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A Review on the Metabolic Effect of Antihyperlipidemic Drug in Chronic Kidney Disease Patients

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ABSTRACT

One of the growing concerns in public health is chronic kidney disease (CKD), characterized by the decrease in glomerular filtration rate and persistent kidney damage. Cardiovascular disease (CVD) is one of the major causes of comorbidity and mortality in CKD population which is associated with dyslipidaemia which show elevated triglycerides, low HDL, and the presence of atherogenic lipoprotein particle, thereby increases the risk of cardiovascular disease.The primary goal of managing dyslipidaemia in CKD is to lower low density lipoprotein cholesterol with statin and ezetimibe serving as main medications used. Other lipid lowering therapy include novel PCSK9 inhibitor, bile acid sequestrant. Statins are generally safe but can cause hepatotoxicity at higher doses, myalgia and uncommonly Rhabdomyolysis. Although uncommon muscle-related adverse effects are possible, ezetimibe offers further LDL-C reduction with a favourable safety profile. Although fibrates are helpful in cases of severe hypertriglyceridemia, they should be used with caution because of renal excretion which can elevate serum creatinine and risk of myopathy especially in combination with statins In general, dyslipidaemia must be well managed in individuals with chronic kidney disease (CKD) in order to lower cardiovascular problems and possibly slow the advancement of renal illness. To balance safety and efficacy, lipid-lowering treatments must be carefully chosen and closely monitored, especially in patients with severe renal disease and several comorbidities.

Keywords Chronic kidney disease, dyslipidaemia, hyperlipidaemic drugs, statins

INTRODUCTION

Chronic kidney disease is a prevalent public health issue, as it has become more common now, as per Kidney Disease Outcome Initiative (KDOQI), chronic kidney disease is defined as a decrease in kidney glomerular filtration rate (GFR) of <60ml/min/1.73m^2 for at a minimum of 3 month or kidney damage. Patients with CKD especially at end stage renal disease who may be treated with haemodialysis, peritoneal dialysis or those who had renal transplantation show higher risk of developing cardiovascular disease due to several risk factors often associated with CKD. High triglycerides, high total cholesterol (TC), high low-density lipoprotein (LDL), and low HDL are all known risk factor of CVD in general populace.

Lipid profile is dependent on kidney function since dyslipidaemia is a common consequence of chronic kidney disease (CKD) and alteration to lipoprotein metabolism, which is linked to decrease in GFR level so lipid profile depends on the degree of proteinuria and kidney function (1). Among patient with CKDs, cardiovascular disease is a significant contributor to morbidity and mortality. The majority of the deaths occur from cardiovascular disease before reaching stage 5 CKD. A significant risk factor for coronary heart disease is dyslipidaemia, which has sparked interest in the detection and treatment of abnormalities in lipoproteins and plasma lipids.

The build-up of partially metabolised triglyceride-rich particles (mostly VLDL) and intermediate density lipoprotein (IDL) are indicative of lipid disorders. This is mostly because aberrant lipase activity. Low HDL cholesterol and hypertriglyceridemia are the result. There is frequently an abnormally high lipid subfraction profile with a predominance of atherogenic tiny dense LDL particle, even when the total cholesterol concentration appears normal (2).

MANAGEMENT OF DYSLIPIDEMIA

In patients with chronic kidney disease (CKD) and kidney transplant recipients, decreasing low-density lipoprotein (LDL) cholesterol is generally favourable for preventing severe atherosclerotic events, however the evidence for the dialysis patients is less clear. The treatment for lipid reduction is advised regardless of the baseline LDL-cholesterol levels in all individuals stage 3 CKD or above. The pillars of treating dyslipidaemia in patients with CKD are mainly statins and ezetimibe, however new and alternative lipid-lowering treatments may soon play a major role. (3)

According to experimental research, tubulointerstitial disease and progressive glomerulosclerosis cause kidney damage that is accelerated by hyperlipidaemia. Treatments that lower cholesterol can lessen kidney impairment and maintain kidney function. Triglyceride-rich apoB -containing lipoproteins have been linked to a faster decline in renal function; however, the pathophysiological mechanisms are not entirely comprehended. A rigorous clinical trial is required to determine the effectiveness of hypolipidemic medication in attenuation of lipid abnormalities and to stop the progression of renal illness, even though the use of lipid lowering therapies may be useful in correcting the lipid abnormalities. (2)

The reduction of triglyceride using hypolipidemic drugs and eating a health low fat diet may help slow the development of kidney disease as well as in reducing the cardiovascular disease seen in CKD patients, which will improve the survivability and lessen morbidity and mortality (2). Antihyperlipidemic drugs used in the control and treatment of dyslipidaemia are: statins, fibrates, cholesterol absorption inhibitors, PCSK9 inhibitors, bile acid sequestrants etc (3).

METABOLIC EFFECTS OF HYPOLIPIDEMIC DRUGS

I. STATINS

Ever since its first introduction 20 years ago, one of the most often prescribed pharmacological class is Hydroxymethyl Glutaryl Coenzyme A Reductase (HMG-CoA) inhibitor. At present 6 statins are available in the market- Atorvastatin, pravastatin, simvastatin, fluvastatin and, pitavastatin. For great majority of medications seem to be safe to take. However, long term statin treatment increases the likelihood of negative effect in patients with various medical comorbidities (4). A meta-analysis carried out by Cholesterol Treatment Trialists' (CTT) Collaboration saw that adverse effects like muscle related complaints and new onset diabetes have been already documented but other side effects like interstitial lung disease, depression, sexual dysfunction, sleep disturbance, and memory loss did not yield any evidence for it. An intensity related study conducted to observe abnormal liver function showed increased abnormality in 80mg atorvastatin vs placebo and the comparison of the atorvastatin 80 mg vs placebo to atorvastatin 20 mg vs placebo showed increased event rate ratio (RR) at the doses of 80mg, this shows that for patients with atorvastatin 80mg daily had detrimental effect on the liver enzymes, which increased liver transaminase enzyme more than double. The chance of myalgia, a common side effect is 1-10% of the patient and less than 0.1% chance for serious side effect like rhabdomyolysis (5).

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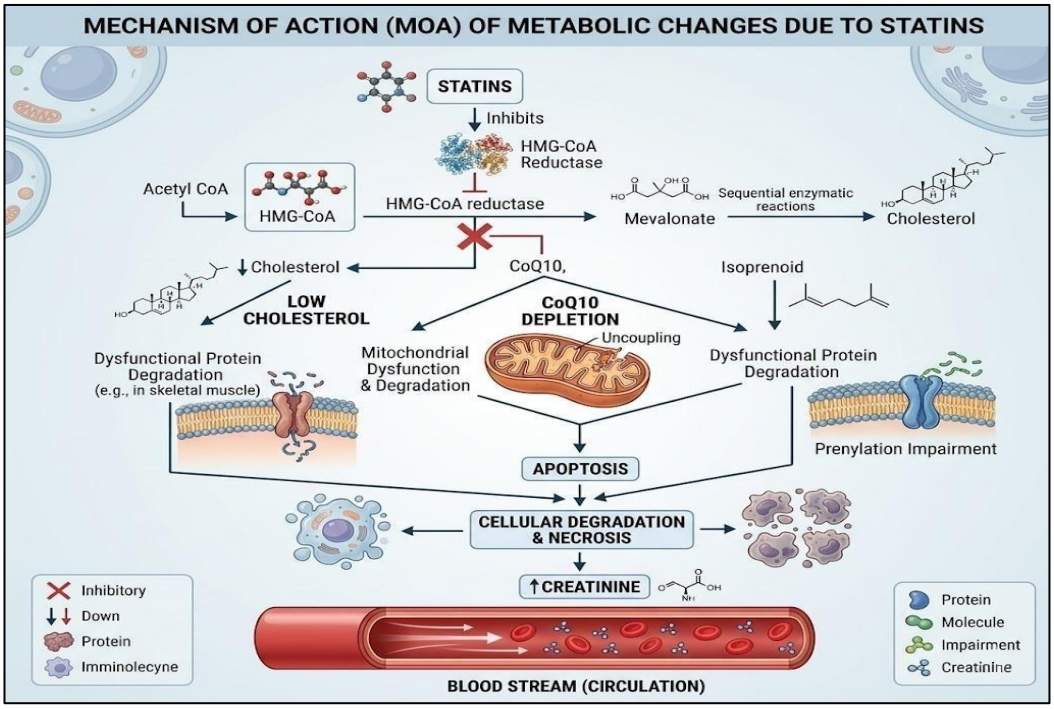

Figure 1;Mechanism of action of metabolic changes due to statins

II. CHOLESTEROL ABSORPTION INHIBITOR

Ezetimibe is a hypolipidemic drug which inhibits the intestinal cholesterol absorption and reduce the biliary cholesterol secretion which lower the low-density lipoprotein cholesterol (LDL-C) by 20%. It is recommended as a second line drug by both American Heart Association and European Society of Cardiology given in combination with statins. Also, the prior studies have shown ezetimibe as capable of reducing cardiovascular event.

Even if, ezetimibe is a well-supported in both research and in use as an antihyperlipidemic drug, concerns of its adverse effects such as cancer, neurocognitive disorders, fracture, gastrointestinal adverse event, myalgia and muscle pain have been noted in some studies. Later studies showed no presence of such adverse event in the subject (6). Myopathy, which is characterised by inexplicable muscle discomfort or weakening, is one severe adverse effect. When prescribed, myopathy, including rhabdomyolysis, occurs in less than 0.1% patients at the maximum dosages (7).

III. FIBRATES

Fibrates are indicated when hypertriglyceridemia (serum triglycerides ≥500 mg/dl) is the primary lipid abnormality, and may reduce triglyceride levels by up to 30% to 50% (3). However, fibrates are excreted by the kidney and may cause myositis, particularly when used in conjunction with statins. Although this hasn't been seen with gemfibrozil, therapy with fibrates may potentially result in rise of serum creatinine unrelated to overt muscle injury. It is unclear if this is an assay effect, a change in creatinine secretion, or an increase in creatinine output rather than a real decline in GFR (8). In patients with hypertriglyceridemia, fibrates often lower serum triglycerides. They can also be used in conjunction with other lipid-lowering medications to raise HDL cholesterol. These medications can cause modest gastrointestinal, cutaneous, liver, and muscle side effects, although they are generally well tolerated. Serum creatinine levels may rise during fibrate administration, especially in older individuals, those with pre-existing renal failure, and when these medications are taken at high doses or in conjunction with renin-angiotensin-aldosterone (RAAS) inhibitors. However, the increase in creatinine caused by fibrates is typically temporary and reversible (3).

IV. BILE ACID SEQUESTRANTS

The intestinal bile acids are bound by the bile acid resins or sequestrants (cholestyramine, colestipol, colesevelam, and colestimide), creating a non-absorbable compound that lessens the bile acids' capacity to solubilise lipids. Reduced bile acid reabsorption encourages the liver to produce these substances, which ultimately lowers LDL cholesterol levels in the bile and plasma. These medications are generally safe, but because of their gastrointestinal adverse effects, they are rarely used. (3)

V. PCSK-9 INHIBITORS

The LDL receptor is broken down by the protease proprotein convertase subtilisin/Kexin type 9 (PCSK9). In addition to maximal statin therapy, the monoclonal antibodies evolocumab and alirocumab, which target PCSK9, successfully lower serum cholesterol till median values of 20–30 mg/dl (3). Nasopharyngitis, myalgia, influenza-like sickness, and injection site reactions were the most frequently reported adverse events (AEs) linked to PCSK9 inhibitors given in a clinical environment. The majority of AEs were resolved during follow-up, and they were typically minor. Nasopharyngitis, upper respiratory tract infections, influenza-like illnesses, myalgia, back discomfort, arthralgia, headaches, and Injection Site Reactions (ISRs) are the most frequently reported adverse events (9). A similar study conducted by chunmei ji et al showed consistent result where subjects had similar AEs, data collected from FDA Adverse Event reporting system (FAERS) database (10).

DISCUSSION

About 10% of adults worldwide suffer from chronic kidney disease (CKD), a condition whose incidence increases dramatically with age. A considerable rise in CV morbidity and death is associated with CKD (3). As one of the most significant modifiable risk factors linked to CKD, dyslipidaemia is a preferred therapy target to lower the burden of CV risk. Research has indicated that a better CV result for patients with chronic kidney disease (CKD) is linked to adequate lipid control using statins, either with or without ezetimibe. All dosages of statins that are not broken down by the kidneys are well tolerated. In fact, atorvastatin dosages of up to 80 mg daily did not cause any significant side effects in haemodialysis patients. Establishing the patient's baseline creatine phosphokinase (CPK) levels before starting statin therapy may be beneficial for CKD patients (8). This will make it easier to assess the patient in the event that side effects such myositis arise. Patients with numerous medical co-morbidities, polypharmacy, alcohol misuse, and hypothyroidism are the most frequent risk factors for statin-related myopathy (4).

Similarly, fibrate is also effective in lower LDL-C as its excretion is through kidney it can cause myositis especially in combination with statin. Along with myositis, it can also cause serum creatine which is not caused by any external injury but it is not seen in people on Gemfibrozil. Even if this change in creatinine has been observed, it is unsure if their actual change in GFR or just a laboratory error, an increase in creatinine production or a change in creatinine secretion (8). By inhibiting the Niemann Pick C1 like 1 (NPC1L1) protein, which prevents intestinal cholesterol absorption and mimics a low cholesterol diet, ezetimibe decreases LDL-C concentrations. Except for the possible risks of extremely low cholesterol intake, which is still up for debate, ezetimibe is biologically safe and does not directly affect the liver and other organs lipid metabolism. Gürgöze et al showed that Myalgia, nasopharyngitis, influenza-like sickness, and ISRs were the most frequently reported adverse events (AEs) linked to PCSK9 inhibitors prescribed in a clinical environment. There were no appreciable variations between the two genders or between evolocumab and alirocumab. The majority of the AEs went away during follow-up, and they were typically moderate (9).

CONCLUSION

Patients with renal impairment frequently have dyslipidaemia, which varies both quantitatively and qualitatively in non-dialysis-dependent patients, individuals with nephrotic range proteinuria, patients with end-stage renal disease (ESRD), and recipients of renal transplants. Ramkumar et al concludes that myalgia is common side effect with a 1-10% patient while rhabdomyolysis is a rare but severe adverse effect of statin. Some statin at higher dose is potentially diabetogenic but only to a lesser extend (4). The kidney eliminates fibrates, which can lead to myositis, especially when combined with statins. Fibrate therapy may also raise serum creatinine levels unrelated to obvious muscle damage (8). Even if the use of some Antihyperlipideic drug show adverse event, the benefit outweighs the risk and even in case of an event, monitoring dose and use of alternative drugs can help overcome such complication (7).

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