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Editorial

Childhood infection and modern malnutrition: Do childhood infections create an inflammatory foundation for atherosclerosis in adult life?

Atherosclerotic vessel disease is one of the major disease burdens of modern times, arising from a predominantly sedentary lifestyle coupled with an overabundance of highly processed foods. Despite growing understanding of the mechanisms leading to atherosclerosis, its prevalence continues to grow because of lack of effective preventive treatment options.

Throughout most of human history, the main causes of death were infection and starvation; atheromatous vessel occlusion was not a major concern when the average lifespan was 35–40 years. From an evolutionary view, the ability to ward off and survive infections and to adapt metabolic processes during times of famine provided a survival advantage. A hyperactive inflammatory response and a moderate insulin resistance, however, become maladaptive with the transition to a sedentary lifestyle, a constant oversupply of carbohydrate-rich, refined foods, and medical support to survive even severe infections [1,2]. The unifying factor that connects immunity, metabolism, physical activity and atherosclerosis is inflammation, which appears to determine every stage of the disease process. Proof for the causal role of inflammation in clinical atherosclerosis was provided by the CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) [3], which showed that targeting interleukin-1β (IL-1β), a central mediator of immunity, effectively reduces cardiovascular events. Intriguingly, cells of the arterial wall not only respond to IL-1β, but can also produce it, mimicking a key feature of immune cells [4,5]. This may create focal hot-spots of sustained inflammation that are largely disconnected from the initial pathogenic or traumatic trigger, and which may play a role in atherosclerosis development. Timely resolution of inflammation generally limits collateral damage to host tissues and prevents early pro-atherosclerotic changes, but the modern diet and low level of physical activity favor the shift towards sustained inflammation and inadequate resolution. In this sense, the landmark Global Burden of Disease Study 2017 [6] highlighted modern malnutrition as an important preventable risk factor for non-communicable diseases including atherosclerosis in adults in 195 countries.

Poor lifestyle patterns, whether by choice or circumstance, therefore determine atherosclerosis risk. Yet we have known for decades that atherosclerotic alterations develop early in development, with vascular intimal thickening evident in vessels of children, and established fatty streaks documented in young adulthood [7–9]. A recent study from Brazil, albeit with relatively low numbers, provides compelling evidence that the foundation for atherosclerosis is established early in life, and to a large extent independently of self-determined lifestyle factors [10]. The authors identified coronary intimal thickening in one-third of infants, nearly three quarters of children and in all studied adolescents. At least in children and adolescents, the majority showed pro-atherogenic alterations in at least 2 affected arteries, independently of sex or cause of death. Assuming these children and adolescents were largely free of the traditional atherosclerotic risk factors of obesity, type 2 diabetes, hypertension, hyperlipidemia and smoking, what could be the culprit spark that first inflames the artery? One candidate is infection history. An acute infection (mainly viral) has been linked with a more than two-fold increase in pro-atherogenic alterations in children autopsied at age 0–15 [11], while in adults, a cumulative infection burden correlates with accelerated atherosclerosis progression [12]. Pathogens invading vascular cells could trigger local injury processes that promote lesion development and growth, while a systemic cytokine response provides an indirect catalyst for atherogenesis and progression [13]. Intracellular pathogens moreover evade host defense mechanisms, potentially affecting atherosclerosis evolution for a long time after apparent clearance. However, sero-epidemiological evidence for a causal association between infective pathogens and atherosclerosis remains incosistent, perhaps because the observed associations are biased by confounding factors. This may explain why antibiotic therapies and vaccinations have failed to lower cardiovascular risk.

Although infection history alone does not determine atherosclerosis risk, it may provide an atherogenesis-prone foundation susceptible to other factors that drive the disease. A narrative review now published in this journal [14] puts forward the plausible concept that certain types of infection in early life - with improper resolution of inflammation – prime for the pro-atherosclerotic impact of metabolic stress in later life. The authors report on the individual and combined impact of nutrition and infection history during development on atherosclerosis in adulthood, scouring the literature from 1950 to the present day. They identified 13 studies in which documented childhood infections could be linked with early signs of atherosclerosis, specifically vascular endothelial thickening, and manifestation of coronary artery disease in adult life. Notably, 12 of these studies were performed in typical western countries, and one in urban Indonesia where the study population

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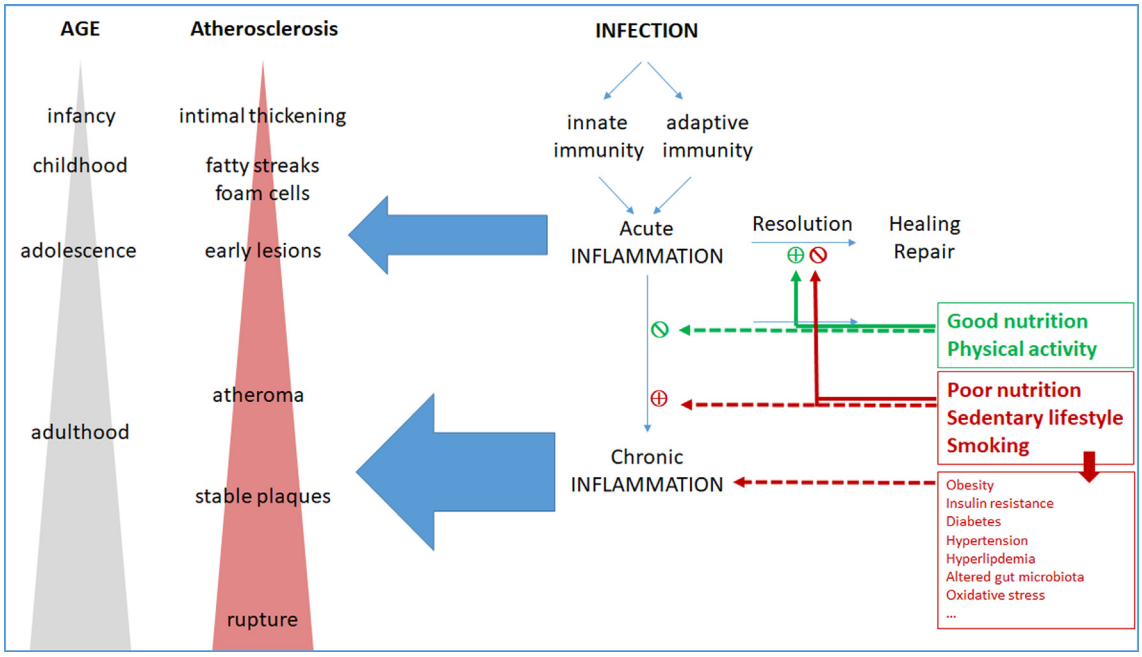

Fig. 1. Simplified scheme how childhood infections may create an inflammatory foundation for the pro-atherogenic influences of malnutrition and lifestyle factors. Early atherosclerotic changes develop in infancy and childhood, with established lesions documented in adolescence and progressing age-dependently in adulthood. Pathogen challenge during development activates both arms of the immune systems, triggering acute inflammation to clear the invading pathogen; a constellation of resolving mediators directs timely resolution of inflammation and supports healing and repair of injured tissues. Failure of this pathway leads to sustained inflammation that promotes atheroma progression. A healthy diet and active lifestyle in adulthood will support resolving mechanisms and counteract chronic inflammatory pathways. Conversely, poor nutrition, low physical activity and unhealthy lifestyle choices will in adulthood impair resolution and promote a chronic inflammatory state, directly and through secondary actions related to comorbidities and stress factors.

had a higher BMI than usual for the rest of the country, indicating an adaptation of this subpopulation to western nutritional habits. The authors moreover highlighted 3 studies in patients with a documented history of infections, that showed a higher presence of cardiovascular disease in those who were also overweight or obese, compared to those with a body mass index <25 kg/m^2. The main insights from this review are that (i) both overeating and childhood infections are associated with atherosclerotic vessel disease in adulthood, although infections do not appear to act independently to cause atherosclerosis, (ii) populations with high infection rate and low calorie hunter-gatherer type diets show a very low prevalence of atherosclerosis, and (iii) a combination of both infections during development and later western-style dietary habits impacts markedly on atherosclerosis.

Although providing interesting insights, this comprehensive overview does not definitely validate the hypothesis that childhood infection primes for the pro-atherogenic influence of metabolic stress in later life. Most studies were either associative or retrospective, and longitudinal tracking of atherosclerosis onset, manifestation and evolution is lacking. A further confounder is that a greater exposure to non-fatal microbes in infancy and early childhood actually lowers the risk of systemic inflammation in later life [15,16], something which our rigorously antiseptic habits rarely allow for anymore. Thus, the umbrella term 'infection,' not differentiating between type and extent of the pathogenic challenge, also hampers the interpretation of the relationship between infection and atherosclerosis.

Nevertheless, the available evidence supports the idea that acute infections may provide a pro-inflammatory foundation for the development of atherogenesis, with poor lifestyle and nutritional habits acting as accelerants (Fig. 1). This consideration may become important in the aftermath of the current pandemic, with long-COVID increasingly recognized to encompass a sustained adverse impact on vascular inflammation [17–19].

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: A.F. has no conflict of interest. D.D. in member of the Scientific Advisory Boards of Omeicos Therapeutics GmbH and Acesion Pharma and obtained honoraria for educational lectures from Novartis, Boston Scientific and Bristol Meyrs Squibb.

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