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Serum YKL-40 and Cardiovascular Diseases

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Abstract

YKL-40 is a glycoprotein synthesized by several cell types, including macrophages, neutrophils, and endothelial cells. It plays a role in several biological processes, such as tissue remodeling, inflammation, and cell proliferation. Research findings have shown that levels of YKL-40 tend to be higher in individuals diagnosed with cardiovascular diseases (CVDs), including atherosclerosis. Elevated concentrations of YKL-40 have been associated with detrimental CV outcomes. In general, while the precise function of YKL-40 in CVDs is still under investigation, it is evident that this glycoprotein has significant potential as a biomarker for CVDs. Furthermore, CVD treatment has the potential to specifically target the protein YKL-40.

Keywords: Atherosclerosis, cardiovascular disease, YKL-40

Introduction

Acute inflammation serves as a protective mechanism against tissue damage, irritation, and infection. However, the presence of chronic inflammation may contribute to the development of several illnesses, such as cardiovascular and liver disease.[1] Atherosclerosis is responsible for the occurrence of ischemic stroke (IS) and myocardial infarction (MI). Atherosclerosis is a pathological condition characterized by the infiltration of lipoproteins into the intimal layer of blood vessels. Monocytes have the ability to differentiate into macrophages that accumulate lipids inside arterial walls.[2] The risk of venous thromboembolism (VTE) and atherosclerosis is increased by inflammation, hypercoagulability, and endothelial damage.[3] Venous thromboembolism has been identified as a potential cause of arterial thrombosis, as shown by previous studies.[4-6] YKL-40 is synthesized by macrophages that have undergone late differentiation,[7] atherosclerotic lesions,[8] endothelial cells, vascular smooth muscle cells, and perhaps activated hepatic stellate cells.[9] YKL-40 has been shown to influence several biological processes, including vascular endothelial growth factor (VEGF), angiogenesis, inflammation, extracellular tissue remodeling, and fibrosis.[10] The study found that people with cardiac problems had elevated levels of YKL-40 in comparison to those who were in good health.[11] Elevated levels of YKL-40 have also been observed in cases of IS and VTE.[12,13] This article provides a comprehensive analysis of the role of YKL-40 in the diagnosis, prognosis, and etiology of cardiovascular disease (CVD).

Methods

This systematic review included the analysis of a total of 52 articles that were published between the time frames of 2006 and 2023. A search was conducted in the PubMed electronic database using the phrase "Plasma YKL-40 and CVDs." The titles and abstracts of all relevant papers obtained via the electronic search were systematically examined by the researcher in an unbiased manner. A total of 47 publications that were assessed were deemed suitable for inclusion in the research. The study's inclusion criteria included an examination of the link between YKL-40 and CVDs, a requirement for the publication to be in the English language, a publication date falling between the range of 2006 and 2023, and the availability of full-text access. Excluded from the research were various sorts of studies, such as in vitro studies, case reports, and ongoing investigations. The study included a total of 39 primary papers, consisting of 5 randomized controlled trials, 1 research article, 1 clinical trial, 1 review, and 1 artificial intelligence transfer, all of which satisfied the predetermined criteria. The steps in the systematic review are shown in Figure 1.

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YKL-40 Molecular Biology

The presence of MG63 osteosarcoma cells in YKL-40 was first discovered in 1989. The protein consists of a total of 383 amino acids, with an N-terminal sequence including tyrosine, lysine, and leucine. The family of 18 glycosyl hydrolases consists of both active and dormant chitinases, such as YKL-40. The putative enzyme active site of YKL-40 has a high degree of conservation, as shown by the substitution of leucine with glutamic acid.[13] Chitinases exhibit a unique affinity for the glycopolymer present in the exoskeletons of insects and the cell walls of bacteria and fungi. The existence and functioning of human chitin and synthases remain unexplored and poorly understood. YKL-40 has been shown to enhance cellular proliferation and survival via the activation of MAPK/ERK and PI3K/AKT signaling pathways in the cytoplasm.[14,15] This suggests that YKL-40 interacts with signaling components located on the cell surface, as seen in Figure 2. YKL-40 has the ability to form a complex with endogenous polysaccharides that resemble chitin, such as heparan sulfate.[16]

Heparan Sulfate Proteoglycans May Bind YKL-40

Heparan sulfate proteoglycans (HSPGs) are known to assemble an extracellular matrix (ECM) on the surfaces of cells. Syndecans, characterized by their single transmembrane domain, serve as prominent cell membrane HSPGs and co-receptors. Perlecan is a highly abundant HSPG found within the ECM of basement membranes. The binding of YKL-40 induces activation of the

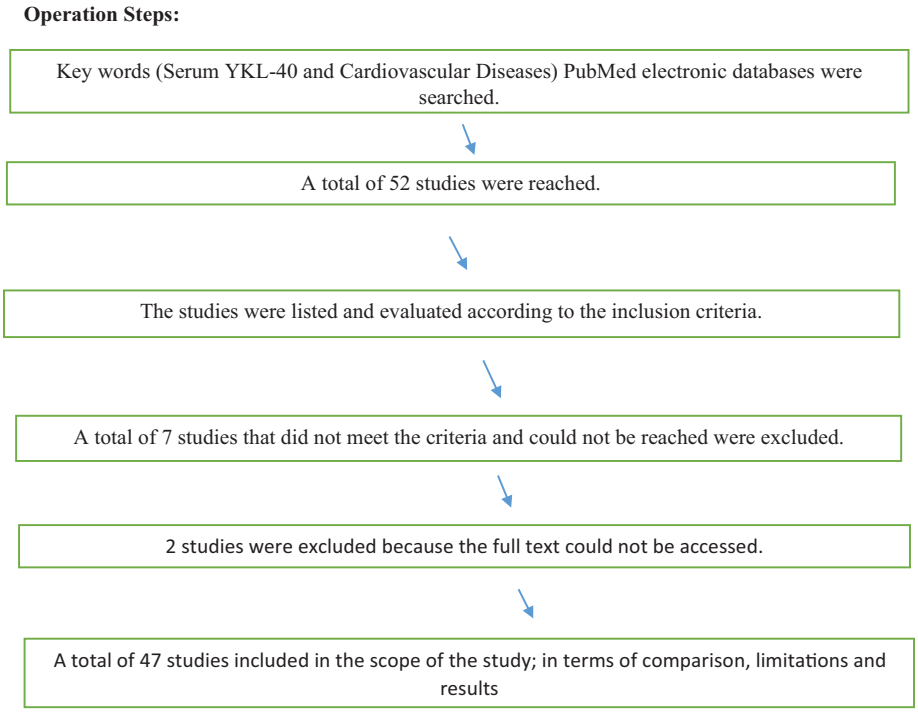

Figure 1. The steps in the systematic review.

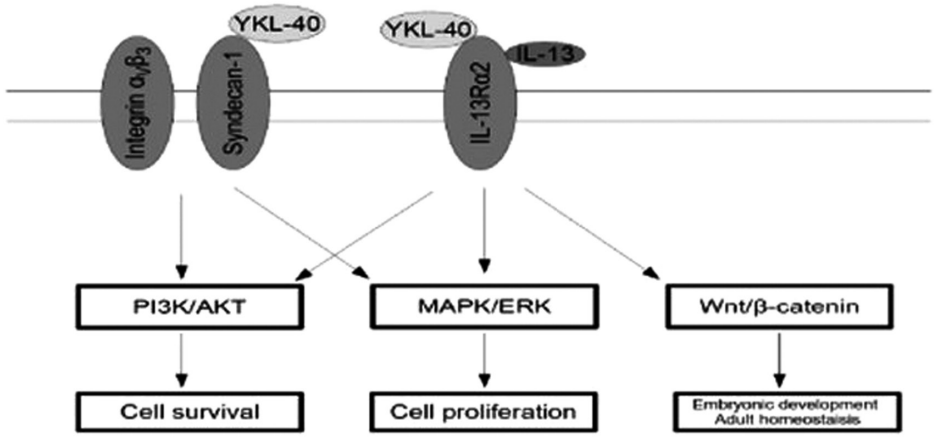

Figure 2. YKL-40 interacts with cell surface signaling components.

MAPK/ERK and PI3K/AKT signaling pathways, thereby facilitating angiogenesis via the upregulation of VEGF production in U87 cells, which are derived from human primary glioma cells. This effect is seen in conjunction with the presence of integrin αVβ3 (45) or αVβ5.[17,18] Perlecan is an additional physiological ligand of YKL-40. Perlecan has a proangiogenic influence on integrin-induced brain proangiogenesis as well as a proangiogenic impact on peripheral angiogenesis.[19,20]

YKL-40 Functions

The presence of inflammation leads to an increase in YKL-40 levels by more than 25%. Patients infected with *Streptococcus pneumoniae* have a 10-fold increase in YKL-40 levels compared to those without the infection. The administration of antibiotics resulted in a more rapid reduction of YKL-40 levels compared to C-reactive protein (CRP) levels. YKL-40 facilitates the catabolism of inflammatory cytokines, which lowers tissue inflammation. However, YKL-40 has also been implicated in the induction of inflammation.[21-23] The expression of YKL-40 has been observed in early human fetal tissues that undergo rapid proliferation, differentiation, and morphogenetic alterations, indicating its potential involvement in fetal development.[24] The precise functions of YKL-40 in both states of well-being and disease are still not fully understood. A potential area of interest is the comparative analysis of the relative affinity between the putative receptors of YKL-40 and the amounts of YKL-40 present in the circulation.[13]

YKL-40 Measurement

The first YKL-40 radioimmunoassay for human subjects used rabbit polyclonal antibodies. Quidel, a company based in California, United States, offers a sandwich-type enzyme-linked immunosorbent assay for the detection of human YKL-40. The Copenhagen City Heart Study used the test. Marathons have been shown to increase YKL-40 levels by 56%. Prolonged centrifugation of serum and ethylenediaminetetraacetic acid plasma samples for a duration of 3–8 hours has been seen to lead to a reduction in the

obtained findings. Neutrophils undergoing degranulation have been reported to release YKL-40 in previous studies.[25-27]

Age, Reference Range, and Genetic Variants

The concentration of YKL-40 exhibits an exponential growth pattern as people age, making it possible to use age-adjusted reference values to assess the levels of YKL-40 in healthy individuals over an extended period of time.[28-30] In their study, Bojesen et al. conducted an analysis on age-adjusted YKL-40 reference values in a cohort of 3130 healthy individuals aged 16 years as part of the Copenhagen City Heart Study. Individuals who are in good health do not have a specific age-adjusted range for YKL-40. Therefore, it is acceptable to use a 95% threshold for calculating percentiles.[30] Multiple genetic variations of the YKL-40 gene have been found. The presence of these genetic variations has the potential to impact the expression or functionality of the YKL-40 protein, and they have been linked to a range of disorders and medical problems. An instance of genetic variation at a specific location within the YKL-40 gene, known as a single nucleotide polymorphism (SNP), has been shown to have a positive correlation with an elevated susceptibility to asthma. Conversely, a distinct SNP at the same gene locus has been seen to be inversely related to the likelihood of developing rheumatoid arthritis. Alterations in the YKL-40 gene have been implicated in the proliferation and metastasis of many cancer subtypes. In general, the investigation of genetic variations associated with the YKL-40 gene has gained significant attention and holds great potential in the realm of scientific inquiry.[26]

Cardiovascular Diseases

YKL-40 has been linked to the development and progression of atherosclerosis, a disease in which lipid-rich plaques build up inside the walls of arteries. Individuals with atherosclerosis have been observed to have increased levels of YKL-40, a protein. It is hypothesized that YKL-40 contributes to the inflammatory response and structural changes in artery walls, both of which are critical factors in the progression of atherosclerosis. Coronary artery disease (CAD) is a prevalent CV ailment characterized by the development of atherosclerosis inside the coronary arteries, which subsequently leads to the diminished blood supply to the myocardium. There exists a correlation between increased levels of YKL-40 and CAD, and several investigations have proposed that YKL-40 might serve as a promising biomarker for prognosticating the occurrence and severity of CAD.[31]

Elevated levels of YKL-40 have been observed in patients who have suffered from MI. These elevated YKL-40 levels in these individuals have been correlated with an unfavorable prognosis and an augmented susceptibility to subsequent CV incidents. The investigation of YKL-40 in the context of heart failure (HF) has included its role as a biomarker as well as its possible involvement in the pathogenesis of the illness. Increased levels of YKL-40 have been shown to be correlated with the severity of HF, suggesting that it might serve as a potential indicator for the development of HF. Ischemic stroke is characterized by the presence of an obstruction in a cerebral blood vessel, leading to a reduction or cessation of blood flow to the brain, resulting in a diminished supply of oxygen and nutrients. Research findings indicate that people who have suffered from an IS have elevated levels of YKL-40 in comparison to those who have not undergone a stroke. The suggestion has been made that elevated levels of YKL-40 may serve as a possible indicator of both the risk and severity of stroke. As a result of atherosclerosis developing in the peripheral arteries, peripheral arterial disease (PAD) is distinguished by decreased blood flow to the extremities. The presence and severity of PAD have been linked to increased levels of YKL-40, suggesting that it might serve as a useful diagnostic or prognostic indicator for this condition.[33] Vitamin D (VitD) suppresses YKL-40, preventing rat CVDs. Hence, human clinical trials will show how VitD and YKL-40 affect CVDs.[32]

Ischemic Stroke and Cerebrovascular Diseases

YKL-40 was increased in 105 IS patients. YKL-40 surpassed CRP in identifying IS patients (n = 105) and connecting disease severity.[33] YKL-40 was more astrocytic than macrophage-based in IS, peaked sooner, and dropped faster than CRP. YKL-40 better portrays neuroinflammation and injury than CRP; hence, it may identify tiny cerebral infarctions. Magnetic resonance imaging (MRI) infarcts and white matter hyperintensities may suggest ischemic cerebrovascular disease with YKL-40. Covert MRI findings in non-stroke patients enhance the chance of an overt stroke. YKL-40 may predict IS.[34] In IS patients, IL-6 and YKL-40 predicted recurrence, poor functional outcome, and clinical risk algorithm improvement.[35] Hok-A-Hin et al.[36] showed that cerebrospinal fluid YKL-40 may not indicate Alzheimer's disease, frontotemporal lobar degeneration, or brain area degeneration. YKL-40 may cause neuroinflammation and vascular pathology. In Chinese IS patients, entry serum YKL-40 may independently predict 1-year poor outcome and all-cause death but not stroke recurrence.[37]

Myocardial Infarction

Multiple studies have shown that the presence of MI may lead to an elevation in the levels of YKL-40. Multiple studies have shown that MI has the potential to elevate the levels of YKL-40, which is recognized as an acute-phase reactant.[38] There may be a potential association between levels of YKL-40 and the existence and severity of ischemic heart disease (IHD), as well as the future risk of its development. In prospective investigations, it was observed that a significant elevation in baseline YKL-40 levels did not serve as a predictive factor for MI. Consequently, it may be inferred that YKL-40 is unlikely to be a causative agent in the development of IHD.[39]

Venous Thromboembolism, Pulmonary Embolism (PE), and Pulmonary Arterial Hypertension (PAH)

An elevated concentration of YKL-40 has been linked to a 2-fold increase in the likelihood of VTE, comparable to the risk observed for stroke.[16] It is worth investigating how YKL-40 might influence the effectiveness of early thrombolytic therapy in individuals with high-to-intermediate risk PE. Research has suggested that the application of YKL-40-targeted therapy might potentially result in a decrease in the incidence of thrombosis among people who are at a higher risk.[40] In their study, Sun et al.[41] showed the crucial role of YKL-40 and its receptors in the pathobiology of pulmonary vascular disease, specifically in the context of fibrotic lung illness. The findings suggest that targeting YKL-40 and its receptors might potentially be a therapeutic approach for the treatment of PAH in this population.

Stable CAD

An elevation in YKL-40 levels among a cohort of 200 stable CAD patients who had diseased major coronary arteries with a stenosis greater than 50% CRP has been shown to have a less substantial association with impaired vasculature, as indicated by previous research.[42] A total of 4298 individuals diagnosed with stable CAD were included in the study and thereafter monitored. Elevated levels of YKL-40 have been shown to be indicative of increased risk for MI, CV death, and mortality from all causes. There was no observed association between levels below 76 µg/L of YKL-40 in stable CAD patients and the occurrence of acute MI or death, as

reported in a study.[43] In their study, Gunay et al.[44] observed that the overexpression of YKL-40 leads to a decrease in the patency of arterial repair.

Chronic HF

In particular, an association has been established between elevated levels of YKL-40 and an augmented likelihood of hospitalization, deteriorating cardiac function, and elevated death rates among individuals diagnosed with chronic HF (CHF). There is a prevailing belief that it has a role in the inflammatory and fibrotic processes, which include the production of scar tissue, observed in the CV system of individuals suffering from congestive HF. Although YKL-40 is not already used as a standard diagnostic or prognostic tool in CHF, it is currently being investigated as a promising area of study. There is a possibility that it might serve as a biomarker for predicting patient outcomes and informing treatment decisions in the future.[45]

Atrial Fibrillation

YKL-40 is drastically elevated in atrial fibrillation (AF) patients. YKL-40 did not predict the success of electrical cardioversion to sinus rhythm. Plasma YKL-40 did not decrease following sinus rhythm restoration.[46] Plasma YKL-40 levels are strongly linked to AF from hospital admissions or emergency department visits, regardless of HF, CRP, and fibrinogen levels.[47] None of the supraventricular arrhythmias had high serum YKL-40 except AF. Treatment-responsive YKL-40 levels predicted long-term recurrence in AF.[48] High plasma YKL-40 before catheter ablation is related to AF recurrence in paroxysmal or chronic AF patients.[49] The main topics of recent studies are shown in Table 1.

Conclusion

It is possible that YKL-40 may protect neurons and heart muscle cells from cell death caused by ischemia by helping cells stay alive in bad environments. Perlecan, the physiological ligand of YKL-40,

Table 1. The Main Topic Points of Recent Studies

Reference no.	Authors	Subjects	Main Theme
Ref.[9]	Tizaoui et al	Autoimmune disease.	YKL-40 is made by late-differentiating macrophages.
Ref.[12]	Shao et al.	Cancers.	YKL-40 has an effect on vascular endothelial growth factor, angiogenesis, inflammation, extracellular tissue remodeling, and fibrosis.
Ref.[14]	Kjaergaard et al.	Ischemic stroke.	YKL-40 levels are higher in ischemic stroke.
Ref.[15]	Kjaergaard et al.	VTE.	YKL-40 levels are higher in VTE.
Ref.[17]	Kim et al.	Human airway epithelial cells.	Clinically, soluble corin may indicate preeclampsia.
Ref.[21]	Clarke et al.	Stroke patients.	Perlecan is another YKL-40 physiological ligand. Perlecan has a proangiogenic effect on integrin-induced brain proangiogenesis and a proangiogenic effect on angiogenesis in the periphery.
Ref.[24]	Kornblit et al.	SIRS and sepsis.	Plasma YKL-40 <505 ng/mL at ICU admission improved SIRS and sepsis survival. Homozygous low-expressing YKL-40 CHI3L1 allele carriers were not linked.
Ref.[28]	Kjaergaard et al.	Danish general population with extreme plasma YKL-40 levels.	We found 8 single nucleotide polymorphisms (SNPs) linked with plasma YKL-40 levels in the general population in a systematic study.
Ref.[32]	Park et al.	Acute ischemic stroke patients.	YKL-40 was increased in 105 ischemic stroke patients. YKL-40 surpassed CRP in identifying ischemic stroke patients (n = 105) and connecting disease severity.
Ref.[40]	Li et al.	Ischemic stroke and TIA patients.	IL-6 and YKL-40 predicted recurrence, poor functional outcome, and clinical risk algorithm improvement.
Ref.[41]	Gunay et al.	Patients who had ulnar or radial artery injury.	YKL-40 overexpression reduces artery healing patency.
Ref.[42]	Hok et al.	Patients with Alzheimer's disease and frontotemporal lobar degeneration.	YKL-40 may cause neuroinflammation, vascular pathology.
Ref.[43]	Kerget et al.	Patient with acute pulmonary thromboembolism.	YKL-40 may influence early thrombolytic treatment in high-intermediate-risk PE. YKL-40-targeted treatments may reduce thrombosis in high-risk individuals.
Ref.[44]	Shi et al.	Chinese acute ischemic stroke (AIS) patients.	Entry serum YKL-40 may independently predict 1-year poor outcome and all-cause death but not stroke recurrence.
Ref.[45]	Kocabas et al.	Cardiac patients.	VitD suppresses YKL-40, preventing rat cardiovascular diseases (CVDs). Hence, human clinical trials will show how VitD and YKL-40 affect CVDs.
Ref.[46]	Sun et al.	Pulmonary arterial hypertension (PAH) patients.	YKL-40 and its receptors are critical to pulmonary vascular disease pathobiology and may be targeted for treating pulmonary arterial hypertension (PAH) in fibrotic lung disease.

has the potential to exhibit neuroprotective and proangiogenic properties. YKL-40 and perlecan have been shown to enhance the production of VEGF, a crucial factor in promoting neuroprotection following a stroke. Further investigation is necessary to explore the interactions of these proteins and their potential significance for the treatment of stroke. An elevated concentration of YKL-40 has been linked to a 2-fold increase in the likelihood of VTE, a finding that is comparable to the risk seen for stroke but not MI. This observation implies that YKL-40 may be involved in the formation of emboli rather than the development of atherosclerosis. While researchers are still trying to figure out exactly what role YKL-40 plays in CVDs, it is clear that this glycoprotein could be used as a biomarker for these diseases.

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