in childhood is associated with increased risk of carotid atherosclerotic plaque in adulthood: the Cardiovascular Risk in Young Finns Study. Circulation 2015;131:1239–46.
[49] Juonala M, Magnussen CG, Venn A, et al. Influence of age on associations between childhood risk factors and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study for the International Childhood Cardiovascular Cohort (i3C) Consortium. Circulation 2010;122:2514–20.
[50] Stevens J, Truesdale KP, Wang CH, Cai J, Erber E. Body mass index at age 25 and all-cause mortality in whites and African Americans: the Atherosclerosis Risk in Communities study. J Adolesc Health 2012;50:221–7.
[51] Juonala M, Singh GR, Davison B, et al. Childhood metabolic syndrome, inflammation and carotid intima-media thickness. The Aboriginal Birth Cohort Study. Int J Cardiol 2016;203:32–6.
[52] Ebron K, Andersen CJ, Aguilar D, et al. A larger body mass index is associated with increased atherogenic dyslipidemia, insulin resistance, and low-grade inflammation in individuals with metabolic syndrome. Metab Syndr Relat Disord 2015;13:458–64.
[53] Qanitha A, de Mol BA, Pabittei DR, et al. Infections in early life and premature acute coronary syndrome: a case-control study. Eur J Prev Cardiol 2016;23:1640–8.
[54] De Paoli F, Staels B, Chinetti-Gbaguidi G. Macrophage phenotypes and their modulation in atherosclerosis. Circ J 2014;78:1775–81.
[55] Keustermans GC, Kofink D, Eikendal A, et al. Monocyte gene expression in childhood obesity is associated with obesity and complexity of atherosclerosis in adults. Sci Rep 2017;7:16826.
[56] Goncalves I, Stenstrom K, Skog G, Mattsson S, Nitulescu M, Nilsson J. Short communication: dating components of human atherosclerotic plaques. Circ Res 2010;106:1174–7.
[57] Bonaccio M, Di Castelnuovo A, Pounis G, et al. A score of low-grade inflammation and risk of mortality: prospective findings from the Moli-sani study. Haematologica 2016;101:1434–41.
[58] Guarner V, Rubio-Ruiz ME. Low-grade systemic inflammation connects aging, metabolic syndrome and cardiovascular disease. Interdiscip Top Gerontol 2015;40:99–106.
[59] Williams AE, Jose RJ, Brown JS, Chambers RC. Enhanced inflammation in aged mice following infection with Streptococcus pneumoniae is associated with decreased IL-10 and augmented chemokine production. Am J Physiol Lung Cell Mol Physiol 2015;308:L539–49.
[60] Janic M, Lunder M, Sabovic M. A new anti-ageing strategy focused on prevention of arterial ageing in the middle-aged population. Med Hypotheses 2013;80:837–40.
[61] Jankowski P, Safar ME, Benetos A. Pleiotropic effects of drugs inhibiting the renin-angiotensin-aldosterone system. Curr Pharm Des 2009;15:571–84.
[62] Mihos CG, Pineda AM, Santana O. Cardiovascular effects of statins, beyond lipid-lowering properties. Pharmacol Res 2014;88:12–9.
[63] McGill Jr. HC, McMahan CA, Herderick EE, Malcom GT, Tracy RE, Strong JP. Origin of atherosclerosis in childhood and adolescence. Am J Clin Nutr 2000;72:1307S–15S.
[64] Wissler RW. USA Multicenter Study of the pathobiology of atherosclerosis in youth. Ann N Y Acad Sci 1991;623:26–39.