Kawanami et al. Renal Replacement Therapy (2016) 2:16
DOI 10.1186/s41100-016-0028-0

Renal Replacement Therapy

REVIEW Open Access

Dyslipidemia in diabetic nephropathy

Daiji Kawanami*, Keiichiro Matoba and Kazunori Utsunomiya

Abstract

Diabetic nephropathy (DN) not only is a major cause of end-stage renal disease (ESRD) in developing and developed countries but also plays a critical role as a risk factor for cardiovascular disease. The pathogenesis of DN is multifactorial and remains to be elucidated. It is well known that dyslipidemia is frequently complicated with diabetes. Recently, dyslipidemia has been recognized to be involved in the progression of DN. In general, diabetic dyslipidemia is caused by impaired action of lipoprotein lipase (LPL) that is localized to the endothelial cells, resulting in increased serum levels of increased triglyceride (TG) and decreased high-density lipoprotein cholesterol (HDL-C). Smaller size and modified low-density lipoprotein (LDL), such as glycated and oxidized LDL, play important roles to induce vascular and renal cellular dysfunction. Previous studies demonstrated that dyslipidemia enhances macrophage infiltration and excessive extracellular matrix (ECM) production in the glomeruli under diabetic conditions, leading to the development of DN. Clinical studies have demonstrated that lipid-lowering therapy shows a protective effect on the renal function. It is well known that statins reduce albuminuria in patients with DN. A series of our studies indicated that this effect is mediated by Rho-kinase inhibition. Rho-kinase plays a key role in the pathogenesis of DN by activating the inflammatory pathway, including oxidative stress, NF-κB, and hypoxia inducible factor (HIF)-1. Intriguingly, Rho-kinase inhibitors have been shown to attenuate glomerulosclerosis as well as atherosclerosis. Therefore, Rho-kinase could be a promising therapeutic target for both DN and cardiovascular disease.

Keywords: Diabetic nephropathy, Dyslipidemia, Cardiovascular disease, Statin, Rho-kinase

Background

Dyslipidemia, an important risk factor for cardiovascular disease, is frequently complicated with diabetic nephropathy (DN). Managing dyslipidemia in DN is extremely important because patients with DN are at a high risk for cardiovascular disease-associated death [1]. Furthermore, dyslipidemia has been shown to play crucial roles in the development and progression of DN [2]. Impaired lipoprotein metabolism, such as increases in very low density lipoprotein (VLDL-C) and low-density lipoprotein cholesterol (LDL-C) and a decrease in high-density lipoprotein cholesterol (HDL-C), is observed in patients with diabetes [3]. In addition to these quantitative changes, quality changes including small dense LDL [4] and oxidized LDL (ox-LDL) make lipoproteins more proatherogenic in diabetes. This review article describes our current understanding of the role of dyslipidemia in the development of DN and the significance of lipid-lowering therapy for the prevention of cardiovascular disease and DN.

Etiology and epidemiology of diabetic dyslipidemia

Typically, patients with type 2 diabetes show increased serum levels of triglyceride (TG) and decreased HDL-C. Furthermore, modifications of LDL, such as glycation and oxidation, are enhanced under diabetic conditions. The prevalence of high LDL-C in patients with diabetes appears to be similar to that of the general population, as demonstrated by the Framingham Study and the United States National Health and Nutritional Examination Survey (NHANES) [5]. In the United Kingdom Prospective Diabetes Study (UKPDS), no differences in total cholesterol levels were reported between diabetic and non-diabetic subjects. The LDL-C levels were comparable in males but higher in females with type 2 diabetes compared to those without type 2 diabetes [6]. On the other hand, increased serum levels of TG and

* Correspondence: daijika@jikei.ac.jp
Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Jikei University School of Medicine, 3-25-8 Nishi-shinbashi, Minato-ku, Tokyo 105-8461, Japan

decreased HDL-C were reported in diabetic patients in these studies. In the Framingham Study, an elevation in serum was observed in 19 % of males and 17 % of females with type 2 diabetes, whereas it was observed in 9 % of males and 8 % of females in non-diabetic subjects [7]. In the UKPDS, 50 % of patients with type 2 diabetes had high serum levels of TG [6]. The Heart Protection Study (HPS) showed that the prevalence of low HDL-C was higher in diabetic individuals (21 % in males and 25 % in females) compared to non-diabetic individuals (12 % in males and 10 % in females) [8].

Lipid metabolism in diabetes and DN

As described above, dyslipidemia in diabetes is characterized by an increase in VLDL, LDL, and TG and a decrease in HDL [9]. Under the diabetic milieu, hormone-sensitive lipase is activated, which results in the release of free fatty acid (FFA) from the adipose tissue. The flux of FFA promotes hepatic triglyceride production, leading to excessive apoB and VLDL synthesis [9]. In addition, lipoprotein lipase (LPL) activity is suppressed under the condition of insulin resistance [10]. These changes result in an increase in the serum levels of TG and remnant particles. Apolipoprotein (apo) B48, a major component of chylomicron, is also increased in diabetes, suggesting an accumulation of chylomicron remnants [11]. It has been demonstrated that insulin resistance is aggravated along with the progression of DN, even in the early stage of microalbuminuria [12]. An elevation in the serum levels of apoC-III, an inhibitor of LPL, is also observed in subjects with DN [3].

It has been reported that the serum level of apoB100 is increased in DN [13]. ApoB100 is synthesized in the liver and transferred into VLDL or LDL particles at one molecule per particle. Therefore, a high serum level of apoB100 indicates an increment in the number of VLDL and LDL particles.

Cholesteryl ester transfer protein (CETP) mediates exchange of cholesteryl ester and TG. CETP activity is regulated by apoC-I, a physiological CETP inhibitor. Recently, Bouillet et al. demonstrated that apoC-I's ability to inhibit CETP activity is impaired in diabetic patients [14], which is explained by glycation of apoC-I [14]. Furthermore, it has been shown that the CETP levels are increased in ESRD patients, although the precise mechanism remains unknown [15, 16]. VLDL receives cholesteryl ester from HDL and transfers TG to HDL by CETP. As a consequence, the amount of cholesterol-rich VLDL remnant particles and cholesterol-depleted HDL particles are increased. TG-rich HDL can be hydrolyzed by LPL or hepatic TG lipase (HTGL), thereby becoming lipid-poor HDL which is filtered by the glomeruli and degraded in renal tubular cells [4]. Insulin has been shown to play an important role in the production of apoA-I, which is a major apolipoprotein of HDL [17, 18]. As such, reduced insulin action is potentially involved in the low HDL levels in type 2 diabetes, especially complicated with DN. Furthermore, inflammatory cytokines including tumor necrosis factor (TNF)-α have been shown to inhibit the production of apoA-I and HDL [17]. Nevertheless, the mechanism underlying low HDL in diabetes is complicated and remains unclear.

Ox-LDL is a well-known atherogenic lipoprotein that is modified by oxidation [4]. Recently, small dense LDL is recognized as another important atherogenic lipoprotein due to its potent oxidative property. The serum level of small dense LDL is increased in insulin resistance and diabetes [3]. Of note, the serum level of small dense LDL is reportedly elevated in patients with DN [3], which may be associated with an increased risk for cardiovascular disease in DN.

Impairment of the renal function by lipids

It has been recognized that lipid nephrotoxicity is involved in the development of DN since the 1970s [19]. Previous studies have shown that dyslipidemia facilitates glomerulosclerosis under diabetic conditions. Dyslipidemia complicated with diabetes has been shown to be involved in the development of DN. We have previously demonstrated that hypercholesterolemia exaggerates albuminuria in diabetic rats [20]. From a mechanistic standpoint, this was the first report to demonstrate the involvement of macrophage infiltration into the glomeruli in the progression of DN [20]. Furthermore, excessive extracellular matrix (ECM) production was found in the glomeruli of diabetic LDL receptor-deficient mice [21]. Finally, lipid-lowering therapy has been shown to improve glomerulosclerosis in the Zucker rat, a model of diabetes complicated with dyslipidemia [22]. Mesangial cells and glomerular epithelial cells (podocytes) have been shown to express receptors for TG-rich lipoproteins (TGRLs) [23–26]. TGRLs stimulate inflammatory pathways via the secretion of proinflammatory cytokines such as TNF-α, transforming growth factor (TGF)-β, and interleukin (IL)-6 [27], which results in the production of reactive oxygen species (ROS), leading to excessive ECM production. It has also been reported that ROS itself potentiates TGF-β-mediated signaling, which may cause a vicious cycle in the process of excessive ROS and ECM production [2, 28]. Ox-LDL binds to scavenger receptors in mesangial cells and podocytes [29, 30], thereby increasing ECM production as well as chemokine production, such as monocyte chemoattractant protein (MCP)-1 which induces monocyte migration toward the glomeruli and results in macrophage infiltration [31]. Macrophages become foam cells through the uptake of ox-LDL and facilitate the inflammatory pathway.

Several factors, including sterol regulatory element binding protein (SREBP)-1 and Toll-like receptor (TLR) 4, have been shown to mediate lipid nephrotoxicity [32, 33]. The expression of SREBP-1, an important regulator of cellular lipid synthesis [34], is upregulated in STZ-induced diabetic rats. Interestingly, the progression of DN is inhibited in SREBP-1-deficient mice. The development of DN is also inhibited in TLR4-deficient mice fed a high-fat diet [32, 33].

Another mechanism by which TGRLs induce glomerulosclerosis is disruption of the endothelial cell glycocalyx [2]. The glycocalyx is composed of proteoglycans, glycoproteins and glycosaminoglycans and located at the interface between the lumen and endothelial surface [35]. The glycocalyx maintains the endothelial function and regulates glomerular permeability depending on the size and charge of the solute [2]. It has been reported that the volume of systemic glycocalyx was significantly lower in patients with type 1 diabetes than in age-matched control individuals [36]. More interestingly, patients with microalbuminuria showed lower volumes of systemic glycocalyx compared to those without microalbuminuria [36], suggesting that disruption of the glycocalyx may cause alterations in glomerular permeability, leading to albuminuria.

Glycation of LDL has been shown to be involved in the development of DN. Glycated LDL is a modified LDL which is generated by non-enzymatic binding of glucose to LDL. Advanced glycation end-products (AGEs) and receptor for AGEs (RAGE) are considered to play critical roles in the pathogenesis of diabetic vascular complications [37]. RAGE recognizes multiple AGE-moieties as ligands including glycated LDL, thereby inducing inflammatory and fibrotic responses [38]. Taken together, abnormal changes in the quantity and quality of lipoproteins occur in DN, which in turn coordinately promote impairment of the renal function in diabetes (Fig. 1).

Significance of lipid-lowering therapy in DN

Statins and Rho-kinase

A significant body of evidence has shown the efficacy and usefulness of statins in the management of DN through its pleiotropic effects beyond lipid-lowering effects [39, 40]. Our previous study was the first report to demonstrate a favorable effect of statins on the reduction of albuminuria in patients with type 2 diabetes [41]. Several studies including the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) [42] and Pravastatin Pooling Project [43] demonstrated that statins may be effective for maintaining the eGFR in patients with type 2 diabetes. In the Treating to New Target (TNT) study, atorvastatin increased the eGFR in patients with chronic kidney disease (CKD) [44]. Intriguingly, the Collaborative Atorvastatin Diabetes Study (CARDS) showed that atorvastatin improved the eGFR

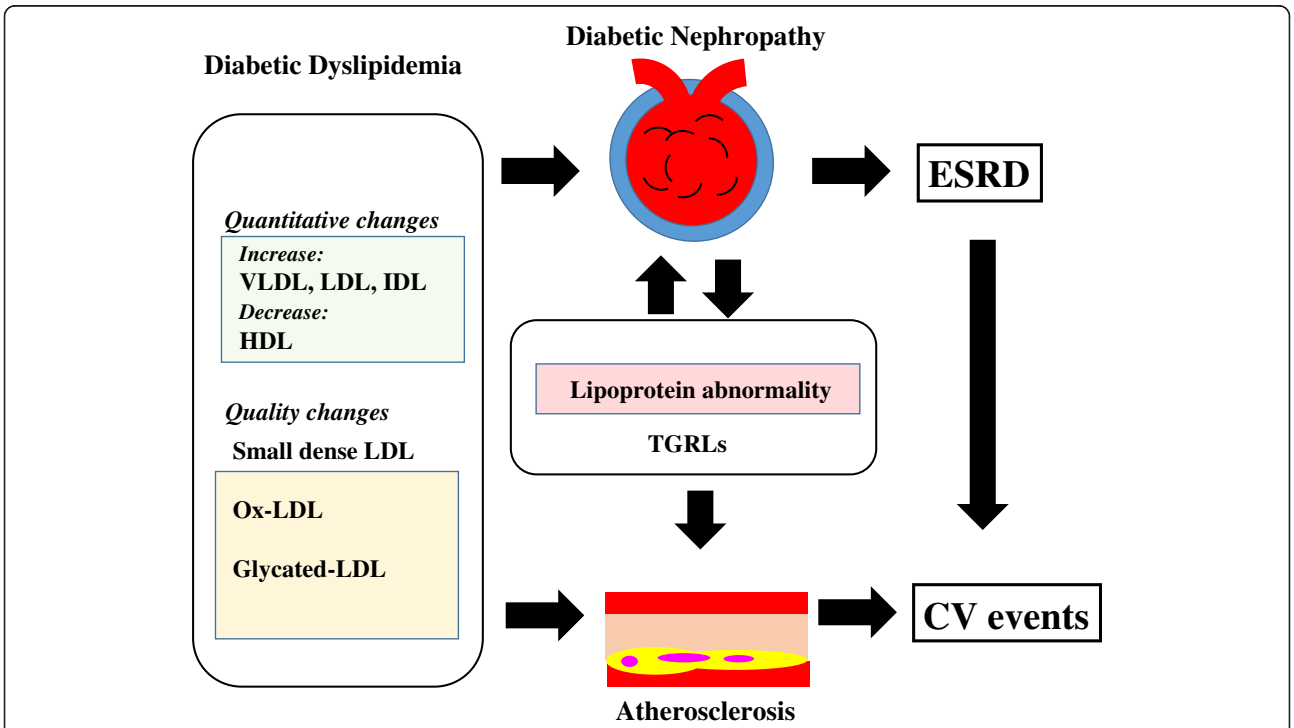

Fig. 1 Role of dyslipidemia in diabetic nephropathy. Dyslipidemia promotes the development of diabetic nephropathy. Abnormal lipoprotein metabolism is accelerated in diabetic nephropathy that causes further renal injury, leading to ESRD as well as cardiovascular (CV) events

in patients with diabetes, in particular, those with albuminuria [45]. Thus far, many groups have focused on the mechanism whereby statins exhibit the renal protective effect.

It is known that statins downregulate small GTP-binding proteins and their downstream signaling pathways, including Rho/Rho-kinase activity [46]. The small GTP-binding protein Rho and its effector, Rho-associated kinase (Rho-kinase), have been implicated as regulators of cell shape changes by rearrangements of the actin cytoskeleton [47]. Rho cycles between an inactive GDP-bound form and an active GTP-bound form in response to various stimuli. GTP-bound Rho activates its effector proteins (e.g., Rho-kinase) to initiate a downstream response [48–50] (Fig. 2). To bind GTP, Rho necessarily undergoes isoprenylation (geranylgeranylation), which enables Rho to anchor into the plasma membrane with a hydrophilic property. Statins inhibit the synthesis of isoprenoids (geranylgeranyl pyrophosphate and farnesyl pyrophosphate), intermediates of the cholesterol synthetic pathway, which results in the suppression of Rho activity (Fig. 3). Hence, we hypothesized that Rho/Rho-kinase may be involved in the development of DN. We found that Rho/Rho-kinase activity is increased in the renal cortex of streptozotocin (STZ)-induced diabetic rats. Interestingly, fasudil, a specific Rho-kinase inhibitor, and fluvastatin ameliorated urinary excretion of albumin concomitantly with a reduction in urinary excretion of 8-hydroxy-2′-deoxyguanosine (8-OHdG), an oxidative stress marker [51], suggesting that fasudil improves DN through the reduction of oxidative stress. Indeed, the expression of NOX4 messenger RNA (mRNA), a catalytic subunit of renal NADPH oxidase, was suppressed in the renal cortex of diabetic rats treated with fasudil. An additional mechanistic analysis revealed that the expression of TGF-β and connective tissue growth factor (CTGF) in the renal cortex of diabetic rats was attenuated with fasudil treatment [51]. These findings indicate that the Rho/Rho-kinase pathway plays a key role in the development of DN. We further investigated the effect of Rho-kinase inhibition on hypoxia inducible factor (HIF)-1α, a transcriptional factor which has been implicated in the pathogenesis of DN [52]. Although HIF-1α was shown to be upregulated in the renal cortex of diabetic mice (*db/db* mice), Rho-kinase blockade attenuates HIF-1α induction and the subsequent fibrotic response under diabetic conditions [53]. It was also suggested that this change in HIF-1α was partly due to the regulation of proteasomal degradation of HIF-1α by Rho-kinase [53].

We next elucidated the role played by the Rho/Rho-kinase pathway in macrophage infiltration into the glomeruli. TNF-α, a potent inflammatory cytokine which is involved in insulin resistance, induced the activation of Rho/Rho-kinase and the expression of MCP-1 in cultured mesangial cells. Y-27632, a specific inhibitor of Rho-kinase, attenuated TNF-α-induced MCP-1 expression, indicating that TNF-α stimulates MCP-1 production via a Rho/Rho-kinase-dependent pathway. This was also confirmed by a chemotaxis assay demonstrating that monocytic migration toward mesangial cells was suppressed by a Rho-kinase inhibitor [54]. The expression of macrophage colony-stimulating factor (M-CSF), another important chemotactic cytokine, was also induced by TNF-α via activation of Rho-kinase in cultured mesangial cells [55]. Small interfering RNA-mediated knockdown of ROCK1 and ROCK2, two isoforms of

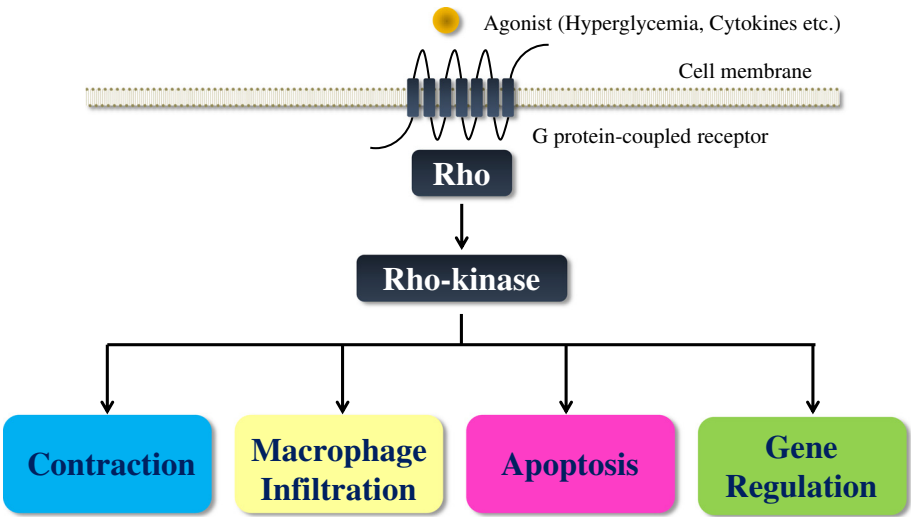

Fig. 2 Rho/Rho-kinase. The small GTP-binding protein, Rho, and its downstream effector, Rho-associated kinase (Rho-kinase (ROCK)), are involved in various cellular functions. Under diabetic conditions, the Rho/Rho-kinase pathway is activated. Transcription factors that are involved in inflammatory response (e.g., NF-κB, HIF-1) are regulated by Rho/Rho-kinase

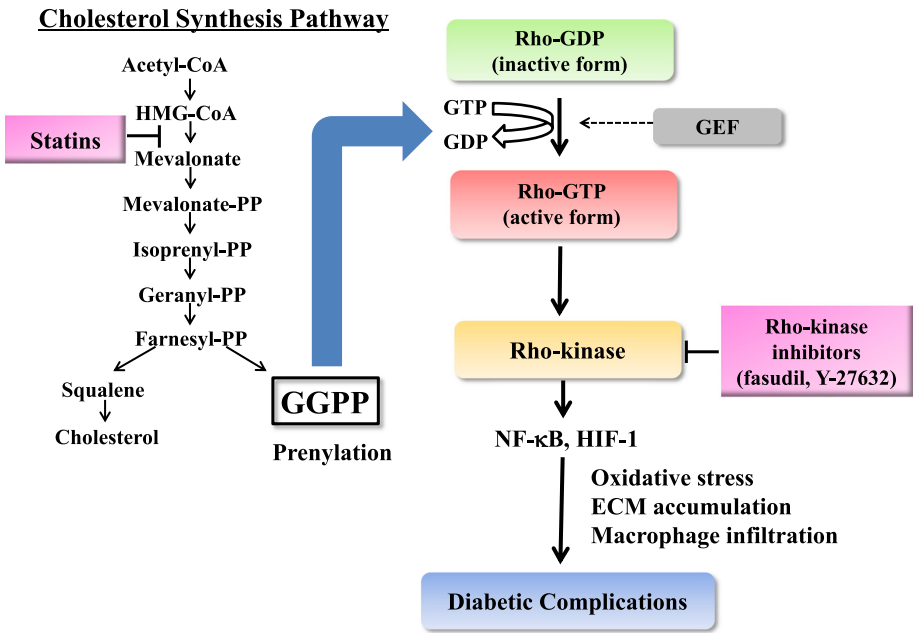

Fig. 3 Inhibition of Rho/Rho-kinase by statins. The pleiotropic effect of statins is exerted by Rho-kinase inhibition. Statins inhibit the production of isoprenoids, which are important for Rho activation. Rho-kinase inhibitors specifically inhibit Rho-kinase function, thereby strongly attenuating diabetic complications. *GGPP* geranylgreanyl pyrophosphate, *GEF* guanine nucleotide exchange factors

Rho-kinase, indicated that both isoforms have a comparable contribution to the M-CSF expression in mesangial cells. Nuclear translocation and subsequent DNA binding of NF-κB RelA/p65 to the promotor site are critical steps for the transcriptional regulation of M-CSF. We found that TNF-α enhances nuclear translocation of RelA/p65 in cultured mesangial cells. Interestingly, Rho-kinase inhibitor suppressed nuclear translocation of RelA/p65 and accordingly reduced the promoter activity of the NF-κB binding site [55]. This study provided new insight on the role of Rho-kinase, demonstrating that Rho-kinase may regulate intracellular translocation of transcriptional factors, likely through re-organization of actin stress fibers. Finally, we have shown that Rho-kinase blockade attenuates other microvascular complications such as diabetic retinopathy [56] and neuropathy [57], as well as atherosclerosis [58]. Importantly, the effect of Rho-kinase inhibitors on diabetic complications is independent of glucose and blood pressure [51, 53]. These findings suggest that Rho-kinase could be a comprehensive therapeutic target that governs both microvascular and macrovascular complications.

A previous study showed that Rho-kinase inhibition attenuates dyslipidemia-mediated CKD [59]. The study investigated the effects of fasudil on spontaneously hypercholesterolemic (SHC) rats, an animal model of CKD. The rats developed proteinuria accompanied by Rho-kinase activation in the renal cortex. Intriguingly, fasudil significantly attenuated proteinuria in SHC rats. Furthermore, the combination of fasudil and olmesartarn exaggerated this effect [59]. A mechanistic analysis revealed that fasudil inhibited the infiltration of macrophages into the glomeruli and podocyte injury, thereby exerting protective effects against dyslipidemia-mediated CKD [59]. It will be interesting to elucidate the relationship between Rho-kinase and dyslipidemia in DN in the future.

Fibrates

The mechanism by which fibrates ameliorate hypertriglyceridemia remains unknown; however, PPARα agonistic property is considered to play a role in the effects of fibrates. PPARα is expressed in the kidney and reported to possess a renal protective effect in a lipid-lowering-independent manner. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study demonstrated that fenofibrate suppresses the development and progression of DN [60]. Furthermore, the FIELD study revealed that long-term administration of fenofibrate retains the eGFR decline rate [61]. The Action to Control Cardiovascular Risk in Diabetes (ACCORD)-Lipid study investigated the effect of combination therapy with simvastatin and fenofibrate [62]. Compared to the control group (simvastatin alone), the combination therapy group (simvastatin plus fenofibrate) significantly suppressed the development of both microalbuminuria and overt proteinuria in patients with type 2 diabetes [62]. In this study, 47.4 % of the type 2 diabetic participants

showed a ≥20 % increase in serum creatinine levels from baseline after the initiation of fenofibrate therapy. However, this increase was reversible and there was no residual loss of eGFR over 5 years [63]. On the other hand, 24.6 % of the participants had no increase in serum creatinine levels [63]. Of note, the participants with no increase in serum creatinine levels after the initiation of fenofibrate therapy appeared to have a lower degree of renal function loss over 5 years of therapy in comparison to the patients who received a placebo [63]. Taken together, these results indicate that fenofibrate has protective effects against DN. However, it has been reported that serum creatine levels are increased or unchanged after fenofibrate treatment [64–66]. Although fenofibrate treatment has been reported to alter the renal hemodynamics [67] and induce the secretion of creatinine from the renal tubules [68], the precise mechanisms by which fenofibrate increases the serum creatinine levels are not fully understood.

Interestingly, bezafibrate has been shown to improve glucose metabolism in diabetic individuals [69]. In this study, dyslipidemic patients with diabetes were administered bezafibrate along with anti-diabetic agents. A 24-week administration of bezafibrate resulted in a significant reduction in the HbA1c levels [69]. In relation to enhancement of β-oxidation of fatty acid by bezafibrate, two potential mechanisms have been raised according to these observations. First, bezafibrate improves fatty acid accumulation in β cells, thereby improving insulin secretion. Second, fat accumulation in the liver and muscles are reduced by bezafibrate [69, 70]. Such effect of fibrates regarding the improvement in lipotoxicity and insulin resistance may be beneficial for DN.

Ezetimibe

Ezetimibe is an inhibitor of a cholesterol transporter in the small intestine (NPC1L1). The Study of Heart and Renal Protection (SHARP) investigated the efficacy and safety of ezetimibe in 9270 patients with CKD (including 3203 patients on dialysis) [71]. In this study, the patients were randomized into the control and simvastatin-ezetimibe combination therapy groups. A significant reduction in LDL-C was observed in the simvastatin-ezetimibe group. Simvastatin-ezetimibe combination therapy also reduced atherosclerosis-related events by 17 % in comparison to patients who received a placebo. The combination of ezetimibe and simvastatin did not worsen the renal function [71]. SHARP is the first study to demonstrate that combination of a statin and ezetimibe is effective in preventing atherosclerosis-associated vascular events without adverse effect on the kidney in patients with CKD. In SHARP, the effects of simvastatin-ezetimibe combination therapy on CKD progression in 6245 non-dialyzed CKD patients were also analyzed [72]. More than 60 % of the patients in the study had advanced CKD (eGFR of <30 ml/min/1.73 m^2) and 15 % of patients had DN [72]. Simvastatin-ezetimibe combination therapy was not associated with a significant change in the incidence of ESRD, while it doubled the baseline creatinine level and led to a decline in the eGFR rate in comparison to patients who received a placebo [72]. These findings indicate that in CKD patients, therapy to lower LDL-C prevents atherosclerotic disease but not the progression of renal disease. To date, SHARP is the largest trial to examine the effects of lipid-lowering therapy in patients with advanced CKD. Further studies will be required to elucidate whether lipid-lowering therapy has preventive effects against the progression of early stage DN. SHARP provided evidence that CKD patients should be indicated for lipid-lowering therapy to prevent atherosclerotic events, regardless of their stage of CKD.

PUFAs

The long-chain polyunsaturated fatty acids (PUFAs) consist of omega-6 PUFAs (e.g., arachidonic acid (AA)) and omega-3 PUFAs (e.g., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)). Omega-6 PUFAs are absorbed through the consumption of plant oils such as canola, which is rich in linoleic acid, and omega-3 PUFAs (EPA and DHA) are absorbed through fish consumption. Among them, fish-oil-derived long-chain omega-3 PUFAs have been shown to attenuate glomerulosclerosis and albuminuria in several investigations on experimental DN [73–75]. Hasegawa et al. reported that an intraperitoneal infusion of ethyl-EPA significantly decreased albuminuria along with inhibition of glomerulosclerosis in KKAy/Ta mice, a model of type 2 diabetes [73]. A mechanistic analysis showed that these observations were mediated by the anti-inflammatory and anti-oxidative stress effects of EPA [74].

A retrospective analysis from the Diabetes Control and Complications Trial (DCCT) revealed that the dietary intake of long-chain omega-3 PUFAs is inversely associated with the degree, but not with the incidence, of albuminuria in type 1 diabetes [76]. A cross-sectional analysis investigating the association between fish consumption and microalbuminuria with or without diabetes has been performed [77]. It demonstrated that no significant association was detected between fish consumption and the incidence of microalbuminuria in patients with or without diabetes, but importantly, diabetic patients that consumed more than two portions of fish a week showed a lower risk for macroalbuminuria than those who consumed less than one portion a week [77]. These epidemiologic studies suggest the potential favorable effect of long-chain omega-3 PUFAs on DN. However, clinical interventional studies investigating the

effect of PUFAs on DN yielded inconsistent findings. Two studies which investigated the effect of long-chain omega-3 PUFAs supplementation on albuminuria in patients with type 1 diabetes failed to show a significant reduction in albuminuria [78, 79]. In contrast, EPA supplementation resulted in a significant reduction in albuminuria in Japanese patients with type 1 and type 2 diabetes [80, 81]. Racial disparities may be involved in these discrepancies, as it has been suggested that the response to long-chain omega-3 fatty acid or fish consumption may differ between Western and Asian populations [82]. Taken together, further clinical studies are required to determine the effect of PUFA consumption and supplementations on DN.

End-stage renal failure and lipid-lowering therapy

The effect of lipid-lowering therapy on the prevention of cardiovascular events has been established in patients with moderate CKD. A meta-analysis indicated that the effectiveness of statins is independent of moderate impairment of the eGFR [83]. In contrast, evidence is lacking regarding the usefulness of statins in ESRD. The Deutsche Diabetes Dialyse Studie (4D; the German Diabetes Dialysis Study) investigated whether atorvastatin may affect cardiovascular events in type 2 diabetic patients on hemodialysis [84]. After a 4-year follow-up, atorvastatin reduced the LDL-C level by approximately 40 % but failed to improve cardiovascular events [84]. The AURORA trial (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) obtained similar results [85]. Rosuvastatin significantly reduced the LDL-C levels, but it was not able to inhibit cardiovascular events [85]. However, a sub-analysis of the AURORA trial demonstrated that rosuvastatin reduced cardiovascular events (32 % reduction compared to control) in patients with diabetes on hemodialysis [86]. On the other hand, statin therapy failed to show secondary prevention of cardiovascular events in the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) study [87]. In this study, statin therapy was initiated at discharge to patients who were hospitalized due to new-onset myocardial infarction. During a 1-year follow-up, statin use significantly inhibited cardiac death in patients with an eGFR (ml/min/1.73 m^2) of 15 and over. Statin use at discharge was associated with an improved 1-year survival of patients with mild-to-severe renal insufficiency. However, this effect was attenuated in patients with ESRD [87]. Taken together, evidence has not yet been established for statin use in preventing cardiovascular disease in ESRD patients. Further studies are required to investigate whether the presence of diabetes affects the effectiveness of statin use in ESRD.

Conclusions

Dyslipidemia is an important therapeutic target in the treatment of diabetes. Furthermore, DN accelerates abnormal lipoprotein metabolism, which causes the progression of DN as well as cardiovascular disease. Statin use should be considered for patients with DN to prevent cardiovascular events and renal impairment. However, further evidence is required to establish the benefits of statin use in patients with ESRD.

There is growing evidence that Rho-kinase plays a key role in the development and progression of DN. Statins inhibit Rho-kinase activation, which may be responsible for the pleiotropic effects of statins. Our recent findings raise the possibility that the use of Rho-kinase inhibitors along with statins provides a more potent and specific protective effect on DN.

Lipid-lowering therapy other than statins, such as fibrate, is also important. However, it should be noted that the combination of statin and fibrate is contraindicated for patients with moderate to severe renal impairment. The clinical background of each patient should be taken into account before starting lipid-lowering therapy.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DK planned the study, searched the literature, and wrote the manuscript. KM assisted in the manuscript preparation. KU helped with editing of the manuscript, critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (to K.U. and D.K.), Takeda Science Foundation (to D.K.), Banyu Foundation International (to D.K.), and the Uehara Memorial Foundation (to D.K. and K.M.).

Received: 12 January 2016 Accepted: 15 February 2016
Published online: 02 May 2016

References

1. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int. 2003;63(1):225–32. doi:10.1046/j.1523-1755.2003.00712.x.
2. Rutledge JC, Ng KF, Aung HH, Wilson DW. Role of triglyceride-rich lipoproteins in diabetic nephropathy. Nat Rev Nephrol. 2010;6(6):361–70. doi:10.1038/nrneph.2010.59.
3. Hirano T. Abnormal lipoprotein metabolism in diabetic nephropathy. Clin Exp Nephrol. 2014;18(2):206–9. doi:10.1007/s10157-013-0880-y.
4. Chehade JM, Gladysz M, Mooradian AD. Dyslipidemia in type 2 diabetes: prevalence, pathophysiology, and management. Drugs. 2013;73(4):327–39. doi:10.1007/s40265-013-0023-5.
5. Jacobs MJ, Kleisli T, Pio JR, Malik S, L'Italien GJ, Chen RS, et al. Prevalence and control of dyslipidemia among persons with diabetes in the United States. Diabetes Res Clin Pract. 2005;70(3):263–9. doi:10.1016/j.diabres.2005.03.032.
6. U.K. Prospective Diabetes Study 27. Plasma lipids and lipoproteins at diagnosis of NIDDM by age and sex. Diabetes Care. 1997;20(11):1683–7. http://care.diabetesjournals.org/content/20/11/1683.
7. Kannel WB. Lipids, diabetes, and coronary heart disease: insights from the Framingham Study. Am Heart J. 1985;110(5):1100–7.

8. Parish S, Offer A, Clarke R, Hopewell JC, Hill MR, Otvos JD, et al. Lipids and lipoproteins and risk of different vascular events in the MRC/BHF Heart Protection Study. Circulation. 2012;125(20):2469–78. doi:10.1161/CIRCULATIONAHA.111.073684.
9. Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. Nat Clin Pract Endocrinol Metab. 2009;5(3):150–9. doi:10.1038/ncpendmet1066.
10. Pollare T, Vessby B, Lithell H. Lipoprotein lipase activity in skeletal muscle is related to insulin sensitivity. Arterioscler Thromb. 1991;11(5):1192–203.
11. Hayashi T, Hirano T, Taira T, Tokuno A, Mori Y, Koba S, et al. Remarkable increase of apolipoprotein B48 level in diabetic patients with end-stage renal disease. Atherosclerosis. 2008;197(1):154–8. doi:10.1016/j.atherosclerosis.2007.03.015.
12. Svensson M, Eriksson JW. Insulin resistance in diabetic nephropathy—cause or consequence? Diabetes Metab Res Rev. 2006;22(5):401–10. doi:10.1002/dmrr.648.
13. Bonnet F, Cooper ME. Potential influence of lipids in diabetic nephropathy: insights from experimental data and clinical studies. Diabetes Metab. 2000;26(4):254–64.
14. Bouillet B, Gautier T, Blache D, Pais de Barros JP, Duvillard L, Petit JM, et al. Glycation of apolipoprotein C1 impairs its CETP inhibitory property: pathophysiological relevance in patients with type 1 and type 2 diabetes. Diabetes Care. 2014;37(4):1148–56. doi:10.2337/dc13-1467.
15. Kimura H, Miyazaki R, Imura T, Masunaga S, Suzuki S, Gejyo F, et al. Hepatic lipase mutation may reduce vascular disease prevalence in hemodialysis patients with high CETP levels. Kidney Int. 2003;64(5):1829–37. doi:10.1046/j.1523-1755.2003.00285.x.
16. Vaziri ND. Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences. Am J Physiol Renal Physiol. 2006;290(2):F262–72. doi:10.1152/ajprenal.00099.2005.
17. Mooradian AD, Haas MJ, Wehmeier KR, Wong NC. Obesity-related changes in high-density lipoprotein metabolism. Obesity. 2008;16(6):1152–60. doi:10.1038/oby.2008.202.
18. Mooradian AD, Haas MJ, Wong NC. Transcriptional control of apolipoprotein A-I gene expression in diabetes. Diabetes. 2004;53(3):513–20.
19. Wellmann KF, Volk BW. Renal changes in experimental hypercholesterolemia in normal and in subdiabetic rabbits. II. Long term studies. Lab Invest. 1971;24(2):144–55.
20. Utsunomiya K, Ohta H, Kurata H, Tajima N, Isogai Y. The effect of macrophage colony-stimulating factor (M-CSF) on the progression of lipid-induced nephrotoxicity in diabetic nephropathy. J Diabetes Complicat. 1995;9(4):292–5.
21. Hammad SM, Hazen-Martin DJ, Sohn M, Eldridge L, Powell-Braxton L, Won W, et al. Nephropathy in a hypercholesterolemic mouse model with streptozotocin-induced diabetes. Kidney Blood Press Res. 2003;26(5-6):351–61. doi:10.1159/000073942.
22. Kasiske BL, O'Donnell MP, Cleary MP, Keane WF. Treatment of hyperlipidemia reduces glomerular injury in obese Zucker rats. Kidney Int. 1988;33(3):667–72.
23. Wheeler DC, Fernando RL, Gillett MP, Zaruba J, Persaud J, Kingstone D, et al. Characterisation of the binding of low-density lipoproteins to cultured rat mesangial cells. Nephrol Dial Transplant. 1991;6(10):701–8.
24. Grone HJ, Walli AK, Grone E, Kramer A, Clemens MR, Seidel D. Receptor mediated uptake of apo B and apo E rich lipoproteins by human glomerular epithelial cells. Kidney Int. 1990;37(6):1449–59.
25. Quaschning T, Koniger M, Kramer-Guth A, Greiber S, Pavenstadt H, Nauck M, et al. Receptor-mediated lipoprotein uptake by human glomerular cells: comparison with skin fibroblasts and HepG2 cells. Nephrol Dial Transplant. 1997;12(12):2528–36.
26. Kramer A, Nauck M, Pavenstadt H, Schwedler S, Wieland H, Schollmeyer P, et al. Receptor-mediated uptake of IDL and LDL from nephrotic patients by glomerular epithelial cells. Kidney Int. 1993;44(6):1341–51.
27. Nishida Y, Oda H, Yorioka N. Effect of lipoproteins on mesangial cell proliferation. Kidney Int Suppl. 1999;71:S51–3.
28. Eiselein L, Wilson DW, Lame MW, Rutledge JC. Lipolysis products from triglyceride-rich lipoproteins increase endothelial permeability, perturb zonula occludens-1 and F-actin, and induce apoptosis. Am J Physiol Heart Circ Physiol. 2007;292(6):H2745–53. doi:10.1152/ajpheart.00686.2006.
29. Schlondorff D. Cellular mechanisms of lipid injury in the glomerulus. Am J Kidney Dis. 1993;22(1):72–82.
30. Nosadini R, Tonolo G. Role of oxidized low density lipoproteins and free fatty acids in the pathogenesis of glomerulopathy and tubulointerstitial lesions in type 2 diabetes. Nutr Metab Cardiovasc Dis. 2011;21(2):79–85. doi:10.1016/j.numecd.2010.10.002.
31. Kamanna VS, Pai R, Roh DD, Kirschenbaum MA. Oxidative modification of low-density lipoprotein enhances the murine mesangial cell cytokines associated with monocyte migration, differentiation, and proliferation. Lab Invest. 1996;74(6):1067–79.
32. Ishigaki N, Yamamoto T, Shimizu Y, Kobayashi K, Yatoh S, Sone H, et al. Involvement of glomerular SREBP-1c in diabetic nephropathy. Biochem Biophys Res Commun. 2007;364(3):502–8. doi:10.1016/j.bbrc.2007.10.038.
33. Kuwabara T, Mori K, Mukoyama M, Kasahara M, Yokoi H, Saito Y, et al. Exacerbation of diabetic nephropathy by hyperlipidaemia is mediated by Toll-like receptor 4 in mice. Diabetologia. 2012;55(8):2256–66. doi:10.1007/s00125-012-2578-1.
34. Brown MS, Goldstein JL. The SREBP pathway: regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor. Cell. 1997;89(3):331–40.
35. Nieuwdorp M, Meuwese MC, Vink H, Hoekstra JB, Kastelein JJ, Stroes ES. The endothelial glycocalyx: a potential barrier between health and vascular disease. Curr Opin Lipidol. 2005;16(5):507–11.
36. Nieuwdorp M, Meuwese MC, Mooij HL, Ince C, Broekhuizen LN, Kastelein JJ, et al. Measuring endothelial glycocalyx dimensions in humans: a potential novel tool to monitor vascular vulnerability. J Appl Physiol. 2008;104(3):845–52. doi:10.1152/japplphysiol.00440.2007.
37. Ramasamy R, Yan SF, Herold K, Clynes R, Schmidt AM. Receptor for advanced glycation end products: fundamental roles in the inflammatory response: winding the way to the pathogenesis of endothelial dysfunction and atherosclerosis. Ann N Y Acad Sci. 2008;1126:7–13. doi:10.1196/annals.1433.056.
38. Iacobini C, Menini S, Ricci C, Scipioni A, Sansoni V, Mazzitelli G, et al. Advanced lipoxidation end-products mediate lipid-induced glomerular injury: role of receptor-mediated mechanisms. J Pathol. 2009;218(3):360–9. doi:10.1002/path.2536.
39. Douglas K, O'Malley PG, Jackson JL. Meta-analysis: the effect of statins on albuminuria. Ann Intern Med. 2006;145(2):117–24.
40. Koya D, Campese VM. Statin use in patients with diabetes and kidney disease: the Japanese experience. J Atheroscler Thromb. 2013;20(5):407–24.
41. Sasaki T, Kurata H, Nomura K, Utsunomiya K, Ikeda Y. Amelioration of proteinuria with pravastatin in hypercholesterolemic patients with diabetes mellitus. Jpn J Med. 1990;29(2):156–63.
42. Athyros VG, Elisaf M, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, et al. Effect of statins versus untreated dyslipidemia on serum uric acid levels in patients with coronary heart disease: a subgroup analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. Am J Kidney Dis. 2004;43(4):589–99.
43. Tonelli M, Keech A, Shepherd J, Sacks F, Tonkin A, Packard C, et al. Effect of pravastatin in people with diabetes and chronic kidney disease. J Am Soc Nephrol. 2005;16(12):3748–54. doi:10.1681/ASN.2005070779.
44. Shepherd J, Kastelein JJ, Bittner V, Deedwania P, Breazna A, Dobson S, et al. Effect of intensive lipid lowering with atorvastatin on renal function in patients with coronary heart disease: the Treating to New Targets (TNT) study. Clin J Am Soc Nephrol. 2007;2(6):1131–9. doi:10.2215/CJN.04371206.
45. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). Am J Kidney Dis. 2009;54(5):810–9. doi:10.1053/j.ajkd.2009.03.022.
46. Zhou Q, Gensch C, Liao JK. Rho-associated coiled-coil-forming kinases (ROCKs): potential targets for the treatment of atherosclerosis and vascular disease. Trends Pharmacol Sci. 2011;32(3):167–73. doi:10.1016/j.tips.2010.12.006.
47. Fujisawa K, Fujita A, Ishizaki T, Saito Y, Narumiya S. Identification of the Rho-binding domain of p160ROCK, a Rho-associated coiled-coil containing protein kinase. J Biol Chem. 1996;271(38):23022–8.
48. Adiels M, Boren J, Caslake MJ, Stewart P, Soro A, Westerbacka J, et al. Overproduction of VLDL1 driven by hyperglycemia is a dominant feature of diabetic dyslipidemia. Arterioscler Thromb Vasc Biol. 2005;25(8):1697–703. doi:10.1161/01.ATV.0000172689.53992.25.
49. Schmidt A, Hall A. Guanine nucleotide exchange factors for Rho GTPases: turning on the switch. Genes Dev. 2002;16(13):1587–609. doi:10.1101/gad.1003302.
50. Budzyn K, Marley PD, Sobey CG. Targeting Rho and Rho-kinase in the treatment of cardiovascular disease. Trends Pharmacol Sci. 2006;27(2):97–104. doi:10.1016/j.tips.2005.12.002.

51. Gojo A, Utsunomiya K, Taniguchi K, Yokota T, Ishizawa S, Kanazawa Y, et al. The Rho-kinase inhibitor, fasudil, attenuates diabetic nephropathy in streptozotocin-induced diabetic rats. Eur J Pharmacol. 2007;568(1-3):242–7. doi:10.1016/j.ejphar.2007.04.011.
52. Isoe T, Makino Y, Mizumoto K, Sakagami H, Fujita Y, Honjo J, et al. High glucose activates HIF-1-mediated signal transduction in glomerular mesangial cells through a carbohydrate response element binding protein. Kidney Int. 2010;78(1):48–59. doi:10.1038/ki.2010.99.
53. Matoba K, Kawanami D, Okada R, Tsukamoto M, Kinoshita J, Ito T, et al. Rho-kinase inhibition prevents the progression of diabetic nephropathy by downregulating hypoxia-inducible factor 1alpha. Kidney Int. 2013;84(3):545–54. doi:10.1038/ki.2013.130.
54. Matoba K, Kawanami D, Ishizawa S, Kanazawa Y, Yokota T, Utsunomiya K. Rho-kinase mediates TNF-alpha-induced MCP-1 expression via p38 MAPK signaling pathway in mesangial cells. Biochem Biophys Res Commun. 2010; 402(4):725–30. doi:10.1016/j.bbrc.2010.10.093.
55. Matoba K, Kawanami D, Tsukamoto M, Kinoshita J, Ito T, Ishizawa S, et al. Rho-kinase regulation of TNF-alpha-induced nuclear translocation of NF-kappaB RelA/p65 and M-CSF expression via p38 MAPK in mesangial cells. Am J Physiol Renal Physiol. 2014;307(5):F571–80. doi:10.1152/ajprenal.00113.2014.
56. Yokota T, Utsunomiya K, Taniguchi K, Gojo A, Kurata H, Tajima N. Involvement of the Rho/Rho kinase signaling pathway in platelet-derived growth factor BB-induced vascular endothelial growth factor expression in diabetic rat retina. Jpn J Ophthalmol. 2007;51(6):424–30. doi:10.1007/s10384-007-0471-0.
57. Kanazawa Y, Takahashi-Fujigasaki J, Ishizawa S, Takabayashi N, Ishibashi K, Matoba K, et al. The Rho-kinase inhibitor fasudil restores normal motor nerve conduction velocity in diabetic rats by assuring the proper localization of adhesion-related molecules in myelinating Schwann cells. Exp Neurol. 2013;247:438–46. doi:10.1016/j.expneurol.2013.01.012.
58. Kawanami D, Matoba K, Kanazawa Y, Ishizawa S, Yokota T, Utsunomiya K. Thrombin induces MCP-1 expression through Rho-kinase and subsequent p38MAPK/NF-kappaB signaling pathway activation in vascular endothelial cells. Biochem Biophys Res Commun. 2011;411(4):798–803. doi:10.1016/j.bbrc.2011.07.031.
59. Kushiyama T, Oda T, Yamamoto K, Higashi K, Watanabe A, Takechi H, et al. Protective effects of Rho kinase inhibitor fasudil on rats with chronic kidney disease. Am J Physiol Renal Physiol. 2013;304(11):F1325–34. doi:10.1152/ajprenal.00447.2012.
60. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366(9500):1849–61. doi:10.1016/S0140-6736(05)67667-2.
61. Davis TM, Ting R, Best JD, Donoghoe MW, Drury PL, Sullivan DR, et al. Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetologia. 2011;54(2):280–90. doi:10.1007/s00125-010-1951-1.
62. Ginsberg HN, Elam MB, Lovato LC, Crouse 3rd JR, Leiter LA, Linz P, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1563–74. doi:10.1056/NEJMoa1001282.
63. Mychaleckyj JC, Craven T, Nayak U, Buse J, Crouse JR, Elam M, et al. Reversibility of fenofibrate therapy-induced renal function impairment in ACCORD type 2 diabetic participants. Diabetes Care. 2012;35(5):1008–14. doi:10.2337/dc11-1811.
64. Ansquer JC, Dalton RN, Causse E, Crimet D, Le Malicot K, Foucher C. Effect of fenofibrate on kidney function: a 6-week randomized crossover trial in healthy people. Am J Kidney Dis. 2008;51(6):904–13. doi:10.1053/j.ajkd.2008.01.014.
65. Westphal S, Dierkes J, Luley C. Effects of fenofibrate and gemfibrozil on plasma homocysteine. Lancet. 2001;358(9275):39–40. doi:10.1016/S0140-6736(00)05271-5.
66. Forsblom C, Hiukka A, Leinonen ES, Sundvall J, Groop PH, Taskinen MR. Effects of long-term fenofibrate treatment on markers of renal function in type 2 diabetes: the FIELD Helsinki substudy. Diabetes Care. 2010;33(2):215–20. doi:10.2337/dc09-0621.
67. Lipscombe J, Lewis GF, Cattran D, Bargman JM. Deterioration in renal function associated with fibrate therapy. Clin Nephrol. 2001;55(1):39–44.
68. Hottelart C, El Esper N, Rose F, Achard JM, Fournier A. Fenofibrate increases creatininemia by increasing metabolic production of creatinine. Nephron. 2002;92(3):536–41.
69. Teramoto T, Shirai K, Daida H, Yamada N. Effects of bezafibrate on lipid and glucose metabolism in dyslipidemic patients with diabetes: the J-BENEFIT study. Cardiovasc Diabetol. 2012;11:29. doi:10.1186/1475-2840-11-29.
70. Bays H, Mandarino L, DeFronzo RA. Role of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: peroxisomal proliferator-activated receptor agonists provide a rational therapeutic approach. J Clin Endocrinol Metab. 2004;89(2):463–78. doi:10.1210/jc.2003-030723.
71. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181–92. doi: 10.1016/S0140-6736(11)60739-3.
72. Haynes R, Lewis D, Emberson J, Reith C, Agodoa L, Cass A, et al. Effects of lowering LDL cholesterol on progression of kidney disease. J Am Soc Nephrol. 2014;25(8):1825–33. doi:10.1681/ASN.2013090965.
73. Hagiwara S, Makita Y, Gu L, Tanimoto M, Zhang M, Nakamura S, et al. Eicosapentaenoic acid ameliorates diabetic nephropathy of type 2 diabetic KKAy/Ta mice: involvement of MCP-1 suppression and decreased ERK1/2 and p38 phosphorylation. Nephrol Dial Transplant. 2006;21(3):605–15. doi:10.1093/ndt/gfi208.
74. Zhang M, Hagiwara S, Matsumoto M, Gu L, Tanimoto M, Nakamura S, et al. Effects of eicosapentaenoic acid on the early stage of type 2 diabetic nephropathy in KKA(y)/Ta mice: involvement of anti-inflammation and antioxidative stress. Metabolism. 2006;55(12):1590–8. doi:10.1016/j.metabol.2006.07.019.
75. Shapiro H, Theilla M, Attal-Singer J, Singer P. Effects of polyunsaturated fatty acid consumption in diabetic nephropathy. Nat Rev Nephrol. 2011;7(2):110–21. doi:10.1038/nrneph.2010.156.
76. Lee CC, Sharp SJ, Wexler DJ, Adler AI. Dietary intake of eicosapentaenoic and docosahexaenoic acid and diabetic nephropathy: cohort analysis of the diabetes control and complications trial. Diabetes Care. 2010;33(7):1454–6. doi:10.2337/dc09-2245.
77. Lee CT, Adler AI, Forouhi NG, Luben R, Welch A, Khaw KT, et al. Cross-sectional association between fish consumption and albuminuria: the European Prospective Investigation of Cancer-Norfolk study. Am J Kidney Dis. 2008;52(5):876–86. doi:10.1053/j.ajkd.2008.02.307.
78. Haines AP, Sanders TA, Imeson JD, Mahler RF, Martin J, Mistry M, et al. Effects of a fish oil supplement on platelet function, haemostatic variables and albuminuria in insulin-dependent diabetics. Thromb Res. 1986;43(6):643–55.
79. Jensen T, Stender S, Goldstein K, Holmer G, Deckert T. Partial normalization by dietary cod-liver oil of increased microvascular albumin leakage in patients with insulin-dependent diabetes and albuminuria. N Engl J Med. 1989;321(23):1572–7. doi:10.1056/NEJM198912073213204.
80. Hamazaki T, Takazakura E, Osawa K, Urakaze M, Yano S. Reduction in microalbuminuria in diabetics by eicosapentaenoic acid ethyl ester. Lipids. 1990;25(9):541–5.
81. Shimizu H, Ohtani K, Tanaka Y, Sato N, Mori M, Shimomura Y. Long-term effect of eicosapentaenoic acid ethyl (EPA-E) on albuminuria of non-insulin dependent diabetic patients. Diabetes Res Clin Pract. 1995;28(1):35–40.
82. Wallin A, Di Giuseppe D, Orsini N, Patel PS, Forouhi NG, Wolk A. Fish consumption, dietary long-chain n-3 fatty acids, and risk of type 2 diabetes: systematic review and meta-analysis of prospective studies. Diabetes Care. 2012;35(4):918–29. doi:10.2337/dc11-1631.
83. Strippoli GF, Navaneethan SD, Johnson DW, Perkovic V, Pellegrini F, Nicolucci A, et al. Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. BMJ. 2008;336(7645):645–51. doi:10.1136/bmj.39472.580984.AE.
84. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353(3):238–48.
85. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360(14):1395–407. doi:10.1056/NEJMoa0810177.
86. Holdaas H, Holme I, Schmieder RE, Jardine AG, Zannad F, Norby GE, et al. Rosuvastatin in diabetic hemodialysis patients. J Am Soc Nephrol. 2011;22(7):1335–41. doi:10.1681/ASN.2010090987.
87. Szummer K, Lundman P, Jacobson SH, Schon S, Lindback J, Stenestrand U, et al. Association between statin treatment and outcome in relation to renal function in survivors of myocardial infarction. Kidney Int. 2011;79(9):997–1004. doi:10.1038/ki.2010.524.