EPIGENETIC STUDY AS A NEW APPROACH FOR THERAPEUTICS AND BIOMARKER OF ATHEROSCLEROSIS IN COVID-19

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ABSTRACT

Introduction : Coronavirus disease 2019 (COVID-19) has affected more than 105 million people globally and resulted in at least 2.3 million deaths. Covid-19 has highlighted the vulnerability of aging populations to emerging diseases. This susceptibility to disease and death is also a major challenge for the development of vaccines and immunotherapeutic agents. Atherosclerosis is one of the main cardiovascular disease, and this disease is one of the most common comorbid diseases affected by Covid-19 and is associated with increased risk of mortality. Biomarker are crucial in decision-making in order to facilitate efficient resource allocation. Recently many researcher develop several biomarker as a new approach in epigenetic area. The discovery of new therapeutic targets as well as biomarkers using epigenetic studies may increase its clinical usefulness.
Methods: In this narrative review, a search was carried out with the help of several search engines that match the criteria, namely "Epigenetic Studies Based On Cardiovascular Disease Especially In Atherosclerosis".
Results: One paper was obtained that supports and fits the criteria, namely the role of miRNA in the formation of atherosclerotic plaques.
Conclusion: miR-486-5p can be used as a new therapeutic target and biomarker in atherosclerosis patients, but this requires further research.

Keywords: Epigenetic studies, Cardiovascular Disease, Atherosclerosis

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INTRODUCTION

Covid-19 disease first case was identified in Wuhan China on December 2019. Covid-19 or previously known as 2019 Novel Coronavirus (2019-nCoV) is the disease caused by an infection of the SARS-CoV-2 virus.[1] April 6th 2021 on https://covid19.who.int, globally there have been 131.487.572 confirmed cases including 2.857.702 deaths reported to WHO. This virus spreads easily and very quickly, so that this viral infection is the cause of a global pandemic. Almost all countries in the world are hit by the Covid-19 disease and this has also caused significant deaths, economic losses and global panic. This virus is spread by contact with droplets of patients who are already infected with the corona virus when they cough or sneeze.[1]

From the beginning of pandemic, heavy Covid-19 cases are attacked significantly more frequently elderly individuals and attendance of comorbidities. Elderly individuals and attendance of comorbidities had the highest death rate, even though Covid-19 related deaths also reported on young or middle aged adults.[2] Even based on cohort study Shi,. Shaobo, 2020, Cardiac injury is a general condition between hospitalized patients with COVID-19 in Wuhan, China, and it is associated with higher risk of in-hospital mortality.[3] The interaction among the spike (S) protein and angiotensin-converting enzyme 2, which cause to the virus entry into host cells, possibility to be embroiled in the cardiovascular manifestations of COVID-19.[4]

The most common comorbidities that are often diagnosed before elderly individuals infected with Covid-19 is hypertension, diabetes, stroke, dementia, COPD, chronic renal failure, and a lot of CVDs was significantly higher in older patients, such as atrial fibrillation, heart failure, stroke, hypertension and ischemic heart disease.[2,5] And some cardiovascular diseases can affect by a pathological condition in the form of atherosclerosis. Atherosclerosis is inflammatory process occurring as develop to accumulation of lipids within the arterial wall. It is a condition that must be handled properly so as not to cause dangerous symptoms.[6]

Until now the Covid-19 pandemic is still happening and who knows when it will be over. This will have far-reaching and long-term effects on CVDs in elderly patients especially in the case of atherosclerotic plaque formation as a cause of various deadly heart diseases. Therefore, it needs tighter care for taking care of elderly during Covid-19 pandemic, one of them is by developing therapeutic therapy. Because Some medications used for the therapy of COVID-19 have rootless safety and efficacy profile, the clinicians need facing the problem this challenge by finding ways improve the ability of care delivery and improving the effectiveness and efficiency of CVDs therapy for elderly patient during the COVID-19 pandemic especially in determining new therapeutic targets and biomarkers in atherosclerosis.[4,7]

Epigenetics research can expand antiviral drugs by evaluating specific epigenetic modulators as targets and exploring new chromatin-based therapies for different virus families (including coronaviruses), which can explain the interaction between the virus and the host. The basic new pattern of action and its role in disease severity.[8] In the past few decades, a large number of studies have shown that epigenetics plays an important role in the conformation and progression of many common diseases (especially age-related diseases).[9] Further in patients with comorbidities, alteration undergone by the virus may be clear and quick. The changes of epigenetics can be important regulators that remodel host chromatin structure, gene expression patterns in a highly flexible mode. These changes can modify the cellular behavior including the host's innate immune response.[10]

The correlation between epigenetics and cardiovascular disease, that is,

epigenetics is an emerging mechanism related to vascular biology and endothelial nutrition regulation. Through chromatin remodeling, epigenetics can modify endothelial function, thereby affecting cardiovascular diseases, because the regulatory function of epigenetics is also effective for endothelial precursor cells and circulating angiogenic cells.[11,12] DNA methylation, modification of histone, and the recently discovered mRNA mechanism represents an important pathway involved in epigenetic research For instance, vascular endothelial growth factor A (VEGF-A) and nitrite oxide synthase (NOS) are major chemical processes in maintaining and regulating cardiovascular functions. Epigenetic mechanisms are able to control their expression. Especially, VEGF□A epigenetic control can expand mainly thru histone modification by RNAs. VEGF□A serve by VEGFR2, which in modify is regulated according to promoter DNA methylation.[12]

This narrative review to refer to explain research which describes new therapeutic targets and biomarkers in atherosclerosis based on epigenetic study which will used to atherosclerosis therapy as mainly comorbidities and major complication of Covid-19 infection. And we can taking care elderly during the pandemic furthermore.

MATERIAL AND METHODS

Search Methodology

For the purpose of this narrative review, we used 4 search engine: PubMed, ScienceDirect, SpringerLink and Nature. The search criteria were restricted to article type based on level of evidence "Randomized Controlled Trial (RCT), Critically-appraised evidence, systematic review, and Meta-Analysis". And the articles were published in English within the last three years, between March 2018 until March 2021. We used three sets of keywords to encompass the eligible article "epigenetic study", "elderly patients", and "cardiovascular disease. The article were accessed, and relevant references were made for the aim of this review.

This study focused on publications satisfying the following several conditions. Article have to implementation of epigenetics study to address CVDs in elderly patients, well it is DNA methylation, histone modifications or non-coding RNA. Explain of reporting or discussing modification in studied patient outcomes or con editions. We excluded any research that did not report a estimated patient outcome, review or opinion article, and qualitative perception articles. After obtaining it, we will take a paper that refine search again on which reveals new therapeutic targets as well as biomarkers in atherosclerosis.

RESULT

Regarding the use of keywords, it was found 14 articles in PubMed, 498 articles in SpringerLink, 186 articles in ScienceDirect, and 36 articles in nature (Figure 1).

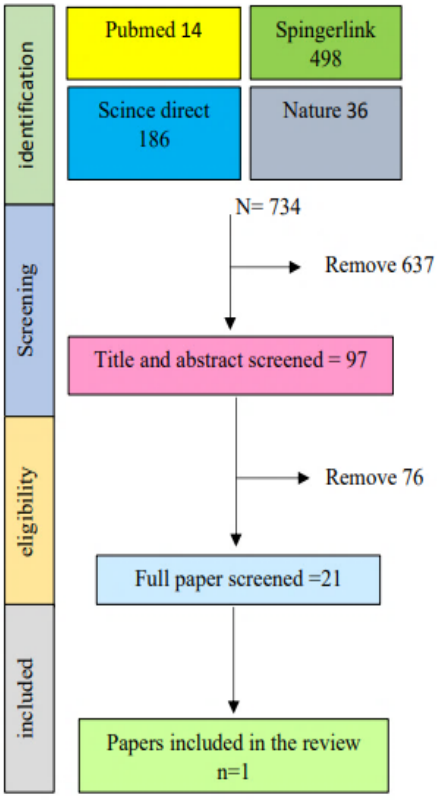

Figure 1. PRISMA selection procedure

Thus the total of articles have been founded were 734. We removed 637 articles which do not match the criteria for the desired keywords using search engine's filter. The authors screened the remaining 97 studies by reading abstracts and titles. Seventy six articles that did not meet our inclusion criteria were removed, and twenty one papers were shortlisted for full screening. The outcome of this process is one paper within the targeted scope and inclusion criteria.

Journals that match the criteria, namely entitled "Regulation of microRNAs in coronary atherosclerotic plaque". This paper describes research in that might be made as new approach for therapeutics and biomarker of atherosclerosis. This study describes miRNA expression in patients with atherosclerosis. They were collected coronary artery plaque (CAP) from 14 coronary artery disease patients who underwent endarterectomy and bypass grafting caused by occlusive atherosclerosis. And Internal Mammary Arteries or IMA samples were used as control that acquired through bypass surgery. Analysis of histopathological conducted either on atherosclerotic or IMA tissues to confirm whether there is or not atherosclerosis. The miRNA profiles were compared using microarrays and quantitative PCR.[13]

The result showed thirty-one differentially miRNAs expressed between CAP and IMA. And miR-486-5p showed a high level of regulation (12-fold), it has been predicted to interact with atherosclerosis-related genes, and is associated with triglyceride levels and arterial stenosis. The regulation of miR-486-5p was verified by PCR ($p = 0.004$). miRNA is regulated in atherosclerotic plaques. The author focused on miR-486-5p, and its role in atherosclerosis needs further study..[13]

DISCUSSION

MicroRNA (miRNA) is a small non-coding RNA that acts as a major player in post-transcriptional gene regulation in various species.[14] According to reports, MicroRNA (miR) is involved in vascular inflammation and may represent a new type of diagnostic biomarker in cardiovascular disease. According to the study of Parahuleva et al., there are significant differences in miRNA expression profiles between atherosclerotic plaques and healthy control arteries. The most up-regulated miR, so-called atherosclerosis, is involved in cellular processes known to be involved in atherosclerosis. Using only a single molecule as a target, interference with miRNA expression in arteries is a potential means to affect plaque development in many ways. In the process of vascular wound healing, the interpretation of the complex cell and environment-specific effects of miRs seems to be crucial for the development of miRNA-based atherosclerosis therapy. In addition, the in vivo specific blockade of miR-21 and miR-92a expression can reduce vascular inflammation and change the development of atherosclerosis, reduce plaque size and promote a more stable disease phenotype. MiR-21 and -92a may be new therapeutic targets for proliferative vascular diseases (such as atherosclerosis, restenosis after angioplasty, and graft vascular disease).[15]

The correlation between miR-486-5p and triglyceride levels suggests that this miRNA may play a role in the regulation of lipid metabolism. It has been previously demonstrated that the expression of miR-486-5p is up-regulated in the serum of patients with coronary heart disease and can distinguish stable and fragile patients with coronary heart disease. Interestingly, the same study showed that miR-486-5p is related to HDL particles and is preferentially distributed in HDL subgroups HDL2 and HDL3. The elevated level of

miR-486-5p in HDL2 is especially related to the vulnerability of CAD patients.[16]

Another study showed that inhibition of miR-486-5p by subcutaneous injection of antagomiRs into hyperlipidemia mice can reduce liver and plasma cholesterol.[17] The prediction analyses suggested that miR-486-5p may target *MAP3K7*. This gene encodes for the serine/threonine kinase TAK1 which is a major upstream signaling molecule of TGF-β1-induced type I collagen and fibronectin expression.[18,19] TAK1 is activated by TGF-β1 and triggers the activation of several downstream signaling cascades such as NF-κB-inducing kinase-IκB kinase.[20] Which is activated in the endothelium of vascular regions susceptible to atherosclerotic injuries.[21,22]

It has also been proposed that miR-486 is related to cardiac hypertrophy, and the up-regulation of miR-486 helps to activate the Bcl-2 related mitochondrial apoptotic pathway, thereby exhibiting anti-apoptotic function in cardiomyocytes.[23] According to these findings in experimental studies, miR-135a and miR-486 are considered to be opposite to the apoptosis pathway regulated by Bcl-2 in myocardial infarction remodeling. On the other hand, in several epidemiological studies, both miR-135a and miR-486 in blood were positively correlated with IHD. Among Austrians, miR-135a and miR-486 in this study were significantly higher than those in Japan people.[24–26]

Niculescu et al. determined the preferential distribution of miRNAs in HDL subgroups (HDL2, HDL3), which proved to be an important difference between the vulnerable CAD group and the stable CAD group. Therefore, we show here that the elevated levels of miR-486 in HDL2 and miR-92a in HDL3 are particularly related to the serum of vulnerable CAD patients (UA and MI groups). The mechanism for enhancing miRNA levels in HDL may involve the transfer of lipids to HDL cells and/or the activity of lipid transfer proteins that exchange lipids between apoB-containing Lp and HDL. It is recognized that HDL carries miRNAs, but it is not yet known how they bind to HDL particles. Recent reports indicate that some miRNAs related to HDL act as communication messengers over long distances from the donor to the recipient cells, but the author cannot point out what tissue they originate from or whether they are involved in the regulation of HDL secretion.[16]

The function of miRNA as a predicted to regulate genes known to be involved in the atherosclerosis pathway has been proven by several studies such as, which has been done by Ocal Berka et.all (2019) about Regulation of microRNAs in coronary atherosclerotic plaque by using a sample of 14 people who have 6 Coronary atherosclerosis plaque (CAP) and internal mammary arteries (IMAs). The present study allowed the identification of differentially expressed miRNAs between healthy vascular tissues (non-atherosclerotic plaques example IMA) and atherosclerosis tissue. The method used in this study was to compare microarrays and PCR analysis as it's quantitative analysis. The results, they observed in microarray experiments that 31 miRNAs were not related to the atherosclerosis pathway and did not have a correlation between atherosclerotic and healthy tissues.[13] However, qPCR show a correlation with patient's clinical data allowed the selection of miR-468-5p to be involved in the formation of atherosclerosis pathways. Because, miR-468 5p correlations with triglyceride levels suggests that this miRNA may have a role in the modulation of lipid metabolism.

This is in accordance with the research conducted by Niculescu Loredan S et.all (2015) with the research title MiR-486 and miR-92a Identified in Circulating HDL Discriminate between Stable and Vulnerable Coronary Artery Disease Patients. The investigation included 111 subjects (38 women and 73 men, aged 24–79 years with cardiovascular disease. 95 patients with CAD (30 SA, 39 UA and 26

MI) and 16 healthy control subjects which show that expression of miR-486-5p has previously been shown to be upregulated in the sera of patients with CAD and was able to discriminate between stable and vulnerable CAD patients. interestingly, this study showed that miR-486-5p was associated with HDL particles, with a preferential distribution in the HDL subpopulations HDL2 and HDL3. Increased levels of miR-486-5p in HDL2 were particularly associated with vulnerability of CAD patients. Thus, high levels of miR-468 circulating in the blood have the potential to be used as a biomarker in CAD. Mechanism that increase miRNA levels in HDL may involve cellular transfer of HDL lipids or due to the transfer activity of proteins containing ApoB and HDL.16 but only few succeeded in finding correlations between circulating miRNAs and other serum parameters already accepted as biomarkers for CAD.[27]

Another study from Niculescu Loredan S et.all (2018) has identified the potential for reversal hyperlipidemia LNA miRNA inhibitor that is injected subcutaneously specifically for miR-468-5p. Showed that the inhibition of miR-486-5p by subcutaneous injection of antagomiRs to hyperlipidemic mice reduced hepatic and plasmatic cholesterol. LNA miRNA inhibitor was given for 2 weeks and there was a significant reduction lipid levels in the liver and plasma of mice. Hyperlipidemia in mice plasma after being given an LNA miRNA inhibitor in decrease total cholesterol levels by 17,14% with a value of p= 0,4411. As expected, the treatment with miRNA inhibitors strongly reduced plasma levels of miR-486 (by 96%, p=0.0086), while in all control HL (hyperlipidemia) groups the miRNAs levels remained unchanged. They observed a similar effect in HL livers, the treatment with miRNA inhibitors strongly reduced the hepatic levels of miR-486 (by 99.4%, p=2.45 × 10−7).[17] They prediction analyses showed that miR-486-5p may target MAP3K7. This gene encodes for the serine/threonine kinase TAK1 which is a major upstream signaling molecule of TGF-β1-induced type I collagen and fibronectin expression. It's known that when collagen type 1 and fibronectin are induced will cause the formation of atheroma plaques in atherosclerosis disease.[18,28] And the group of Liu et al. showed that miR-486 could indirectly inhibit ABCA1-mediated cholesterol efflux in THP-1 macrophages by direct targeting of histone acetyltransferase.[29]

Niculescu Loredan S et.all (2018) reported that miRNA inhibitors, miR-486 can directly regulate SOAT2 and SREBF1, which are two key enzymes involved in lipid metabolism. SOAT2 (or formerly ACAT2) is responsible for the formation of cholesteryl esters (CE) in the liver, preventing the accumulation of free cytotoxic cholesterol (FC).[30] Therefore, the inhibitory effect of SOAT2 may lead to the cytotoxic accumulation of FC in hepatocytes, but it can also stimulate the excretion of FC into bile. They showed that a high-fat diet can induce a significant increase in liver and plasma miR-486 levels, as well as an increase in liver weight, lipid accumulation and loss of SOAT2 gene expression in the liver of HL hamsters.[31] This study proved that the restoration of SOAT2 expression by inhibiting miR-486 in vivo can reduce liver cholesterol levels and plasma cholesterol levels.

CONCLUSION

Micro RNA is branch of epigenetic study. Berkan et al, showed that miR-486-5p is highly potential as a new therapeutic target and biomarker in atherosclerosis patients, but this requires further research.

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