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UNDERSTANDING EFFECTS OF CHOLESTEROL LOWERING THERAPIES ON THE PROGRESSION OF DIABETIC NEPHROPATHY RENOPROTECTION

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ABSTRACT

Diabetic Nephropathy (DN) is a leading cause of morbidity and mortality and its prevalence is continuously increasing in industrialized nations. Hyperglycemias,hyperlipidaemia and hypertension are underline factors that are addressed in the progression of diabetic nephropathy. Glomerular injury is linked to an increase in lipoprotein synthesis and a decrease in peripheral lipoprotein catabolism. These abnormalities often lead to marked increases in total plasma cholesterol concentrations, particularly very low-density lipoprotein and low-density lipoprotein (LDL) fractions. The extracellular mesangial matrix is capable of binding considerable amounts of LDL or modified LDL. Cross linking of mesangial matrix with LDL, mimicking the progression of glomerular lesion in DN. At present, no promising therapy is available to treat patients with DN due to lack of understanding of mechanism involved in the pathogenesis of nephropathy. Through this review we are trying to explore the, use of cholesterol lowering therapies, which will provide potential therapeutic benefit to diabetic nephropathy.

KEYWORDS: Diabetic Nephropathy,Hyperlipidaemia, End-stage renal failure, Cholesterol lowering therapies.

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INTRODUCTION

Diabetic nephropathy (DN) is one of the most serious complications of diabetes and the most common cause of end-stage renal failure (ESRD). Features of early diabetic renal changes are glomerular hyper filtration, glomerular and renal hypertrophy, increased urinary albumin excretion, increased basement membrane thickness and mesangial expansion with the accumulation of extracellular matrix proteins such as collagen, fibronectin and laminin. Diabetic nephropathy is characterized by proteinuria, a decline in renal function, glomerulosclerosis and interstitial fibrosis [1]. Diabetic nephropathy is diagnosed on the basis of the extent of albumin protein excretion in urine (proteinuria) [2, 3]. The usual daily limits of proteinuria are as follows: normal <30 mg, microalbuminuria 30–300 mg and macroalbuminuria >300 mg [4]. Lipid deposits can be found in the glomeruli and renal interstitium of patients with diabetic nephropathy as well as in a variety of other renal diseases [5, 6]. This has renewed interest in the possibility that hyperlipidemia and abnormalities in cholesterol metabolism may contribute to the progression of diabetic nephropathy [7]. Data suggested that cholesterol exacerbate the development of diabetic nephropathy [32, 35].

DIABETIC NEPHROPATHY

The classical definition of diabetic nephropathy is a progressive rise in urine albumin excretion, coupled with increasing blood pressure, leading to declining glomerular filtration and eventually ESRD [1, 8]. The DN associated with long-standing diabetes [33, 34]. Prevention of ESRD by early detection and treatment is of importance to stop the growing need for dialysis and renal transplantation [37].

STAGES OF DIABETIC NEPHROPATHY

The kidney disease associated with long-standing diabetes, a Kimmelstiel-Wilson disease (or Kimmelstiel-Wilson syndrome) or intercapillary glomerulonephritis is a type of diabetic nephropathy. The natural history of diabetic Nephropathy evolves through 5 clinical stages; which are most clearly characterized in type-1 because its onset is distinct and precise in time as shown in Table 1[4].

Table 1
***Stages of Diabetic Nephropathy*[4]**

Stage's	Clinical term	Histological Features	Functional Features	Clinical Features
Stage I	Initial Stage	Glomerular Hypertrophy	Increased GFR	Supra normal Clcr, Increased Kidney size.
Stage II	Early Renal involvement	GBM thickening Increased messangial matrix.	Increased GFR Normal UAE rate.	Supra normal Clcr,
Stage III	Incipient Nephropathy	Futhers GBM thickening and messangial matrix Expansion.	Increased UAE rate.	Persistently high UAE rates,Supranormal to normal Clcr,Increased in Blood pressure.
Stage IV	Clinical Nephropathy	Well-define diffuse and/or nodular diabetic glomerulosclerosis	Protenuria on routine urine analysis. Gradual reduction in GFR.	Proteinuria progressing to nephropatic syndrome , Established hypertention.Gradual increased in SCr.
Stage V	End Stage Renal Failure	Significant glomerular closure and obsolescence	GFR<15ml/min.	Hypertention.Anaemia, Uremic Syndrome.

Notes: Clcr: Creatinine Clearance, GFR: Glomerular filtration Rate, GBM: Glomerular basement membrane, SCr.: Serum Creatinine, UAE : Urinary albumin excretion.

ASSOCIATIONS OF HYPERLIPIDEMIA AND DIABETIC NEPHROPATHY

Dyslipidemia frequently accompanies renal disease, and a growing body of evidence emphasizes its importance in the pathogenesis and progression of renal injury [9, 10]. However more recently work explains that, hyperlipidemia accelerates the progression of diabetic nephropathy disease [11, 12] and lipid-lowering therapies reverse this effect [13, 14,15,16,17]. There is growing evidence that hyperlipidemia and hyperglycaemia both contributes diabetic nephropathy disease progression.

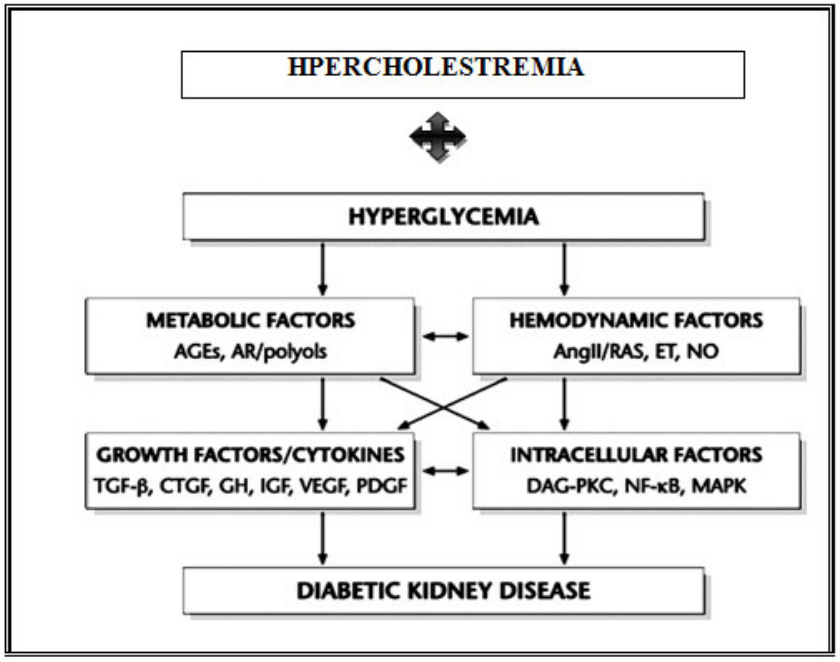

FIGURE 1

Schematic illustration of the potential hierarchy and interactions between metabolic, hemodynamic, and intracellular factors and growth factors/cytokines in the pathophysiology of diabetic kidney disease.

PROGRESSION OF DIABETIC NEPHROPATHY BY LIPIDS (Pathophysiology and mechanism involves)

Studies in a variety of animal models have shown that hypercholesterolemia accelerates the rate of progression of kidney disease [18]. A high-fat diet causes macrophage infiltration and foam cell formation in rats, leading to glomerulosclerosis [19]. In humans more than a decade ago, a relationship between serum cholesterol levels and glomerular filtration rate (GFR) decline was shown in 31 patients with type-1 diabetes and established overt nephropathy [5]. The power of serum cholesterol levels in predicting the progression of diabetic nephropathy [6] in type-1 diabetes was confirmed by the study done by Danish group with 301 patients of diabetes having overt nephropathy were followed for the period of 7 years [38,40]. A finding was observed by Appel and Radhakrishnan in study with type-2 diabetes and overtnepropathy patients reported that total cholesterol and LDL cholesterol measured at baseline were independent risk factors for ESRD (End stage renal disease) [39,40].

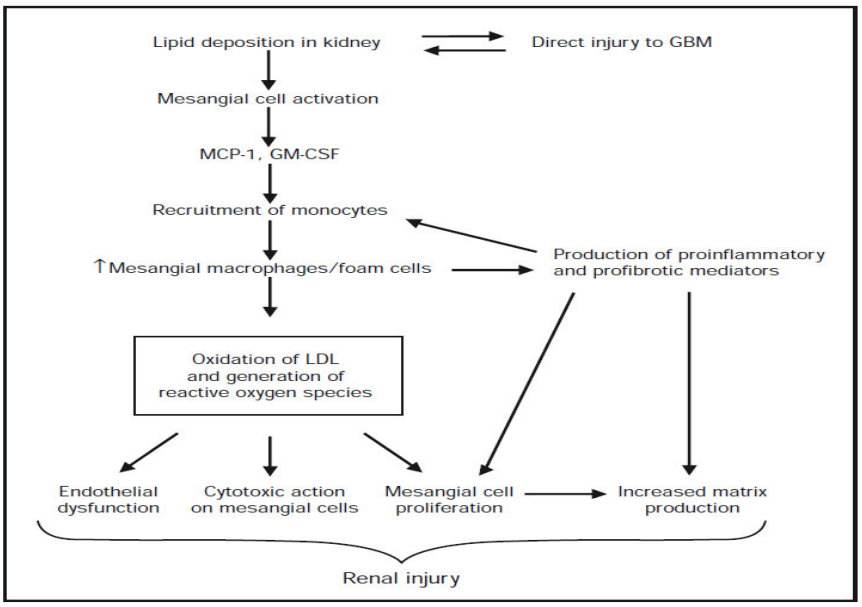

FIGURE 2
Schematic showing how lipid deposition can produce renal damage.

[GBM-Glomerular basement membrane, LDL-low density lipoprotein, MCP-1-Monocytes chemo attractant protein, GM-CSF-Granulocytes macrophages colony stimulating factor]

CHOLESTEROL LOWERING THERAPIES IN DIABETIC NEPHROPATHY
THERAPIES AFFECTING CHOLESTEROL SYNTHESIS

High cholesterol diets exacerbated the development of diabetic nephropathy with elevation in urine albumin excretion, glomerular and renal hypertrophy and mesangial matrix expansion. HMGCoA reductase inhibitors can reduce the endogenous cholesterol biosynthesis therefore imparting benefits to diabetic nephropathy.

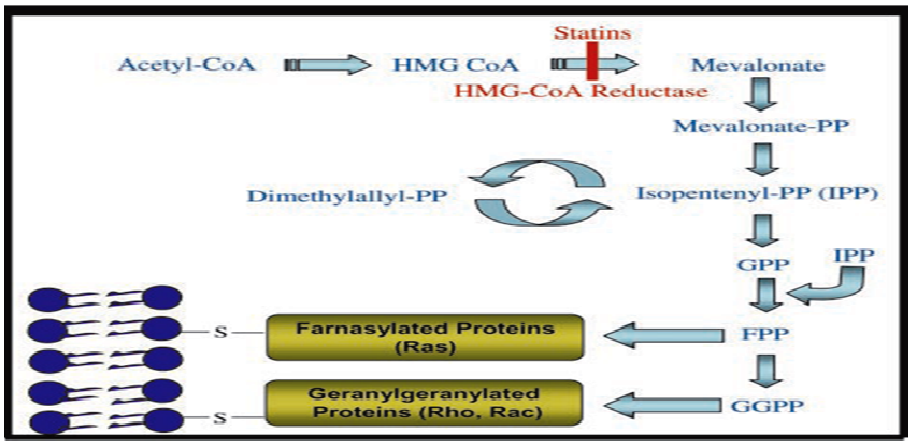

FIGURE 3
Mevalonate Pathway
(Mechanisms for the action of HMGCoA reductase inhibitors)

Diagram of the cholesterol biosynthesis pathway. By preventing isoprenylation of small GTPase proteins, HMGCoA reductase inhibitors lead to modulation of various signalling pathways.

HMGCoA reductase inhibitors or statins profile

3-Hydroxy-3-methyl-glutaryl CoA (HMGCoA) reductase inhibitors may confer renoprotection action through their lipid lowering properties [20]. It is usually assumed that the beneficial effects of HMGCoA reductase inhibitors result from the competitive inhibition of endogenous cholesterol biosynthesis. However, by inhibiting the synthesis of L-mevalonic acid HMGCoA reductase inhibitors may also exert effects by preventing the synthesis of various isoprenoids, such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) [21]. Both FPP and GGPP are important lipid attachments for the post translational modifications of a variety of small GTPase proteins, such as Ras and Rho GTPases [22]. However, transcriptional regulation of p21expression in a p53-independent manner by lovastatin has also been report [23]. HMGCoA reductase inhibitors inhibit the isoprenylation of Ras and Rho GTP-ase signalling pathway. These effects may lead to decreased monocyte/macrophage infiltration in the glomerulus, decreased mesangial proliferation and expansion. The modulation of Rho GTPase /p - 21 signalling pathway could be one of possible molecular mechanism by which HMGCoA inhibitors confer renoprotective action on diabetic nephropathy and by understanding the molecular mechanism, which will help to limit the progression of diabetic nephropathy and to develop selective-targeting approaches for statins to prevent diabetic nephropathy [24]. HMGCoA reductase inhibitors have been demonstrated to decrease TGF-β production and suppress the enhanced Ras-dependent activation of MAPK (Mitogen-activated protein kinase) cascade. HMGCoA reductase inhibitors lower the level of nuclear transcription factor (NF-$k\beta$) activity. Simvastatin decreased mesangial cell proliferation and monocyte/macrophage infiltration [25]. HMGCoA reductase inhibitors have been shown to inhibit the proliferative actions of PDGF (platelet-derived growth factor) and transforming growth factor beta (TGF-β) [26]. Clinical relevance of these observations is yet to be determined and trying to accumulating evidence in this review. Data suggested that neomycin has been shown to reduce intestinal cholesterol absorption in dose dependent manner by 26%-49% [27]. Several other compounds have been noted like Acyl-CoA cholesteryl acyl transferase (ACAT) inhibitors, microsomal triglyceride transfer protein (MTP) inhibitors, bile acid sequestrant, ursodeoxycholic acid, fibrate/HMGCoA reductase inhibitors plant stanol ester etc.

Classification of HMGCoA reductase inhibitors

There are a number of classification criteria for statins, including:1) how they are obtained, 2) liver metabolism, 3) physicochemical properties, 4) Specific activity. (1)How they are obtained**:** statins are obtained after fungal fermentation**:** lovastatin (Mevacor), pravastatin (Lipostat, Pravachol) and simvastatin (Zocor), others by synthesis: fluvastatin (Lescol), atorvastatin (Sortis, Lipitor). (2)Liver metabolism**:** All statins have the liver as target organ. The percentage of the dose retained by the liver is as follows: >70% for fluvastatin and lovastatin, >80% for simvastatin and 46% for pravastatin [25].(3)Physico-chemical properties**:** Pravastatin is extremely hydrophilic, fluvastatin has intermediate characteristics, and lovastatin, simvastatin, atorvastatin and cerivastatin are hydrophobic [26.] (4)Specific activity**:** Atorvastatin, cerivastatin, fluvastatin and pravastatin are administered as active compounds (acid form). Lovastatin and simvastatin are administered as inactive forms (lactones), which have to be enzymatically hydrolyzed to generate active forms [26].

THERAPIES AFFECTING INTESTINAL CHOLESTEROL ABSORPTION

Many compounds have been noted to inhibit the intestinal cholesterol absorption. In comparison to other compound, ezetimibe was more pronounced to limit the progression of diabetic nephropathy [23, 24.]

Intestinal cholesterol absorption inhibitors profile

Ezetimibe (formerly known as SCH 58235) is a compound of the 2-azetidinone class that has been shown to produce a marked

inhibition of intestinal cholesterol absorption (up to 96%) in animals [27, 36]. Ezetimibe (and/or its phenolic glucuronide) acts at the brush border of the small intestine and inhibits the uptake of dietary and biliary cholesterol into the enterocytes. In comparison to other compound the intestinal inhibition of cholesterol by ezetimibe was pronounced than that observed for others inhibitors. Report suggested that maximal effect is observed when delivered in fat carriers in conjugation with fat meals, but does not appear to affect the absorption of triglycerides or fat-soluble vitamins. Ezetimibe, a drug that has been recently registered, produce a selective inhibition of cholesterol absorption in small intestine [28]. Ezetimibe has been shown to inhibit cholesterol absorption in animal model as well as in human [29].Several reports of clinical trial have revealed plasma LDL cholesterol lowering action of ezetimibe [30, 31].Reports underline that, the reduced intestinal cholesterol absorption was compensated by increase in cholesterol synthesis mainly ***de novo*** hepatic cholesterol synthesis, so it is co administered with HMGCo A reductase inhibitors. HMGCoA reductase inhibitors can reduce the compensatory increase in hepatic cholesterol synthesis [36]. Therefore the combination of ezetimibe and HMGCoA reductase inhibitors result in incremental lowering in LDL cholesterol and could be therapeutic choice to control the diabetic nephropathy.

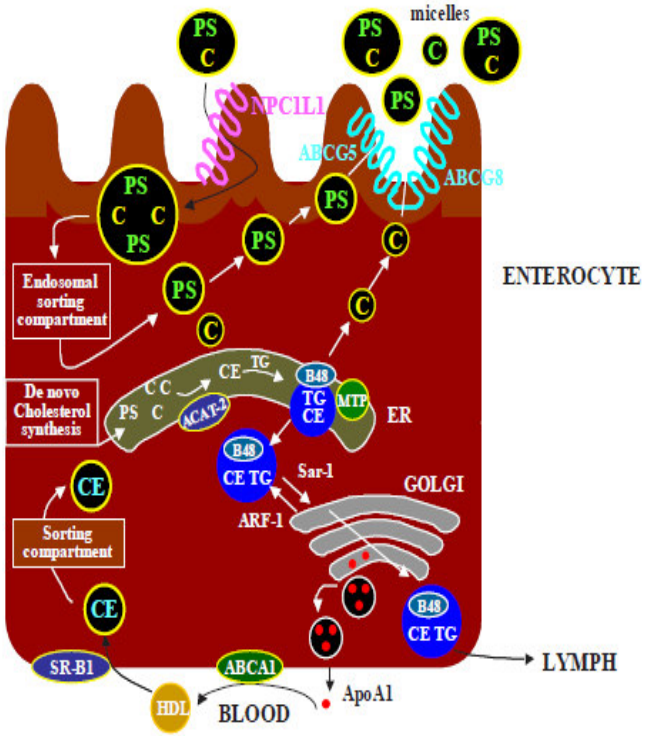

FIGURE 4
Mechanism of intestinal absorption of cholesterol

Overview of the principal steps in the intestinal absorption of cholesterol (C). The intraluminal phase involves the digestion/hydrolysis of dietary lipids and micellar solubilisation of cholesterol. The membrane transport phase involves cholesterol release from micelles at the brush border membrane and uptake into enterocytes via several sterol transporters, including Niemann-Pick C1like 1 protein (NPC1L1), amino peptidase N (CD13), and annexin-2/caveolin-1 (ANX2/CAV1). The brush border membrane also contains ATP-binding cassette (ABC) transporters (ABCG5 and ABCG8), which primarily move plant sterols and to a lesser extent cholesterol out of the enterocytes

CURRENT STATUS OF STATIN AND INTESTINAL CHOLESTEROL ABSORPTION INHIBITORS

U.S. Food and Drug Administration approved LIPTRUZET™ (ezetimibe and atorvastatin) Tablets, Merck Inc. Co., USA. in 2013. According to Medlineindia online available reports suggested that several combination of Atorvastatin (5-20 mg) and Simvastatin (10-20 mg) with Ezetimibe (10-20 mg) are marketed by various manufacturers in India.Central Drug Standard Control Organization (CDSCO), Director General of Health Services, Ministry of health and family welfare, Govt. of India realised the following data.

Table 2
Fixed Dose Combinations Approved by Drug Controller General-India [DCG (I)] Till December, 2013

Sr.No	Name of Drug	Indication	Date of approval
1.	Atorvastatin 10mg/20mg + Ezetimibe10mg/10mg tablet	For the treatment of patients with primary hypercholesterolemia □	08.11.2004 □
2.	Ezetimibe 10mg/10mg + Simvastatin 10mg/20mg FC Tablet □	For the treatment of patients with primary hypercholesterolemia □	05.11.2005 □
3.	Simvastatin (10/20mg) + Ezetimibe (10mg/10mg) Tablets □	For primary Hypercholesterolemia	05.11.2005
4.	Rosuvastatin calcium eq. to Rosuvastatin 10mg + Ezetimibe 10mg tablets □	For the treatment of patients with primary hypercholesterolemia. □	23.02.2007
5.	Ezetimibe 10mg + Fenofibrate 160mg tablet	For combined hypertipidemia	04.04.07 □
6.	Atorvastatin (40mg) + Ezetimibe (10mg) Tablet (addl. Strength). □	For the treatment of patients with primary hypercholesterolemia □	30.07.2007
7.	Ezetimibe 10 mg + Fenofibrate 145 mg Film coated tablets □	For the treatment of combined hyperlipidemia in patients with normal hepatic and renal function □	01.09.2009
8.	Rosuvastatin Calcium IP eq to Rosuvastatin 5mg + Ezetimibe 10mg. (Additional Strength)	For the treatment of patients with primary hypercholesterolemia.	05.12.11 □

Thus the accumulated reports and findings illustrated that by inhibition of cholesterol synthesis and by inhibition of intestinal cholesterol absorption could limit the progression of severity of diabetic nephropathy in dyslipidemic subjects and it is yet to explore more.

CONCLUSION AND FUTURE DIRECTION

Recent literature reviews have suggested that high cholesterol diet lead to severity of diabetic nephropathy. Better understanding of cholesterol lowering therapies has a potential to lead to development of more effective renoprotective agent for use in clinical setting and could be a therapeutic option in subject with diabetic nephropathy. Our review, that is in continuation that the use of cholesterol lowering therapies may provide potential therapeutic beneficial to renoprotechtion which will limit the progression of DN. These therapies may be considered as novel therapies which target the diseases. It is hoped that information generated from this review will may help in developing such renoprotective therapies that may use in clinical setting. Finally, the finding of from this review will give impetus for future investigation to study novel cholesterol lowering therapies on diabetic nephropathy.

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