Nanotechnology used in Coronary Heart Disease

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Abstract:
Globally, cardiovascular illnesses claim countless lives, many of which can be avoided. The prevalence of cardiovascular disease is rising as a result of a rise in obesity cases, sedentary lifestyles, and diets heavy in sugar, salt, and saturated fat. These contributing variables, in conjunction with increasingly sophisticated diagnostic techniques, have produced figures that unequivocally demonstrate an increasing trend in the prevalence of cardiovascular disease. Oral medications or invasive surgery are presently the only options for treating cardiovascular disorders. Novel therapies for better patient outcomes are desperately needed in this field of medicine. With improved prognoses and fewer side effects, nanotechnology may offer a way to treat diseases more successfully.

Keywords: Nanomedicine, Cardiovascular disease, Nanotechnology, Medical therapeutics

Introduction:

According to WHO estimates from 2017, 17.7 million people died from cardiovascular diseases (CVDs) globally in 2015. By 2030, that number is expected to rise to 23.6 million. CVDs remain the leading cause of mortality worldwide. Cardiovascular diseases include, but are not limited to, myocardial infarction (MI), deep vein thrombosis, pulmonary embolism, and coronary heart disease. These conditions cause tissue death and ischemia. The two main illnesses that cause death among these are MI and heart failure.

A MI, also referred to as a heart attack, Is caused by complete blockage of the main arteries supplying the heart, which lowers blood flow and the amount of oxygen and nutrients that reach the heart. In the end, this causes necrosis or apoptosis in the heart due to coronary blockage, which causes myocardial tissue death.As a consequence of diminished cardiac functionality, heart failure is a clinical illness condition that manifests as peripheral oedema, exhaustion, and dyspnea . The inability of the heart muscle to pump effectively enough to meet the body's metabolic needs is known as this type of cardiomyopathy . According to ,the leading cause of heart failure is disease of the coronary arteries. heart failure is a general term that covers a variety of cardiac syndromes, such as irregular heartbeat, pericardial, endocardial, or left ventricular dysfunction.

Progression of atherosclerotic plaque showing narrowing of the blood vessel:

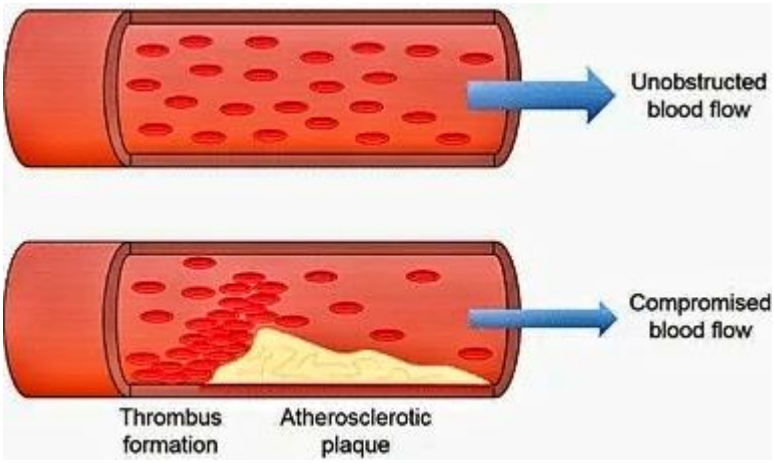


Fig. 1 From: The use of nanotechnology in cardiovascular disease

Numerous vascular diseases start with atherosclerosis. The components of atherosclerotic plaques are calcium, fat, cholesterol, and macrophage cells that accumulate in the vasculature and harden as the plaques expand.

This leads to blood vessel narrowing, decreased blood flow, rupture, and finally ischaemia (Fig. 1). According to histology, weak fibrous plaque caps with elevated concentrations of matrix metalloproteinases (MMPs) cause the plaque to become weaker and eventually burst, which results in a cardiovascular event . The development of atheromatous plaques is significantly influenced by lifestyle variables. Consuming foods high in sugar, salt, and saturated fat is generally acknowledged to significantly enhance the chance of developing a CVD.Restoring normal blood flow through or around damaged vasculature is the main goal of current treatments for cardiovascular diseases (CVDs), along with preventing further cardiovascular insults. Statin therapy is effective in preventing the thickening and subsequent development of atherosclerosis plaques, as well as in affecting fibrous and dense calcium volumes, external elastic membranes, and other structures . First-line treatments for CVD prevention include dual antiplatelet medications, which work to lower platelet aggregation and clot formation by utilizing P2Y12 inhibitors like clopidogrel and cyclooxygenase inhibitors like aspirin . The hazards of using antiplatelet therapy, which have extremely negative side effect profiles, and inadequate patient outcomes necessitate improvements in these treatments.

Treatment with nanotechnologies :

Using nanotechnology to improve and preserve a high quality of life and excellent health, the field of nanomedicine consists of the diagnosis, treatment, and prevention of illness or injury . One area of nanomedicine, for instance, is concerned with controlling and manipulating biomacromolecular and supramolecular substances that are essential to human health, such as DNA, RNA, cell membranes, and lipid bilayer.

Use of nanotechnology for cardiovascular disease :

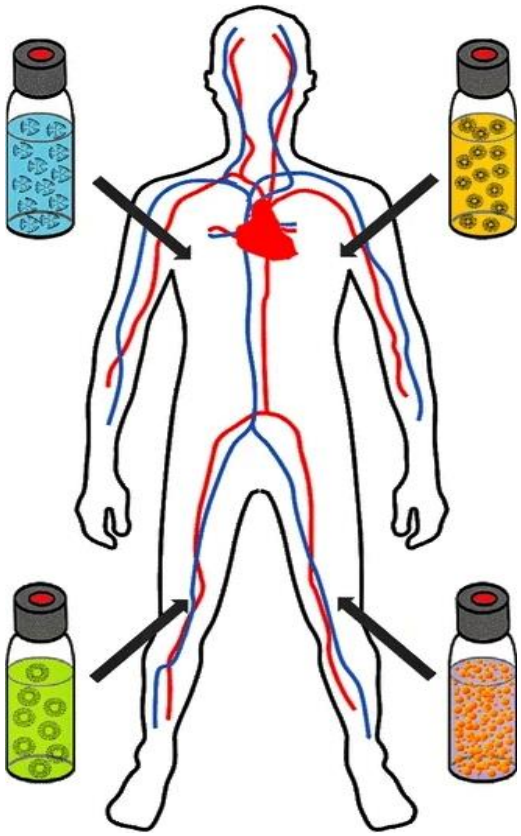


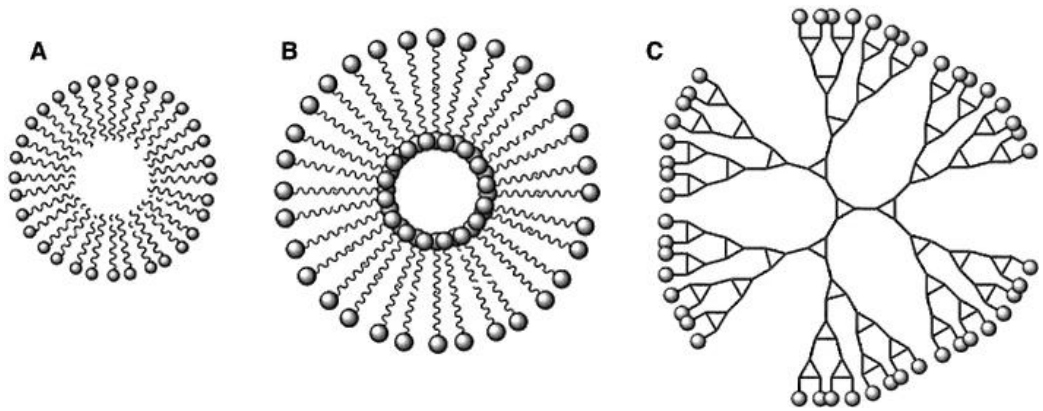
Fig. 2 From: The use of nanotechnology in cardiovascular disease

nanoparticles in particular are generally acknowledged to possess physicochemical characteristics that enhance biological function. These characteristics include a high surface energy resulting from their large surface area to volume ratio, wettability, reactivity, and roughness. According to the British Standards Institute, nanoparticles are minuscule particles that have all three dimensions inside the nanoscale, spanning fromA diverse range of nanotechnologies have been devel-Oped for biomedicine within the past 2 decades, each With their own unique properties and advantages. These Include micelles, liposomes, dendrimers, nanoparticles, And the use of nano-coatings (Fig. 3). Currently, therapeutic applications of nano-Technology within medicine are focused around cancer Treatment and diagnosis ; however,

The focus is shifting to other areas of therapeutics, such As cardiovascular medicine and Antimicrobial resistance .

Nanocarriers for the delivery of therapeutic agents: a micelle, b liposome, and c dendrimer :

Fig 3.From: The use of nanotechnology in cardiovascular disease



Liposomes :

Around 50–200 nm in size, liposomes form phospholipid bilayer structures, with aqueous cores encased in naturally occurring phospholipids like cholesterol .Liposomes are useful drug delivery vehicles because they have both hydrophilic and hydrophobic properties. Liposomes can be categorized into three groups according on the number and size of their bilayers. Variables such as size, preparation technique, surface charge, and lipid makeup all affect the characteristics that a liposome displays . Large unilamellar vesicles (LUV) resemble SUVs, while multilamellar vesicles (MLV) have multiple bilayers of lipid . Small unilamellar vesicles (SUV) have a single lipid bilayer.Moreover, some regions of the liposomal surface can be targeted by attaching antibodies or other tar-getting moieties to it. Platelet-targeted liposomal drug delivery may show promise in treating myocardial infarction, atherosclerosis, and thrombosis because of the mechanisms of platelet aggregation involved . Regarding cardiovascular medicine uses, liposomes may be used to treat intermittent claudication and peripheral artery disease. Phase III clinical trials for liposomal drug delivery of prostaglandin E-1 (PGE-1), commercially known as Liprostin, are currently being conducted . Vasodilation, suppression of platelet aggregation and leukocyte adhesion, and anti-inflammatory effects are only a few of the many pharmacological characteristics of PGE-1.For the specific purpose of treating thrombosis, liposomes were created. Myocardial infarction and stroke are linked to thrombosis, which is an obstruction of the blood vessels. It was recently reported that liposomes containing the thrombolytic medication urokinase were surface functionalized with a cyclic argils-glycyl-aspartic acid (cRGD) peptide . In order to provide targeted distribution, cRGD peptides bind specifically to the GPIIb/IIIa receptors on active platelets. liposomes in the cRGD showed comparable effects to the free drug at 75% lower drug dosage in a mouse model of mesenteric thrombosis.Berberine has been reported to be encapsulated and delivered in a number of trials.High doses of the tiny fluorescent isoquinoline quaternary alkaloid berberine have been shown to be beneficial.C57BL/6J mice were used in the development and testing of berberine-loaded liposomes for the prevention of unfavorable remodeling following myocardial infarction and reduction of IL-6 release . Comparing the liposomal berberine formulation with the unloaded liposomes and free medication, the liposomal formulation considerably preserved the cardiac ejection fraction 28 days after MI by 64%. This work demonstrates the possibility of a liposomal berberine formulation as a possible therapy for unfavorable remodeling following myocardial infarction.Compared to polymer-based systems, which are expected to be therapeutically useful earlier, liposomes have been used for a comparably longer time. But as has been noted in other liposomal drug delivery systems, there are certain drawbacks.

Polymer-based nanoparticles:

Because polymeric nanoparticles are manipulable and have the potential to be reabsorbed by the body, they have garnered special attention in the field of nanomedicine . The site of action of polymeric nanoparticles and the least intrusive way to introduce them into systemic circulation determine the best route of administration. Although intravenous injection is the most widely used mode of delivery, other effective methods include mucosal, transdermal, oral, and dermal . A broad category of systems includes polymeric nanoparticles. These comprise dendrimers, solid nanoparticles, amphiphilic nanoparticles (which form rods, vesicles, and micelles), and star-shaped systems. According to Hoskins et al., each of these systems has a distinct design and set of characteristics.Several polymers, including poly(methyl methacrylate) (PMMA), poly(acrylamide), poly(styrene), and poly(acrylates), are not biodegradable yet, research utilizing these materials has shown evidence of longterm toxicity . have highlighted the importance of biodegradable polymers, which include synthetic polymers like poly(lactide) (PLA), poly(lactide-co-glycolide) copolymers (PLGA), poly(ε-caprolactone) (PCL), and 17 and poly(amino acids) (Elsabahy and Wooley .The most common use of expanded polytetrafluoroethylene (ePTFE) grafts is to replace blood arteries that have been compromised by atherosclerotic plaques or ischaemia, restoring normal blood flow. Poly(lactic-co-glycolic

acid) (PLGA) nanoparticles covalently linked to ePTFE surfaces were used in a study to investigate their potential medicinal uses. Aminolyzation with 3-aminopropyl triethoxysilane was carried out after the ePTFE surface was oxidized with H2O2/H2SO4. the nanoparticles displayed good stability on the ePTFE surface and biocompatibility of the graft with mouse fibroblasts, which showed no significant cytotoxicity, suggesting promise for the use of ePTFE for the treatment of CVD by adding antithrombotic medications to the polymer grafts. In 2012, Korin and colleagues conducted research on the impact of biodegradable poly(lactic-co-glycolic) acid.Additionally, the outcomes suggested a decreased side effect profile by indicating that fewer doses of tPA were needed if it was added to the polymeric grafts. According to this research, there are uses for this technology in the treatment of CVDs that have the potential to revolutionize cardiovascular medicine. Many studies have looked at quercetin (Qu) either as solid drug nanoparticles' or encapsulated within polymeric nanoparticles . Antioxidant medication Qu has been demonstrated to offer protection against CVDs. presented a novel poly(lactic-co-glycolic acid) (PLGA) loaded with Qu for the prevention of atherosclerosis, according to a recent study.

Micelles :

Micelles Made from either lipid- or polymer-based amphiphilic molecules, micelles are amphiphilic structures with distinctive hydrophobic cores and hydrophilic shells ,They develop naturally as a result of a decrease in free energy brought on by the aggregation of hydrophobic particles from the surrounding aqueous medium and the formation of a micelle core stabilized by hydrophilic pieces that are exposed to the water . The concentration of an amphiphile in solution causes the system's free energy to rise because of unfavorable environmental conditions and interactions between water and the amphiphile's hydrophobic section. This interaction causes the system's entropy to decrease and the water's structure to become more organized .The hydrophilic shell lengthens circulation duration and systemic exposure to the micelle, while the hydrophobic core permits drug encapsulation. They can enter tissues by bridging membranes thanks to their small size and physicochemical characteristics . Because of their incredibly low excipient:drug ratios, polymeric nanoparticles exhibit greater stability than liposomes and low-molecular-weight surfactants. As a result, not only is there a lower possibility of systemic toxicity from the carrier vehicle, but they are also more economical. The synthesis is quite controllable, and they are easily customized to the intended use by adding tracking molecules or targeting ligands. Polyester or poly(amino acid) derivatives make up the majority of the polymers utilized in micellar drug delivery.The use of a block co-polymer micelle made of poly(ethylene glycol) (PEG)-block-polycation carrying a (PEG-b-P[Asp(DET)]) side chain as a gene delivery vector for the treatment of vascular disease was successfully demonstrated in an in vitro study . This micelle showed low cytotoxicity in vascular smooth muscle cells and efficient gene expression. In order to completely comprehend the in vivo result of gene transfer, the degree of plasmid DNA (pDNA) gene expression in the vascular region was measured after implanting the PEG-b-P[Asp(DET)] micellar formulation into a rabbit carotid artery. Using a balloon catheter to create neointimal hyperplasia in the carotid, encapsulated pDNA was then injected.Using the FLAG sequence (p-MP-FLAG), pDNA was found to be present. To verify the gene's expression, the artery was stained with an anti-FLAG antibody. The results showed that the micellar formulation outperformed the controls, homopolymer P[Asp(DET)] and branched polyethyleneimine (BPEI). Compared to the micellar vectors under study, the control vectors showed a notable thrombus-induced vascular blockage . Because nanomicelles have better safety and efficacy profiles than viral vectors, research on non-viral vectors is directed by the constraints of present viral vector technology, such as antigenicity and oncogenicit .There has been news of an intelligent delivery system that reacts to the microenvironment of oxidative atherosclerotic plaque.Poly(ethylene glycol) and Poly(propylene sulphide) (PEG-PPS) were used to create block copolymer micelles. In order to reduce inflammation and the amount of reactive oxygen species (ROS) produced during the treatment of atherosclerosis, andrographolide was solubilized using the micelles.

Andrographolide is a substance obtained from plants that shows effects on cardiovascular protection by upregulating endothelial nitric oxide synthase expression and downregulating inducible nitric oxide synthase expression ., the stimuli-responsive micelles not only absorbed the ROS on their own at the pathologic locations, suppressing the pro-inflammatory cytokines, but also reacted quickly to stimuli that released drugs.For the purpose of treating thrombosis, lumbrokinase (LK) can now be delivered specifically with cationic-mixed polymeric micelles . LK is an earthworm-derived fibrinolytic enzyme that has been proven to have antithrombotic properties. The micelles were composed of a block copolymer of polycaprolactone-b-poly(2-(dimethylamines) ethyl methacrylate) (PCL-PDMAEMA), and a block reported on the solubilization of olmesartan medoxomil (OLM) through the blend-ing of various Pluronic® combinations (F127 & P123) as another example of mixed micelle systems. OLM is an antihypertensive medication with inadequate bioavailability due to its poor water solubility .To get beyond this physicochemical barrier, OLM was put into carriers of mixed micelles. Three medications were developed, including different F127:P123 ratios and Pluronic® combination ratios of 1:40, 1:50, and 1:60. According to the study, the drug suspension's release efficiency was only 35%, while the combined micelles could achieve up to 43% (El-Gendy et al.

Dentrimers :

The Greek word "dendron," which means "tree," is the source of the term "dendrimer," which appropriately describes the structure of these repeatedly branched molecules ., dendrimers are special because of their low polydispersity, high functionality, and multibranched, three-dimensional architecture. Comparing dendrimers to other nanotechnologies, there are numerous obvious benefits to using them as non-viral vectors for medicinal applications. Apart from being superior to other viral and non-viral counterparts, they have higher solubility, greater stability, less immunogenicity, and the ability to help deliver therapeutic molecules, DNA, and RNAs efficiently . Due to the large number of branches at their surface, dendrimers have the disadvantage of frequently having highly charged exteriors, dendrimers are categorized according to their structure as having a focal core, several peripheral functional groups, and construction blocks with several repeating units inside the inner core. The nanoscale environment created by extensive branching in a dendrimer has made it possible to host chemical species within the focal core. Furthermore, dendrimers have the ability to exhibit different functional groups at different locations on their periphery, which opens up a range of interactions with other dendrimers and the surrounding molecular environment. In addition, the repeating units provide flexibility within the dendrimer, enabling medicinal molecules to be manipulated and encapsulated therein .Vascular homeostasis is maintained by nitric oxide (NO), a powerful vasodilator that also controls the proliferation of vascular cells. As a result of these actions, it may be particularly effective in preventing atherosclerosis has demonstrated the possibility of using NO encapsulation within dendrimers as a focused treatment for tissue injury. poly(propylene imine) dendrimers successfully released NO, indicating promise for their prospective use as drug delivery systems. In an attempt to regulate the elevation of inflammation in tartrated areas within injured vasculature, dendrimers with potential as gene delivery agents for the treatment of CVDs have also been studied. Research has demonstrated that DNA plasmid-carrying dendrimers improved survival.

Recently, Zhang et al. (2017) reported the delivery of nattokinase (NK) using a dendrimer made of poly(glutamic acid) and poly(ethylene glycol) (PEG) (Gn-PEG-Gn). The thrombolytic medication NK has a minimal risk profile and strong safety standards, however it is highly vulnerable to environmental deterioration. For the medication to be clinically beneficial, meticulous formulation is therefore necessary. More research is being done to determine the system's potential in vivo, as the NK-loaded G3-PEG-G3 dendrimer shown good thrombolytic activity in vitro .The development of a poly(amidoamine) (PAMAM) dendrimer-based system as drug carriers for the simultaneous delivery of hydrochlorothiazide (HCTZ) and ramipril (RAPL) was the subject of another study (Singh et al. 2017). De Leeuw and Birkenhäger (1987) and

Roush and Sica (2016) state that HCTZ, an antidiuretic, and RAPL, an antihypertensive, are medications used to treat high blood pressure. The solubility of RAPL rose 4.91 times at 0.8% (w/v) dendrimer concentration when amine-terminated dendrimer was used, whereas dendrimer with carboxy-terminated functional groups was the best for HCTZ solubilization (3.72 times). In contrast to the free medicines, the new formulations caused a faster rate of dissolution. In comparison to the single drug-loaded den-drimer, hybrid formulations exhibited comparable dissolving patterns. The formulation technique showed potential for use, the authors said.

Gel-based nanoparticles:

The gelated nanoparticles on the polymer-based particles are the least prevalent. These nanoparticles generate hydrogel matrices into which pharmaceuticals can be integrated when the concentration of polymers in them increases. More medication release delay and longer-term stability are possible with these methods.Vascular cell regeneration in the ischemic heart was evaluated by monitoring the gelation behavior of core/shell nanoparticles loaded with vascular endothelial growth factor (VEGF) and their use in the regeneration process The gel nanoparticle's shell consisted of Pluronic F-127 (poly(ethylene oxide)
poly(propylene oxide)-poly(ethylene oxide) triblock copolymer), whereas the gel's core was made of lecithin containing VEGF . The formation of the temperature-induced gel occurred when the nanoparticles were mixed with a solution containing mono-caprylate propylene glycol at room temperature. The cardiac tissue was subjected to functional analysis tests after both gelated and non-gelated nanoparticles were applied to the in vivo sample.the outcomes showed that gelated VEGF-loaded core/shell nanoparticles improved cardiac function (cardiac output and ejection fraction) more than non-gelated nanoparticulates.

Stents covered with nanotechnology:

Intraoperative treatments that are frequently utilized in clinical practice to relieve blockages in the cardiac vasculature include coronary artery bypass graft (CABG) and percutaneous transluminal coronary angioplasty (PTCA)/percutaneous coronary intervention (PCI). Major cardiac surgery is required for CABG, while PTCA is a non-surgical technique that uses a balloon to expand an artery and, in some cases, a stent to keep it open (NICE 2008). The small wire mesh used to make the stents is what keeps the previously blocked artery open by allowing adequate blood flow to pass through it (Fig. 4).

Use of a stent to widen an occluded blood vessel:

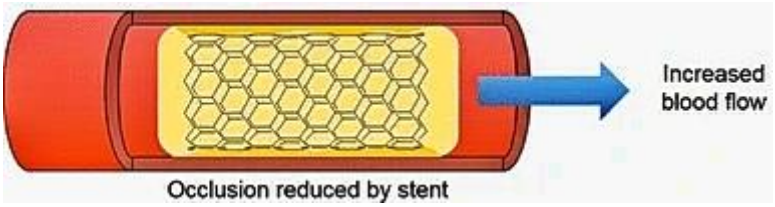


Fig. 4 From: The use of nanotechnology in cardiovascular disease

A considerable danger of restenosis within the vasculature results from the overwhelming problem associated with the use of stents in the replacement of heart tissue. Over-distention of the ill patient leads to restenosis.Utilizing drug-eluting stents (DES), which release the integrated medication to the area of their implantation, is one strategy that can be used to lower the incidence of in-stent stenosis. The stents can be coated with a variety of polymers, including polycaprolactone (PCL), polyethylene glycol (PEG), and poly(lactic-co-glycolic acid) (PLGA) . a potential nanocomposite polymer to cover bare metal stents and enhance endothelium revascularization is polyhedral oligomeric silsesquioxane poly(carbonate-urea)

urethane (POSS-PCU) polymer with anti-CD34 antibodies attached. POSS-PCU demonstrated superior biocompatibility and hemocompatibility in vitro, according to the study's findings. Research on POSS-PCU application in heart valve replacement sector provides additional support for this.It has also been shown, nevertheless, that using drug-eluting stents in animal models caused inflammation at the location where the stents overlapped and delayed vascular repair. The degree of fibrin deposition and neointima development observed in overlapping paclitaxel-eluting stents (PES) was higher, which raised questions about drug toxicity, safety in human subjects, and potential systemic problems at the overlap sites . Human trials have been initiated for the application of POSS-PCU as a nanocomposite coating on stents. In patients with de novo coronary artery disease, the first-in-man trial (FIM) examined the long-term effects and effectiveness of non-polymeric drug-coated stents (DCS), with follow-up intervals of four, twelve, and five years.Stents and drug-eluting stents are among the most well-established medical devices for the treatment of cardiovascular disease. Though nanotechnology has been used in their coating to lessen the likelihood of rejection in vivo and restenosis, as was previously mentioned, there are issues with their use, and a shift is occurring away from these technologies and toward flexible polymer scaffold.

Imaging diagnostics with nanoparticles:

In order to address a gap in the realm of imaging, nanoparticles can also be used in medicine. Because of their superior bioavailability profiles, simplicity of manipulation, and adaptability, nanoparticles have tremendous potential in medical imaging.

The versatility of nanoparticles enables the combination of functional groups, ligands, and contrast materials to create multimodal and multifunctional imaging vehicles with tunable properties . To diagnose inflammation non-invasively, use cardiovascular magnetic resonance imaging (CMR): Since inflammation is a prominent consequence of coronary heart disease due to its pathophysiology, early detection of the condition through the use of these techniques can improve prognosis, the amount of macrophages and the degree of plaque revascularization. gadolinium or fluorine-19 (19F) contrast agents can also be used in contrast-enhanced cardiac magnetic resonance imaging (ceCMR) to identify cardiac oedema, necrosis, and fibrosis. Contrast agent is rapidly cleared from healthy myocardium, but it is retained in injured regions . When induced MI was shown in in vivo models, T1-weighted imaging demonstrated the efficacy of CMR as a diagnostic tool by detecting gadolinium-contrast agent in >90% of the myocardium after shock.

Because athero-sclerotic plaques and the degree of atherosclerosis may be more easily identified, these advancements in diagnostic imaging will also enable more patient-centered therapy.In tumor imaging as well as cardiovascular medicine, gold nanoparticles have demonstrated remarkable promise. Gold is a noble metal that is stable, biocompatible, and basically inert . Gold particles range in size from 1 to 500 nm and can take on a multitude of shapes and forms, such as stars, crescents, prisms, spheres, rods, and cages. Renal excretion of gold particles occurs. PEG chains can be attached to the surface of nanoparticles to increase their hydrophilicity and circulation time, hence altering the rate of elimination by glomerular filtration . Heart-related optical imaging using gold nanoparticles is possible: photoacoustic imaging relies on the detection of both optical and ultrasonic imaging, with light serving as an excitation source and ultrasound as a detector.

Future prospectives:

In an effort to improve and extend life, medical technology—and therapies for cardiovascular diseases, in particular—has made tremendous strides. It is estimated that just 15% of existing practice guidelines for CVD are backed by high-quality data, making the need for innovative solutions in this area critical . Prognoses have improved as a result of improved nutrition, lifestyle, medial intervention, early detection, preventative techniques, and standard of living.

CVDs account for a sizable fraction of all premature deaths in those living in the European Union under the age of 75. In order to effectively treat this pandemic and avoid about 80% of all cases, it is necessary to find solutions as soon as possible.This emphasizes how urgently more study and development in this area are needed. Many trials investigating the therapeutic application of nanotechnology in cardiovascular care are now being conducted. One such project is the European Commission-funded NanoAthero project. The successful completion of thrombus imaging and the use of innovative carriers to treat susceptible plaques are among the goals of this phase I trial (European Commission, 2017). Furthermore, according to the US National Library of Medicine (2018), Habib et al. are currently researching the feasibility of diagnosing heart failure using breath samples and sensors based on nanomaterials. The application of nanotechnology in drug-eluting stents in contrast to bare metal stents is the subject of additional clinical trials: There are 8,000 participants in the study.

Conclusion :

Translational clinical trials provide evidence that nanotechnology can be used to treat cardiovascular disease (CVD). This review presents this data. The successful completion of clinical trials for nanomedicines, nanomaterial devices, and associated technologies may soon lead to their release on the market, since there is a growing global investment in the field of nanotechnology and appropriate infrastructure. It's a given that advances in nanotechnology will have a favorable impact on patient lives worldwide and that they will help to improve patient health and well-being. More in vivo research and clinical trials must be ordered in order to completely comprehend the systemic behaviors of nanoparticulates in order to make the largest possible impact on medicine.

Targeting specific disease states with customized treatment is becoming increasingly important in the field of therapeutics, and nanotechnology could be the most effective means of achieving this aim. In addition, searching for alternatives to the current pharmacological and surgical management is essential to stop these exponential rises in healthcare expenses. The idea that nanotechnology has not yet fully revolutionized medicine is supported by a wealth of evidence, nonetheless.

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