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Review article

Immature Platelet Fraction to Unveil the Contribution of HMG-CoA: Mechanistic Insights into Clinical Benefits

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Abstract

The immature platelet fraction (IPF) has emerged as a critical marker in providing valuable insights into platelet production and turnover dynamics. HMG-CoA, an essential enzyme in cholesterol biosynthesis, plays a significant role in regulating platelet maturation and function. Changes in cholesterol metabolism can potentially lead to abnormalities in platelet activation, aggregation, and thrombotic processes. This underscores the broader implications of metabolic disorders, such as hypercholesterolemia, in cardiovascular diseases where platelet dysfunction is a critical factor. Understanding the mechanistic links between HMG-CoA and platelet biology offers insights into therapeutic strategies aimed at mitigating cardiovascular risks associated with dyslipidemia and related conditions. Moreover, recent advances in nanotechnology have shown promising strides in the prevention, diagnosis, and treatment of hyperlipidemia and cardiovascular diseases. Integration of nanotechnological approaches with the understanding of HMG-CoA and IPF dynamics could potentially revolutionize personalized medicine strategies, offering novel avenues for improving patient outcomes and managing cardiovascular health effectively.

Keywords: immature platelet fraction; IPF; HMG-CoA; nanotechnology

1. Introduction

The World Health Organization reports that cardiovascular diseases (CVD) are the leading cause of death worldwide, with ischemic heart disease (IHD) accounting for 16% of all fatalities. Currently, the world's leading cause of mortality is cardiovascular disease (CVD). Acute coronary syndrome (ACS), a potentially fatal illness that includes myocardial infarction (MI), and unstable angina is common in individuals with CVD. Every year, about 1.2 million people with ACS are admitted to hospitals due to cardiovascular events. Enhanced low-density lipoprotein (LDL) concentration and enhanced platelet activation are the two main pathophysiological processes driving atherosclerosis. Thus, lowering the high morbidity and death of this illness requires the use of safe and efficient antiplatelet and antihyperlipidemic drugs (Zivkovic et al., 2023).

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Hyperlipidemia, also known as dyslipidemia, is an imbalance in lipid metabolism that manifests in the bloodstream as an increase in triglycerides, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) and a reduction in high-density lipoprotein cholesterol (HDL-C) (Xiao et al., 2016). Elevated lipid levels are a characteristic of hyperlipidemia, which can result from several inherited or acquired conditions. Research has shown that persons with hyperlipidemia are at a much higher risk of developing cardiovascular disease. Hyperlipidemia is a major risk factor for the development and worsening of coronary heart disease. Hyperlipidemia and other lipid disorders are considered to be the initial trigger for atherosclerotic cardiovascular disease (El-Tantawy & Temraz, 2019). Elevated levels of LDL-C are an independent risk factor for acute ischemic stroke. Approximately 70% of circulating cholesterol in the body is carried by LDL-C, the primary lipoprotein responsible for cholesterol transport (Nixon et al., 2017). High LDL-C levels are associated with the progression of atherosclerosis and increased mortality from heart attacks and strokes (Grundy, 1998). The main lipoprotein involved in the transportation of cholesterol is LDL-C, which accounts for around 70% of all circulating cholesterol in the body (Zhang et al., 2017).

The importance of LDL-C in lipid metabolism is underscored by the fact that its elevation is linked to various metabolic conditions, including obesity, diabetes mellitus, thyroid abnormalities, and unhealthy lifestyle choices (Pirillo et al., 2021). The introduction of statins in the late 1980s marked a significant advancement in lipid management, as these drugs target hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase—a key enzyme in endogenous cholesterol synthesis. Statins are synthetic HMG-CoA reductase inhibitor that lower plasma cholesterol levels by blocking endogenous cholesterol synthesis (see Figure 1). In addition to reducing cholesterol, statins also modestly decrease triglyceride levels, although the precise mechanisms are still under investigation. These drugs are known to cause gastrointestinal side effects more frequently than other adverse events. The lipid-lowering effects of statins are primarily due to their ability to reduce endogenous cholesterol synthesis and to upregulate LDL receptor expression, which enhances the absorption and clearance of LDL-C from plasma (Vaughan et al., 2000; Igel et al., 2002).

Atherothrombotic events rely on platelets, and individuals with acute coronary syndrome (ACS) are more likely to have negative outcomes if their platelets are hyperactive. Individuals with increased platelet size and reticulated platelets have increased platelet reactivity despite antiplatelet therapy (Guthikonda et al., 2008). Compared to older circulating platelets, reticulated platelets (RPs) or immature platelets have an increased mean volume, a remnant quantity of messenger ribonucleic acid generated from megakaryocytes, and a content of dense granules. The consensus is that compared to mature platelets, reticulated platelets are more prothrombotic due to their increased activity. A high rate of platelet turnover is suggested by the detection of these platelets in the circulation, which indicates higher platelet synthesis from megakaryocytes in the bone marrow. The proportion of reticulated platelets (RPs) to total platelets is called the immature platelet fraction (IPF) (Bernlochner et al., 2015).

Diseases including hemorrhage and thrombocytopenic purpura, which are marked by accelerated platelet turnover, are associated with an elevated immature platelet fraction (Jiménez et al., 2006). Conditions including diabetes and smoking have also been linked to high IPF. Patients who experienced arterial thrombotic events, such as ACS, were shown to have increased IPF (Grove et al., 2009). Independent factors of poor cardiovascular prognosis and cardiovascular mortality have recently been identified in patients with IPFs. There is evidence that people with atrial fibrillation can reduce their IPF

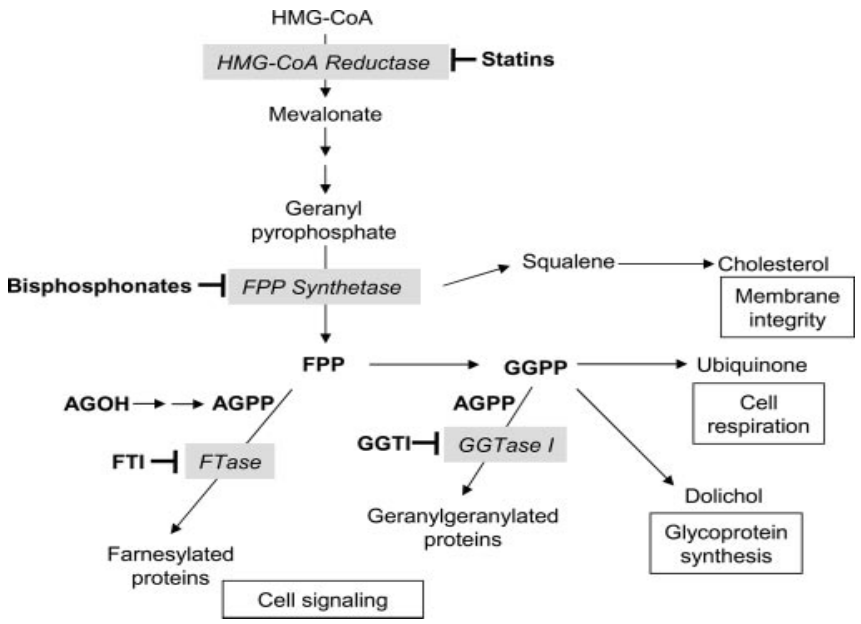

Figure 1. Biosynthetic cycle of synthetic HMG-CoA reductase inhibitor (Reproduced from Onono et al., 2010)

with the use of ablation treatment. Patients with coronary disease have an impaired response to several antiplatelet drugs and increased IPF. Figure 2 represents the immature platelet fraction (IPF) role and its relation with CVD.

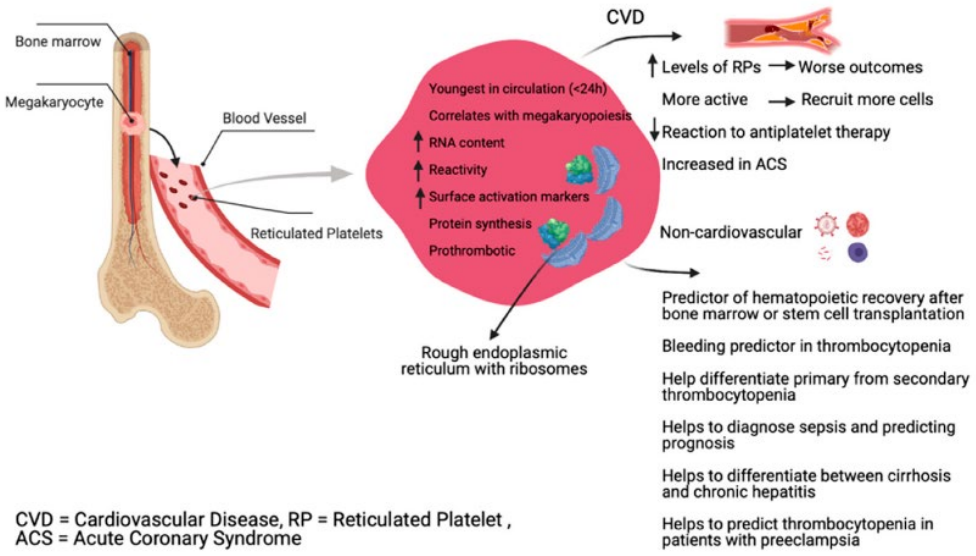

Figure 2. Immature platelet fraction (IPF) relation with CVD (Reproduced from Hamad et al., 2021)

Several investigations have shown that individuals with coronary artery disease, particularly those with acute coronary syndrome (ACS), had high IPF. In particular, individuals with ACS have an increased risk of mortality and significant adverse cardiovascular events when their RP levels are high. Myocardial ischemia/reperfusion (I/R) injury might be an intriguing area where RP could play a key role. This kind of injury occurs when blood flow returns to damaged tissues following a period of ischemia. In the setting of myocardial infarction (MI), the interventional reopening of a blocked coronary artery might lead to I/R damage. It is intriguing to observe how RP reacts to antiplatelet medication as RP does appear to show some resistance to commonly used antiplatelet drugs.

2. Cholesterol Inhibition by HMG-CoA Reductase Relative to Immature Platelets

The mechanistic link between HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) and platelet biology is primarily mediated through the action of statins, which are inhibitors of HMG-CoA reductase. This highlights the multifaceted role of statins in cardiovascular health. By inhibiting cholesterol synthesis and improving lipid profiles, statins not only reduce low-density lipoprotein cholesterol (LDL-C) levels but also enhance endothelial function, attenuate inflammation, and decrease platelet activation. These combined effects significantly contribute to the prevention of thrombotic events and overall cardiovascular disease management of cardiovascular disease. Understanding these mechanisms offers insights into how targeting HMG-CoA impacts both lipid metabolism and platelet function in individuals at risk for cardiovascular events. Statins have been shown to be more effective than other lipid-lowering agents in reducing total and LDL-C levels. This superior efficacy is thought to result from the potency and duration of HMG-CoA reductase inhibition, although the precise mechanism underlying this prolonged effect remains to be fully elucidated.

Lower cholesterol levels may also diminish platelet activation and aggregation, thereby influencing thrombus formation. According to a study by Ness et al. (1998), statins prolong the binding of microsomal HMG-CoA reductase receptors, as demonstrated by hepatic gene expression analysis in rats treated with statins. Additionally, statins significantly lower triglyceride levels. Although HMG-CoA is not directly involved in triglyceride regulation, several hypotheses have been proposed to explain this effect. One explanation is that statin-induced upregulation of LDL receptors leads to increased VLDL clearance and reduced LDL availability for binding (Bakker-Arkema et al., 1996).

Interestingly, statins are capable of lowering LDL-C levels in patients with homozygous familial hypercholesterolemia, despite the absence of functional LDL receptors. This effect is likely due to a marked suppression of cholesterol synthesis, thereby reducing LDL production (Marais et al., 1997). Furthermore, statins decrease the oxidative susceptibility of LDL particles (Aviram et al., 1998). Overall, statins are recognized for their beneficial influence on platelet function by mitigating cardiovascular risk factors such as hyperlipidemia and systemic inflammation.

2.1 Statins and their effects on lipoprotein composition

Assessing lipid indicators beyond LDL-C provides valuable insights into their relationship with immature platelets and overall cardiovascular health. These indicators include total cholesterol, high-density lipoprotein cholesterol (HDL-C), lipoprotein (a), and remnant

lipoproteins. When evaluating the overall efficacy of statins in cholesterol management, it is important to consider additional lipid parameters such as triglycerides and HDL-C.

While statins effectively lower LDL-C, some clinical trials have suggested that increasing statin dosages may yield minimal or no further improvements in HDL-C levels (Ballantyne et al., 2005). Statins also significantly reduce triglyceride concentrations, largely due to enhanced clearance of very low-density lipoprotein (VLDL), which is rich in triglycerides (Zodda et al., 2018).

Another critical consideration in assessing the full impact of statin therapy is their ability to favorably alter the composition of lipoproteins. Statins have been shown to improve the LDL subfraction profile, shifting it toward larger, less atherogenic particles. This beneficial change is associated with a reduction in both triglyceride and cholesterol levels, further enhancing cardiovascular protection.

Statins are widely regarded as the gold standard for managing dyslipidemia. Their effectiveness can be evaluated not only by their ability to lower LDL-C but also by their impact on HDL-C and triglyceride levels, as well as their influence on lipoprotein composition. Evaluating whether statin therapy helps patients achieve recommended LDL-C targets is also essential for determining the success of overall treatment (Acil et al., 2007).

2.2 Significance of HMG-CoA reductase inhibitors in atherosclerosis

An increased risk of cardiovascular disease has been associated with raised levels of C-reactive protein (CRP), an early marker of inflammation. Patients with statin treatment showed reduced CRP levels in most randomized comparative trials that were six to thirty weeks long (Asher & Houston, 2007). A significant and dose-dependent decrease in CRP levels was observed in patients with type 2 diabetes mellitus who did not have coronary heart disease. Several randomized trials found that fibrinogen levels did not alter or, far less often, decreased when statins were administered. Endothelial dysfunction is a key indicator of atherosclerotic disease in congestive heart failure patients and a predictor of future cardiovascular events. Non-invasive techniques like flow-mediated vasodilation of the brachial artery (FMD) or responsiveness of forearm blood flow to acetylcholine infusion may often detect that patients with hypercholesterolemia have impaired endothelial function. Statins improved endothelial function in patients with hypercholesterolemia, kidney transplant recipients, and type 1 diabetes without hypercholesterolemia but experiencing endothelial impairment (Asberg et al., 2001).

2.3 Cardiovascular disease prevention with statins: primary and secondary measures

It has been demonstrated through multiple *in vitro* studies and *in vivo* animal models that statins inhibit HMG-CoA reductase. By all accounts, HMG-CoA reductase has little impact on the regulation of triglyceride levels. However, two side effects have been postulated to account for statin-related dramatic lowering of triglyceride levels. First, triglyceride levels are reduced because VLDL distributes triglycerides throughout the body (Lee et al., 2022); this is because cholesterol is essential for the normal creation of VLDL particles, and a strong suppression of cholesterol synthesis may hinder the assembly and secretion of VLDL particles. Second, statins reduce hepatocyte cholesterol levels significantly, as the LDL receptor is responsible for the binding and cellular uptake of apolipoprotein B and E.

This, in turn, decreases triglyceride levels by boosting VLDL particles and LDL binding, according to this idea (Boyd et al., 2000).

An increased risk of cardiovascular disease (CVD) is associated with elevated total cholesterol and low-density lipoprotein cholesterol (LDL-C) (Catapano et al., 2016). Because lowering blood levels of fat is the main way in which statins work pharmacologically, this also lowers the risk of cardiovascular disease (Byrne et al., 2019). Statins are used in primary prevention to reduce a patient's risk of CVD development in the absence of illness symptoms. People who have a history of CVD, high blood pressure (BP), obesity, or high cholesterol levels are included in this group. Ruptures of unstable atherosclerotic plaques typically cause acute episodes in chronic heart disease (CHD) patients (Clarke & Waskell, 2003).

3. Nanomedicine in Cardiology

A heart attack, or myocardial infarction (MI), occurs when the major arteries that provide blood, oxygen, and nutrients to the heart are completely blocked, resulting in a reduction in blood flow and oxygen levels. Myocardial tissue dies as a result of coronary occlusion-induced necrosis or apoptosis. Reperfusion as soon as possible after arterial blockage is the current gold standard for treating myocardial infarction (MI). Pharmacological therapy, coronary artery bypass graft (CABG), or percutaneous coronary intervention (PCI) are invasive techniques that can do this. The current recommendations for treating heart failure first-line include angiotensin-converting enzyme (ACE) inhibitors and β-receptor blockers (Shah et al., 2017). The existing data on the prevalence of CVDs emphasize the importance of developing novel treatments and enhancing existing technologies to fight these illnesses. Several vascular disorders have atherosclerosis as a precursor. Deposited in the vascular, atherosclerotic plaques harden with time and consist of macrophage cells, lipids, cholesterol, and calcium.

Nanotechnology is more than just a method of making already existing technologies smaller; it is a foundation for opening up new possibilities in every area of healthcare. To promote and preserve a good quality of life and health, the discipline of nanomedicine uses nanotechnology for the diagnosis, treatment, and prevention of disease or injury. For instance, nanoparticles' wettability, reactivity, roughness, and high surface energy are the result of their huge surface area-to-volume ratio and are generally believed to enhance biological function.

Recent developments in nanomedicine have provided more effective means of reducing toxicity, increasing the half-life of drugs, and decreasing side effects by modifying the properties of nanoparticles in a way that does not compromise their biocompatibility. Over the last 20 years, numerous nanotechnologies have been created for use in biomedicine, each with its own set of advantages and characteristics. Nanotechnology makes extensive use of nanoparticles, micelles, liposomes, dendrimers, and nano-coated stents to lessen the likelihood of cardiovascular disease and myocardial infarction. Nanotechnology has the potential to revolutionize cardiovascular treatment, and several studies are currently looking into this possibility (Chandarana et al., 2018).

3.1 Nanotechnology principles to address issues related to elevated cholesterol levels

Nanotechnology offers several benefits for the administration of statins, the most notable of which is an increase in their oral bioavailability. Improving statin oral bioavailability

requires thinking about two things: (i) how to make them dissolve better in the GI tract, and (ii) how to decrease or eliminate first-pass metabolism after oral absorption. The goal of pharmacological treatment is to obstruct the process that causes changes in blood lipid levels. Drugs that contain non-statin such as ezetimibe and PCSK9 inhibitors cholesterol-lowering drugs have shown cardiovascular advantages in recent studies, while new drugs, such as bempedoic acid (BDA) and inclisiran, have shown encouraging outcomes in pre-clinical and clinical outcome trials (Bardolia et al., 2021). Meanwhile, LDL apheresis and statins are the mainstays of hypercholesterolemia treatment (Thompson, 2008). Multiple studies have shown that nanoparticles help with better quantitative estimates of lipid levels. Poor drug absorption and high dosage required to get the intended effect, leading to increased toxicity in healthy cells, are common features of current conventional therapy. Drugs and other therapeutic compounds can be delivered to the desired location at reduced dosages using the nano-based method, which offers tremendous capabilities. The nanoparticle has the potential to be a delivery platform for elevated cholesterol levels because of its tiny size, high surface area, low immunogenicity, cost-effectiveness, and reduced toxicity (Gupta et al., 2018).

3.2 Potential characteristics of polymers in drug delivery

Polymers are molecules with a high molecular weight that are composed of numerous repeating units that are compressed. Polymers have the dual ability to change the flow properties of liquid dosage forms and to create solid dosage form particles. Safety, efficacy, hydrophilicity, lack of immunogenicity, biologic inactivity, adequate pharmacokinetics, and the presence of functional groups for drug covalent conjugation, targeting moieties, or copolymer formation are the general characteristics that make a polymer a viable candidate for drug delivery (Wei et al., 2021). The foundation of pharmaceutical drug delivery systems is polymers. One key instrument for regulating the drug release rate from a formulation has been the use of polymers. Additionally, they are usually employed as proactive, taste-making, and stabilizing agents (Raizada et al., 2010). Modern drug delivery systems owe a great deal to polymers, which allow for cyclic dosing, controlled release of hydrophilic and hydrophobic drugs, and the gradual but continuous release of therapeutic substances over long periods. The field has come a long way from its humble beginnings using commonplace materials, with the help of chemical engineers' innovations. Modern advances in drug delivery rely on the rational design of polymers optimized for specific payloads and designed to carry out a wide range of biological functions.

Polymer therapies are a fast-expanding area of biopharmaceutics. A polymeric drug or an inert carrier with a treatment attached covalently is the most common example of a bioactive polymer chain. Polymeric micelles, multicomponent polyplexes, polymer-drug conjugates, and polymer-protein conjugates are all examples of such structures. Polymer conjugation enhances the pharmacokinetic and pharmacodynamic characteristics of biopharmaceuticals. The rational design of polymers that are suited for particular cargos and made to exert various biological activities is now the foundation for modern advancements in drug delivery (Liechty et al., 2010).

Polymer-based nanoparticles using PLGA:

The use of polymeric materials in nanoparticle-based drug delivery systems has gained significant attention in recent years. Among these, poly(lactic-co-glycolic acid) (PLGA), a copolymer of polylactic acid (PLA) and polyglycolic acid (PGA), has emerged as a widely

utilized and FDA-approved biodegradable polymer. PLGA-based nanoparticles, typically under 300 nm in size, have demonstrated promising therapeutic potential. Notably, these nanoparticles have been shown to mitigate cardiac ischemia-reperfusion (I/R) injury by activating the AKT/PI3K signaling pathway. Furthermore, PLGA nanoparticles exhibit anti-inflammatory properties that help reduce tissue damage in conditions such as myocardial infarction (MI) (Matoba & Egashira, 2014).

3.3 The intersection of nanotechnology and cardiology

Nanoliposomes, comprised of phospholipid membrane-based nanosized vesicles, have shown great promise as drug-delivery vehicles for cardiovascular diseases. They provide prolonged drug release, which boosts effectiveness and enables tailored distribution to certain locations. Treatments for cardiovascular illnesses, such as atherosclerosis, restenosis, and myocardial infarction, may undergo a sea change due to recent developments in drug-delivery vehicles utilizing nanoliposomes and nanoparticles. A novel delivery device was developed to deliver nanoparticles directly to the heart after a myocardial infarction. The method taps into the myocardium's overexpressed angiotensin II type 1 (AT1) receptor using liposomes attached to a ligand specific to that receptor. Nanoparticles may boost treatment efficacy by selectively targeting cardiac cells, according to *in vitro* and *in vivo* studies (Cheraghi et al., 2017).

In the event of an acute myocardial infarction, another innovative approach is the utilization of a nano system that can deliver oxygen to the heart. These nanoparticles, when injected intravenously, preferentially target the area of injury and release oxygen, which promotes angiogenesis, protects cardiac cells, and prevents fibrosis. Myocardial infarction (MI) healing capabilities of mesenchymal stem cells (MSCs) are enhanced by iron oxide nanoparticles (IONPs) through an upregulation of Cx43 expression in cardiomyoblasts. Active gap junctional contact between cardiac cells and MSCs is facilitated by this process. To facilitate controlled microRNA distribution and long-term monitoring of implanted mesenchymal stem cells (MSCs) used in heart regeneration treatment, a nano-platform called PFBT@miR-1-Tat NPs was synthesized. Researchers in one study created an injectable hydrogel that included a VEFG gene nanocomplex with graphene oxide (GO). Myocardial capillary density, scar area, and cardiac function were all enhanced by a hydrogel in rats that had suffered an acute myocardial infarction model. This hybrid hydrogel-based gene therapy approach has the potential for treating ischemic heart conditions (Paul et al., 2014). Hydrogels have surfaced as a potentially effective treatment option for heart function restoration and cardiac tissue regeneration (Saludas et al., 2017).

3.4 PEG-based nanoparticles

Polyethylene glycol's (PEG) ability to impede or delay the reticuloendothelial system's (RES) clearance of nanoparticles from circulation explains why it has seen extensive use in scientific publications. Pharmaceutical delivery systems can also benefit from PEG. There was a size-dependent effect when PEG-modified polystyrene nanoparticles were applied to the heart following myocardial infarction and the damage caused by reperfusion. This nanoparticle's optimal size to target the ischemic zone after myocardial infarction was 20–200 nm (Alconcel et al., 2011). Since PEG is non-biodegradable and has a large molecular size, low immunogenicity, and low antigenicity, it is also frequently utilized in NPs. Consequently, PEGylation of NPs protects them from antibody and protease recognition, enhances their solubility, and prolongs their half-life (Karam et al., 2022).

3.5 Advanced liposome delivery methods

Liposomes are vesicle-based systems widely used for drug delivery. They form through the self-assembly of spherical lipid bilayers composed of lipids and surfactants in an aqueous medium. Enhancing oral bioavailability has historically been a major goal in the development of liposomes for the delivery of small molecules. Targeted liposomes, engineered with surface-bound ligands, offer a promising strategy to improve the accumulation of encapsulated drugs in specific organs and tissues. These ligands enable selective binding to target cells, thereby enhancing therapeutic precision. Immunoglobulin G (IgG) and its fragments are particularly favoured as targeting moieties because they can be conjugated to liposomes without compromising liposomal stability or antibody functionality. Methods such as covalent linkage or hydrophobic insertion into the liposomal membrane enhance the targeting capability of these systems (Mobed & Chang, 1998). Liposomes can also be designed with components that are sensitive to pH changes, allowing for controlled drug release. Upon endocytosis, the reduced pH within endosomes triggers the release of the liposomal contents into the cytoplasm, facilitating intracellular delivery (Singh et al., 2016). In cardiovascular medicine, diagnostic and therapeutic liposomes have been explored for targeting myocardial infarction of particular interest are factors such as liposome size, the targeting efficiency of immunoliposomes, and circulation time. These parameters influence the liposomes' ability to localize to sites of hypoxia-induced plasma membrane damage in cardiomyocytes, potentially aiding in membrane repair and improving therapeutic outcomes (Tarun & Amit, 2014).

3.6 Emerging biologics and nanotechnology for cardiovascular therapy

Traditionally, cardiovascular diseases have been treated with small-molecule drugs. However, these compounds often face limitations related to their chemical properties, which can affect bioavailability, distribution, and efficacy, especially in pathologically altered tissues. A paradigm shift is underway, with increasing interest in biological therapeutics—such as monoclonal antibodies, peptides, small interfering RNA (siRNA), and DNA—for the treatment of cardiovascular disorders. Nanotechnology-based formulations have demonstrated considerable promise in delivering siRNA in animal models, representing a potential leap forward in precision medicine (Whitehead et al., 2014). siRNA therapeutics have also been successfully delivered using exosomes, which are endogenous vesicles involved in intercellular communication. Exosomes facilitate the transfer of cytosolic components, including microRNAs and other RNAs, and are emerging as promising carriers for nucleic acid therapeutics. Therapeutic peptides also hold significant promise in cardiovascular applications; however, their systemic delivery is hindered by enzymatic degradation, poor vascular permeability, and limited tissue distribution. Strategies to overcome these challenges include PEGylation (conjugation with polyethylene glycol), which prolongs circulation time, and cyclisation of linear peptides to enhance metabolic stability. For long-term, localized drug delivery, implantable biomaterials have been explored. Despite their utility, challenges such as immune response and complications associated with polymer suturing onto cardiac tissue remain significant.

DNA nanotechnology has emerged as another innovative approach, with applications beyond its traditional genetic role. Engineered nucleic acid nanodevices can be designed to sense environmental changes and deliver drugs in a targeted manner.

These approaches use DNA as a structural and chemical building block, rather than as a carrier of genetic information (Singh et al., 2014).

4. Possible Future Directions for the Treatment of CVD associated with Immature Platelet Fraction (IPF)

In terms of future directions, the IPF has been explored in various studies to understand its role and to predict platelet recovery in patients with cancer or bone marrow transplantation. It has also been studied in liver transplantation, where it can help assess platelet production and be used to predict platelet recovery in patients. Research on molecular mechanisms shows that HMG-CoA influences platelet maturation and function. This includes exploring specific signaling pathways and genetic factors that mediate the interaction between cholesterol metabolism and platelet hematology.

Novel therapeutic strategies targeting HMG-CoA such as combination therapy using statins in conjunction with other antiplatelet agents may enhance their protective effects against thrombotic events and target specific pathways that focus on selectively targeting the signaling pathways activated by statins, such as the PI3K/Akt pathway involved in endothelial progenitor cell differentiation. This could enhance neovascularization and improve outcomes in ischemic conditions and its downstream effects on platelet function. Other strategies include exploring pharmacological agents or dietary interventions that modulate cholesterol metabolism while preserving optimal platelet function. Advancements in nanotechnology offer promising avenues for developing targeted drug delivery systems and diagnostic tools in cardiovascular medicine. Future research should focus on integrating nanotechnological approaches with IPF analysis to enhance precision medicine strategies and improve therapeutic outcomes (Wang et al., 2021).

The increasing prevalence of preventable risk factors for cardiovascular disease (CVD), such as sedentary lifestyles, alcohol and tobacco use, and diets rich in saturated fat, trans fats, and cholesterol, highlights the need for increased research into nanotechnological approaches to early risk factor identification and treatment. Wearable trackers that monitor sleep, food consumption, and physical activity (among other things) and the simultaneous monitoring of multiple heart parameters are just a few examples of how nanotechnology could transform healthcare. Other applications include sensors that help patients remember to take their drugs as prescribed and portable exam kits that listen for irregularities in heart sounds (Sethi et al., 2023).

Future research should explore the use of IPF and HMG-CoA profiling in guiding individualized treatment strategies. This includes integrating genomic, proteomic, and metabolomic data to tailor interventions based on patient-specific characteristics and risk profiles.

5. Conclusions

In conclusion, the immature platelet fraction (IPF) serves as a valuable tool in hematology, offering insights into platelet production dynamics. HMG-CoA, pivotal in cholesterol biosynthesis, significantly influences platelet maturation and function. The potential dysregulation of cholesterol metabolism underscores its impact on platelet activities, highlighting implications for cardiovascular diseases where platelet dysfunction is crucial. Integrating these insights into clinical practice could lead to improved diagnostic strategies and targeted therapeutic interventions aimed at managing cardiovascular risks associated

with dyslipidemia and related conditions. Furthermore, advancements in nanotechnology offer promising avenues for enhancing prevention, diagnosis, and treatment approaches in this context, signaling a potential paradigm shift toward personalized cardiovascular medicine.

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7. Authors' Contribution

All authors contributed equally to the conceptualisation, literature review, critical analysis and writing of this review article. All authors have read and approved the final manuscript

8. Conflicts of Interest

The authors declare no conflict of interest.

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