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Leukotrienes in the atherosclerotic cardiovascular diseases — a systematic review

Agnieszka Wachsmann-Maga[1], Marek Kaszuba[2], Mikołaj Maga[2, 3], Aleksandra Włodarczyk[4], Jakub Krężel[3], Paweł Kaczmarczyk[1, 3], Katarzyna Bogucka[3], Paweł Maga[1, 3]

[1]Department of Angiology, Faculty of Medicine, Jagiellonian University Medical College, Krakow, Poland
[2]Departament of Rehabilitation in Internal Medicine, Faculty of Health Sciences, Jagiellonian University Medical College, Krakow, Poland
[3]Clinical Department of Angiology, University Hospital in Krakow, Krakow, Poland
[4]Faculty of Medicine, Jagiellonian University Medical College, Krakow, Poland

Abstract

Introduction: *The role of inflammation in the pathogenesis of atherosclerotic diseases is strongly suggested. There are multiple studies indicating the possibility of a pathophysiological connection between atherosclerotic changes and leukotrienes (LTs) — the products of arachidonic acid metabolism. The goal of this systematic review, performed in line with the PRISMA statement, was to investigate the potential role of LTs in the pathophysiology of atherosclerotic cardiovascular diseases (CVD).*

Material and methods: *The MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews were searched to identify the potentially eligible studies. Publications that contained information on any type of LTs identified in blood or urine were included in the review. A database search identified 2082 records. Reliable LTs identification in patients with CVD was used in 30 publications.*

Results: *Stable and acute forms of coronary artery disease are characterized by the overproduction of different types of LTs. The level of LTB_4 and LTC_4 in the blood is elevated in patients with cerebral ischemia. Patients with acute and chronic peripheral artery disease have elevated levels of LTE_4 in urine.*

Conclusions: *The findings of this systematic review show that there is a clear tendency to indicate the association of cardiovascular atherosclerotic diseases with increased production of LTs. This dependency detailed characteristic remains unclear and the question on the impact of elevated leukotrienes on clinical atherosclerotic disease manifestations is still open.*

Key words: atherosclerosis; coronary artery disease; leukotrienes; review

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Introduction

Atherosclerosis is a widespread disease process of the arteries, which affects millions of people worldwide [1]. The role of inflammation in the pathogenesis of atherosclerotic diseases is strongly emphasized. There are multiple studies indicating the possibility of a pathophysiological connection between atherosclerotic changes and the products of arachidonic acid metabolism including leukotrienes (LTs) [2–4].

Address for correspondence: Agnieszka Wachsmann-Maga MD, Department of Angiology, Jagiellonian University Medical College, Krakow, Polska, e-mail: agnieszka.wachsmann@gmail.com

LTs are potent biologically active substances, which relate to many biochemical cellular processes. They belong to the group of eicosanoids being mediators of inflammation. LTs are synthesized in the metabolic pathway of oxidation of arachidonic acid (AA) and eicosatetraenoic acid (EPA) — the essential fatty acid by the enzyme called arachidonate 5-lipooxygenase [5, 6]. Five types of LTs are distinguished. The first one, LTA_4 being an unstable substance, is a transition substrate of other varieties of leukotrienes. LTB_4 is a product of hydrolase-mediated metabolization, and LTC_4, LTD_4, LTE_4, called all together as cysteinyl leukotrienes, are products of glutathione-S-transferase activity. The mixture of LTC_4, LTD_4, LTE_4 is known as a slow-reacting substance of anaphylaxis (SRS-A) [7]. All of these substances are bioactive factors, which are involved in many different processes in human organisms [8]. They play important role in inflammation which is the cause of pulmonary diseases such as asthma or bronchiolitis. As active substances present in white blood cells, they are also involved in the processes of utilizing pathogens [9, 10].

The results of the recent study [11] suggest that LTs, as inflammatory mediators, play important role in the process of atherosclerosis, but it is still a subject for further analysis.

Objectives (review question)

The goal of this systematic review was to investigate the potential role of LTs in the pathophysiology of atherosclerotic cardiovascular diseases (CVD).

Material and methods

To present a reliable assessment of the leukotrienes' role in atherosclerotic CVD, based on available data, a systematic review of the published literature has been conducted according to the PRISMA Statement [12].

Inclusion criteria

Publications that contained information on any type of leukotriene identified in blood or urine were included in the review. Additionally in every study enrolled cardiovascular atherosclerotic disease status should have been correlated with the level of these substances. Only studies, which were conducted on human subjects with no age restrictions, and published in a language limited to English were included.

Data sources and search strategy

Three databases: MEDLINE, EMBASE and Cochrane Database of Systematic Reviews have been searched to ensure comprehensive coverage of the literature. MeSH Terms were used for searching in Pubmed, as well as Emtree terms — in Embase (see Supplementary Table 1). Firstly, the search for reviews with a main topic similar to the topic of this systematic review has been performed and no such publications have been identified. Then all types of primary studies published until August 2020 and fulfilling inclusion criteria, have been identified in the databases and included in the review.

Screening

During the screening phase of the review, two reviewers worked independently. They identified eligible records based on title and abstract. Disagreements between them were resolved by a consensus reached with a third reviewer. Duplicates were excluded from initial references. The publications, that fulfilled inclusion criteria or were of unknown significance, were thoroughly analyzed based on full text. The full-text analyzes of the publications were also performed by two reviewers. In case of incompatibility, the independent reviewer made the final decision if the record should be included in the review.

Data extraction

The data were collected using a data-extraction form with detailed information categories referring to the topic of this review. The reviewers were obligated to assess the quality of the included studies as well as the completeness of data in the extraction table (see Supplementary Table 2). The data from each publication were independently extracted by two reviewers. Any discrepancies in the data extracted were resolved via discussion or adjudication by a third reviewer if necessary. Secondary studies were analyzed to identify any reference, which was the primary study consistent with the subject of the systematic review and which was not previously identified. In case insufficient data will be available for quantitative synthesis, we planned a narrative synthesis of the data with a clear overview of any outcome measures.

The risk of bias assessment

The methodological quality of the studies selected for the summary of the review was assessed based on Joanna Briggs Institute (JBI) [13] critical appraisal tools dedicated specifically to different study types. The risk of bias of the studies included in this systematic review was assessed by two critical appraisers and disagreements were resolved through discussion or by establishing a consensus with a third appraiser.

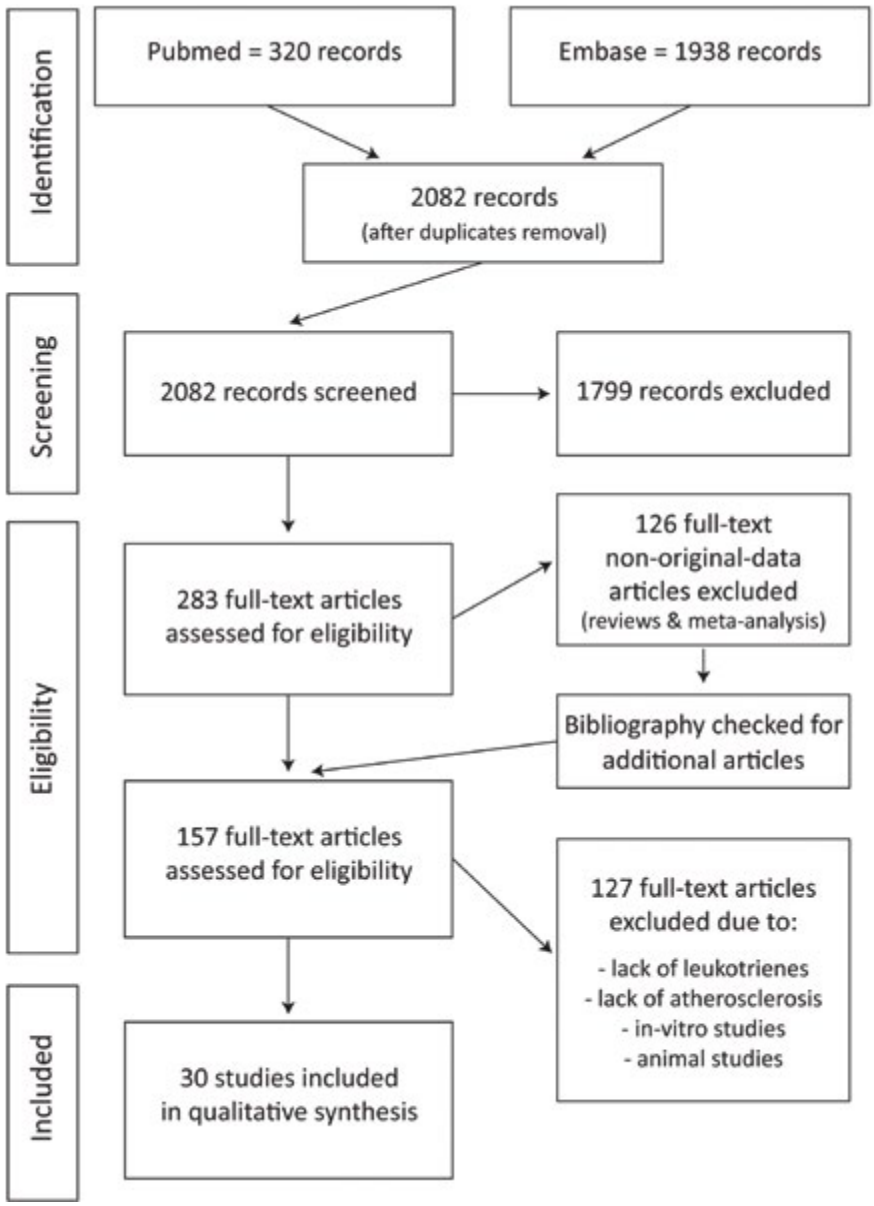

Figure 1. Flow chart [37] presents the study selection process

Results

Search results

Initially, in this systematic review, 2258 records were identified, with a number of 2082 articles after duplicate removal. During the screening of 2082 records, 283 full--text articles were assessed for eligibility. From this number, 126 full-text publications were excluded due to the fact they were reviews. All of these publications' references were inspected to find any additional primary studies. Finally, 157 original studies were included in the next step of this review. After their assessment for eligibility 30 studies were included in the final qualitative synthesis. The rest 127 publications were not included due to a lack of reported LTs level assessment, lack of atherosclerotic disease diagnosed in studies subjects, no-human character or in-vitro type of study (Fig. 1).

Study characteristics

Thirty studies finally analyzed in this review were performed in different countries. The period when the articles were published ranged from 1988 to 2020. Most studies (n = 20) were case-control studies. Cohort studies (n = 9), as well as non-randomized experimental study (n = 1), were also identified (see Supplementary Table 2). No systematic reviews nor meta-analyses

regarding simultaneously LTs and atherosclerosis were found.

Patient characteristics

All of the included publications could be divided into three categories based on the disease diagnosed in study subjects. The first group of articles consisted of publications in which the leading atherosclerotic disease was coronary artery disease (CAD) (stable coronary artery disease as well as unstable angina and myocardial infarction). This group was the most numerous (n = 21). The second group consisted of studies where patients were diagnosed with cerebral ischemia or carotid artery disease (n = 7). The last and least numerous was the group with peripheral arterial disease (PAD) diagnosed patients (n = 2).

Leukotrienes assessment

LTs were assessed in all included studies. In 21 studies the concentrations of LTs were measured in blood. Only one work performed a measurement also in a cerebral spinal fluid (CSF). The rest of the studies used urine to assess the level of LTs (n = 9). Detailed information on types of LTs in each study as well as a methodology of their measurement is presented in the table (see Supplementary Table 2).

Leukotrienes in CVD

The largest number of studies qualified for this review was related to coronary artery disease (CAD). In the group of patients with CAD, a few forms of the disease were taken under the consideration. The authors studied acute myocardial infarction (MI), as well as unstable (UA) and stable angina (SA). In this group of 15 studies, the connection between the level of leukotrienes and the presence of the disease has been proved. In all cases of CAD, the LTs level was increased, in comparison with healthy subjects or with subjects with noncardiac chest pain (NCCP). It concerned LTB_4 as well as LTE_4; the first one was measured in blood, the second one in urine. A lack of connection was found in 3 studies. Furthermore, the analysis of the link between the level of severity of CAD and the level of LTs showed that there were 9 studies that proved such dependency and only 2 studies suggesting a lack of it.

Stable CAD

Gautier-Veyret E. et al. showed that the level of LTE_4 in the urine of patients with CAD is higher than in patients without CAD [14]. Also Allen S. P. et al. pointed out the role of LTE_4 in CVD demonstrating that the level of LTE_4 calculated per creatinine concentration in urine is higher among patients with CAD than in healthy controls [15]. LTB_4 row level [16] or calculated per number of blood cells [17] was also higher in patients with SA compared to healthy controls.

Indirect evidence for the influence of the coronary process on the level of LTs was suggested in the study published by Brezinski and al. They proved that Percutaneous transluminal coronary angioplasty (PTCA) in patients with CAD triggered the intraluminal release of peptidoleukotrienes (LTC_4 and LTD_4). Intracoronary blood, taken from these patients before PTCA, showed no detectable levels of these eicosanoids [18].

Acute coronary syndrome

ACS was characterized by a higher level of LTB_4 in blood than in patients with NCCP [19]. LTB_4 measured in blood was higher when measured 2 and 6 months after non-ST-elevation acute coronary syndrome in comparison to healthy controls, as well as 2 months after such episode when compared to stable CAD patients [20]. When measured within the first 24 hours of MI it was elevated also when compared with UA, stable CAD and non-CAD patients. In two studies the level of LTB_4, when measured in blood among patients with MI was more than double of that in healthy controls [21, 22]. It was also shown that LTB_4 can be released by ionomycin in the blood more in the group of patients with a history of MI than in healthy people [23]. During the acute phase of MI and 1 day after it, LTB_4 and SRS-A were elevated in the blood when compared with no-CVD patients [7]. After 24 hours of MI their level in the blood decreased [24].

Although Carry M. et al. noted the differences in urine, LTE_4 concentration between MI patients and patients with non-ischemic chest pain, UA or without CAD, the statistical significance of these differences has not been assessed in their study [25].

Stodółkiewicz E. et al. demonstrated that the level of urinary LTE_4 in patients 1 year after MI is lower than in CAD patients with no history of MI [26]. In another study, published by these authors, urinary LTE_4 level was higher in patients with CAD and with multivessel disease than in those with less severe disease and single vessel involvement [27].

Also, patients with UA had a higher level of LTB_4 than patients with stable or no CAD [24]. One study showed that patients with UA presented also a higher level of urinary LTE_4 than patients with SA, non-CAD, and non-ischemic cardiac pain, just like in patients with SA in comparison to patients with non-ischemic cardiac pain [8].

Fosshaug L.E. et al. demonstrated that 12-epi-6-trans- LTB_4 concentration in blood, the metabolite of LTB_4, is higher in patients with ST-elevation-myocardial infarction than in stable CAD patients, and the rest of

the substances assessed in the study (LTB_4, LTE_4, LTC_4/ /LTD_4) were not [11].

Carotid artery disease

In 5 of 8 publications included in the systematic review and referred to carotid artery disease, the correlation between the level of LTs and this disease was found. In one study it was noted that patients with increased intima-media thickness (IMT) had a higher level of LTB_4 in their blood [28]. Among patients with cerebral ischemia the level of LTC_4 measured in CSF [29] and LTB_4 assessed in the blood [30] were higher when compared with controls without such a condition. Katsura K. et al. in patients with cerebral infarction showed higher levels of LTB_4, LTC_4 and SRS-A measured in blood in comparison with healthy controls [31]. Chan S.J. et al. proved the correlation of LTB_4 concentration in blood not only with ischemic stroke but also with the level of disability caused by this condition [32].

PAD

Two publications included in this systematic review referred to the leukotriene level in PAD. In the first one, the patients with acute or chronic PAD had higher LTE_4 concentration in urine calculated for creatinine than healthy controls. [17]. In the second one Maga et al. noted a correlation of LTE_4 level in urine with restenosis among patients with PAD when assessed 3, 6, and 12 months after PTA [16].

Six studies included for the final synthesis showed no significant connection between the level of leukotrienes in blood or urine and CVD status.

Discussion

The connection between LTs and atherosclerosis has been studied for many years. Although it is an important issue, still the role of LTs in the atherosclerotic process has not been definitely established and none of the anti-leukotriene drugs are recommended for the treatment of CVD. Studies included in this systematic review in most cases confirm this kind of connection, although in some cases there is a lack of evidence for it. The connection between LTs and atherosclerotic disease was demonstrated in 24 analyzed publications. In the group of patients with atherosclerotic disease, most of the publications presented a positive correlation between the levels of LTs and CVD (15 studies). The correlation concerned mostly leukotriene B_4, which was assessed in the blood (serum), but also there were a few publications providing evidence that LTE_4 level in urine, as well as other LTs may correlate with atherosclerotic status.

Most of the studies included in this review showed elevated levels of LTs in patients with atherosclerotic CVD. Another type of evidence for an association of LTs with CVD is the correlation of some leukotriene levels with disease severity, both for CAD and cerebral ischemia.

During the process of conducting this systematic review, publications, in which the association between the level of LTs and atherosclerotic diseases was proved indirectly, were also found. Ingelson et al. provided such indirect evidence by noting that asthmatics who underwent a montelukast treatment were protected by its antileukotriene actions against CVD, especially recurrent stroke [33].

The lack of systematic reviews on the topic of LTs in atherosclerosis so far makes this review unique and an important item in the literature on the subject. The weak side of this study is the fact, that the studies included in the systematic review are often not high quality. Many of them were only conference abstracts, which had very little detailed information including methodology. Another pitfall of included studies is that the results of the LTs measurements are not consistent with the units or determination methods. A considerable amount of work included in this review was published in the '90s, which relates to the lack of a detailed methodology. Due to this fact and because populations in different studies were characterized by high heterogeneity, a meta-analysis could not be performed. It must be also noted, that the publication with the most number of patients presented the results of the study performed by He Guoping et al. in China [19]. During the search, 4 conference papers published by these authors were identified, but the data from 3 of them were found also in the full-text article [23, 34, 35] and only one abstract could be analyzed separately [36].

Taking into account the risk of bias in the publications that qualified for the final analysis, we used JBI tools [13] intended for the critique or appraisal of the research evidence. The risk of bias according to JBI tools in many publications and their aspects was assessed as high or unclear, although most of the analyzed studies presented a low risk of bias (see Supplementary Fig. 1).

Despite the above limitations and doubts, the number of links pointing to the relationship of CVD and LTs is significant and very suggestive. The data collected in this review contribute to further research and can be used to design clinical trials focused on the use of drugs affecting the leukotriene pathway in the prevention and treatment of atherosclerosis-based CVD.

Conclusion

The findings of this systematic review show that there is a clear tendency to indicate the association of cardiovascular atherosclerotic diseases with increased production of LTs. On the other hand, this dependency detailed characteristic remains unclear and the question on the impact of elevated leukotrienes on clinical atherosclerotic disease manifestations is still open. The world of science is still missing well-designed observational studies with good methodology, which could contribute to the final of proof of the connection between this kind of arachidonic acid conversion products and atherosclerosis. Also, clinical research on the use of anti-leukotriene drugs in the treatment of CVD could be an important advance in this direction.

Conflict of interest

The Authors declare that there is no conflict of interest. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Upon a reasonable request, the review protocol and the study data will be available from the corresponding author. The review has not been previously registered.

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