World Journal of

Diabetes

Bile acid (CA, CDCA) → TGR5 activity in L cell in intestine ↑

BAS

FXR activity in liver ↑ → FXR activity in liver ↓

TGR5 activity in brown adipose tissue or skeletal muscle ↑

SREBP1c ↓ ← SHP ↑ → SREBP1c ↑ ← SHP ↓

TG level ↓ → TG level ↑

PEPCK ↓ ← LXR activity ↑

Energy metabolism ↑ → Circulating GLP-1 ↑

Gluconeogenesis in liver

Improvement of glycemic control

Possible mechanisms of the effects of bile acids and bile acid sequestrants on glucose and lipid metabolism.

Editorial Board

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AIM AND SCOPE

World Journal of Diabetes (*World J Diabetes*, *WJD*, online ISSN 1948-9358, DOI: 10.4239), is a bimonthly, open-access, peer-reviewed journal supported by an editorial board of 323 experts in diabetes mellitus research from 38 countries.

The major task of *WJD* is to report rapidly the most recent results in basic and clinical research on diabetes including: metabolic syndrome, functions of α, β, δ and PP cells of the pancreatic islets, effect of insulin and insulin resistance, pancreatic islet transplantation, adipose cells and obesity, clinical trials, clinical diagnosis and treatment, rehabilitation, nursing and prevention. This covers epidemiology, etiology, immunology, pathology, genetics, genomics, proteomics, pharmacology, pharmacokinetics, pharmacogenetics, diagnosis and therapeutics. Reports on new techniques for treating diabetes are also welcome.

EDITORIAL

Contribution of animal models to the research of the causes of diabetes

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Abstract

In most publications, animal models of diabetes have mainly been investigated for their multiple etiologies as well as for changes leading to diabetes and their genetic derivation. Aspects which seem important and need a special research endeavor are the mechanism of the causes of diabetes and the lapse into complications in different species, their molecular basis and possible arrest and prevention. A concise list and and short discussion of the intensively studied rodents is presented of spontaneous or nutritional background causing Type 2 diabetes but omitting diabetes evoked by transgenic manipulations or gene knockout techniques.

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INTRODUCTION

Animal models of diabetes have been described in several recent publications[1-3]. In most publications it is mainly the multiple heterogenous etiologies that have been investigated as well as the mechanism of changes leading to diabetes and the genetic derivation. Other aspects which seem important and need a special research endeavor are the causes of diabetes complications in the different species, the molecular basis of their induction and possible arrest and prevention. A list and discussion of the intensively studied rodents is presented of spontaneous or nutritional background causing Type 2 diabetes but omitting models produced by transgenic manipulations or gene knockout techniques.

OBESE-DIABETIC MICE *DB/DB* AND *OB/OB*[4]

These are intensively studied mice models of obesity and diabetes affecting a common pathway, a defect in the leptin receptor (db) and a defect in the leptin gene (ob). The nomenclature for these species currently used is $Lepr^{db}$ and $Lepr^{ob}$.

There is evidence now that the deficiency of leptin action in the areas of metabolism, ingestive behavior and reproduction (insulin resistance, hyperphagia, infertility) is mediated by the nervous system and expressed in the hypothalamic neurons. $Lepr^{ob}$ mice are exquisitely sensitive to the administration of recombinant leptin whereas $lepr^{db}$ mice are extremely leptin resistant with clear impact on metabolism in non-neuronal tissues.

Apart from the basal deficiencies caused by the respective mutations, there are apparent complications in the tissue immune system, muscle and adipose tissue metabolism, endocrine pancreas and pancreatic beta cells leading to beta cell loss and insulin dependence. In addition, with time, these animals suffer from vasculopathy, neuropathy, nephropathy and myocardial disease.

KK AMD KKA^Y DIABETIC MICE, MODELING FOR TYPE 2 DIABETES AND OBESITY[5]

The KK spontaneously diabetic mouse was established by inbreeding of the local strains of Japanese mice. It exhibits moderate obesity, polyphagia, polyuria, persistent glucosuria and moderate hyperglycemia with hyperlipidemia. Yellow obese gene (A^y) has been transferred into KK mice by repeated crossing of yellow obese mice with KK mice (black fur at weaning), resulting in more moderate diabetic changes than in the original KK mice but with a stronger expression of obesity. Regional differences in leptin gene downregulation expression have been found in adipose tissue during fasting. Among the complications, there are renal lesions similar to human nephropathy including glomerular basement membrane thickening and proteinuria. These mice have been recommended as useful for drug testing because of their low weight and clear responses.

SHROB (KOLETZKY) RAT[6]

The spontaneously hypertensive and obese rat, emerging from the SHR corpulent lines of rats, exhibits many primary and secondary characteristics of human metabolic syndrome as a nonsense mutation affecting all forms of leptin receptor, designated fa^k: Hyperphagia, enhanced lipogenesis, extensive growth of adipose tissue, impaired glucose tolerance without overt hyperglycemia, marked hyperinsulinemia with insulin hypersecretion from enlarged islets, insulin resistance, reduced expression of insulin receptor (IR) and insulin receptor substrate protein (IRS1) and a defect in the insulin signaling pathway.

Since the SHROB rat is not hyperglycemic, the complications in this animal cannot be directly linked to glucose hyperoxidation. Glomerulopathy with proteinuria occur involving focal segmental nephrosclerosis and hypertensive vascular lesions, most probably due to overactivity of the rennin-angiotensin system.

Atherosclerosis is related to impaired clearance of circulating leptin due to complete absence of functional leptin receptor. Retinal neurovascularization, progressive capillary dropout and vascular abnormalities and retinal hemorrhage are also evident.

JCR: LACP RAT[7]

This animal, inbred from the corpulent hyperphagic rat cp strains, also presents when young with most of the manifestations of metabolic syndrome with particular micro and macrovascular lesions. It shows insulin resistance, hyperinsulinemia but without loss of hypersecretion capacity, hyperlipidemia including both cholesterol and triglycerides, vasculopathy, atherosclerosis and a unique cardiovascular disease with cardiac ischemia which calls for the application of a cardioprotective pharmacological agent. It slowly progresses to full blown type 2 diabetes. The origin of the lesions is polygenetic related to the unknown components of the genome derived from corpulent rat strains.

Among the complications are vasculopathy and atherosclerosis with thrombi linked to the arterial surface and intimal lesions in the vascular smooth muscle cells, glomerular sclerosis and impaired wound healing.

ZUCKER DIABETIC FATTY RAT[8]

Several diabetic males and females were identified in the obese Zucker fa/fa colony and selectively inbred. After 10 generations the zucker diabetic fatty (ZDF) trait was established. The rats are hyperglycemic and hyperinsulinemic until the total failure of beta cells associated with reduction of islet mitochondrial enzymes. They are also mildly hypertensive and hyperlipidemic. Two mutations of the leptin receptor reduce its affinity for interaction with leptin and are responsible for ZDF obesity.

The rise in triglyceride rich lipoproteins appears to be correlated with the change from the hyperinsulinemic to insulinopenic stage. A decrease in the endothelial-dependent vasodilation and decreased resting blood flow have been observed, indicating a disturbed endothelial regulation. Ocular changes include retinal hypercellularity and thick capillary basement membrane. Reduced wound healing and reduced nerve conduction velocity with nerve edema have been reported.

COHEN DIABETIC RAT[9]

The Cohen diabetic rat is a model of nutritionally induced type 2 diabetes originally developed by A.M. Cohen in Jerusalem. A diabetogenic diet rich in sucrose and poor in copper was fed to the "Sabra" albino rat strain of the Hebrew University with two contrasting results. A sensitive group developed full blown type 2 diabetes whereas a resistant group remained without hyperglycemia. The sensitive group developed beta cell dysfunction, reduced insulin secretion with insulin resistance. The hyperglycemia was reversible by diet adjustment.

Chief complications were nephropathy with mesangial expansion and thickening of the glomerular basement membrane, proliferative retinopathy, testicular atrophy and gastrointestinal disorders, skeletal pathology amd embriopathy.

GOTO KAKIZAKI RAT[10]

Goto kakizaki (GK) rat is a nonobese substrain of Wistar origin, developing type 2 diabetes due to impaired beta cell mass function and glucotoxicity stemming from polygenic inheritance. The GK rats were initiated by Y Goto and coworkers in Sendai, Japan by repeated selecting and breeding of animals with a reduced glucose tolerance chosen from a large pool of rats for several generations. The diabetes in the chosen isolated rats was reproducible

even after > 100 generations. The primary defect was in the beta cell with "starfish - shaped" abnormalities but with somewhat differing phenotypical properties in substrain colonies maintained by various investigators.

Among the complications investigated in GK rats are nephropathy with thickening of the glomerular basement membrane, reduced nerve conduction velocity and segmental demyelinization, osteopathy, altered retinal endothelial retinopathy and cell/pericyte ratio.

OTSUKA LONG EVANS TOKUSHIMA FATTY RATS[11]

Three kinds of diabetes models have been developed by selective breeding in a group of Long Evans rats obtained from Charles River Co in Canada by K Kawano and associates in Tokushima, Japan: a line of type 2 diabetic rats known as Otsuka Long Evans Tokushima Fatty (OLETF) which were hyperphagic consuming up to 30 g of food daily; a line known as Long Evans Tokushima Lean resembling type 1 insulin-dependent diabetes; and a Long Evans Tokushima non-diabetic control line. The OLETF rats exhibited glucose intolerance and insulin resistance, hypertriglyceridemia with marked triglyceride infiltration into pancreatic islets, obesity and increased blood pressure. The onset of diabetes with its complications was significantly attenuated by diet restriction.

The outstanding complication was nephropathy with proteinuria. Glomerular oxidative lesions were evident similar to those in human nephropathy, fibrin-cap, capsular drop and aneurysmal dilatation of intraglomerular vessels.

PSAMMOMYS OBESUS GERBIL[12]

Psammomys obesus (previously named "sand rat") is a gerbil living in the desert or semi desert areas of North Africa and the Near East. The gerbil is not hyperphagic or diabetic in the wild but is ill adapted to nutritional excess. When transferred to the laboratory, it becomes hyperinsulinemic and hyperglycemic with marked insulin resistance when its native diet of salt bush (*Atriplex halimus*) is substituted for a laboratory rodent diet. After a few weeks on the laboratory diet, the animals develop insulin resistance with hyperinsulinemia, then gradually lose their pancreatic beta cells and their insulin levels markedly decrease. It is of interest that their insulin resistance is related to the inhibition of IR action, a shift in the tyrosine to serine phosphorylation on IRS and a blockade of insulin signaling. Insulin resistance and the change in phosphorylation pattern is related to the increase in the activity of an enzyme of the protein kinase isoenzyme group protein kinase C epsilon (PKCε) which inhibits the tyrosine phophorylase. The intraperitoneal injection of a peptide removed from the catalytic region of PKC abrogated the inhibitory serine phosphorylation of IRS by PKCε and enabled the functioning of downstream insulin signaling[13]. *Psammomys* is a good model for studies of insulin signaling pathway in muscles.

Most diabetes complications of *Psammomys* are related to insulin resistance and hyperglycemia. Cataracts are often evident and retinal lesions also occur. Among other complications, angiopathy, degeneration of intervertebral discs, spondylitis and hearing impairment have been described as well as nephropathy due to Na-K ATPase hyperactivity.

CONCLUSION

There is no need to underscore the huge contribution of animal models to the investigation of the causes of diabetes. However, much remains to be researched on the road of understanding and preventing the complications of the disease, particularly the processes of the development of diabetic tissue lesions. This is of outstanding importance to the amelioration and prevention of human diabetes and promoting pharmacological approaches to combating diabetes.

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Role of the renin angiotensin system in diabetic nephropathy

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Abstract

Diabetic nephropathy has been the cause of lot of morbidity and mortality in the diabetic population. The renin angiotensin system (RAS) is considered to be involved in most of the pathological processes that result in diabetic nephropathy. This system has various subsystems which contribute to the disease pathology. One of these involves angiotensin Ⅱ (Ang Ⅱ) which shows increased activity during diabetic nephropathy. This causes hypertrophy of various renal cells and has a pressor effect on arteriolar smooth muscle resulting in increased vascular pressure. Ang Ⅱ also induces inflammation, apoptosis, cell growth, migration and differentiation. Monocyte chemoattractant protein-1 production responsible for renal fibrosis is also regulated by RAS. Polymorphism of angiotensin converting enzyme (ACE) and Angiotensinogen has been shown to have effects on RAS. Available treatment modalities have proven effective in controlling the progression of nephropathy. Various drugs (based on antagonism of RAS) are currently in the market and others are still under trial. Amongst the approved drugs, ACE inhibitors and angiotensin receptor blockers (ARBs) are widely used in clinical practice. ARBs are shown to be superior to ACE inhibitors in terms of reducing proteinuria but the combined role of ARBs with ACE inhibitors in diabetic nephropathy is under debate.

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INTRODUCTION

Diabetic nephropathy is the leading cause of end stage renal disease (ESRD). It is also a leading cause of diabetes mellitus-related morbidity and mortality worldwide. Pathogenesis of diabetic nephropathy is related to uncontrolled or chronic hyperglycemia. It is characterized by hypertrophy of glomeruli, hyperperfusion, thickening of basement membranes and glomerular hyperfiltration[1]. In addition there is microalbuminuria and subsequently progressive glomerulosclerosis. Later, tubulointerstitial fibrosis occurs causing reduction in glomerular filtration rate (GFR)[2,3].

The purpose of this article is to give an insight into the involvement of renin angiotensin system (RAS) in diabetic nephropathy. It highlights various pathophysiological, genetic and inflammatory issues related to RAS in diabetes.

RENIN-ANGIOTENSIN PHYSIOLOGY

The RAS present in the kidneys, is comprised of angiotensinogen, renin, angiotensin I (Ang I), angiotensin con verting enzyme related carboxypeptidase (ACE2), angiotensin converting enzyme, angiotensin II (Ang II), aldosterone, Ang II type 1 receptor (AT1R) and the Ang II type 2 receptor (AT2R).

Renin is a proteolytic enzyme produced by juxtaglomerular cells in the kidney. Renin acts on angiotensinogen to form Ang I which then gets converted to Ang II by angiotensin-converting enzyme (ACE)[4] present in many tissues (particularly the pulmonary vascular endothelium). Ang II is a pressor agent and exerts its action by direct effect on arteriolar smooth muscle causing increased vascular pressure. In addition it stimulates production of aldosterone by the zona glomerulosa of the adrenal cortex which helps in sodium reabsorption in the kidney. The heptapeptide angiotensin III may also stimulate aldosterone production.

When blood volume is low, angiotensin causes blood vessels to constrict resulting in increased blood pressure and release of aldosterone. In the kidneys, efferent arterioles are constricted more than afferent, forcing blood to build up in the glomerulus and increasing glomerular pressure. The GFR is thus maintained, and blood filtration can continue despite lowered kidney blood flow.

In addition to circulating renin-angiotensin, many tissues like uterus, placenta, vascular tissue, heart, brain, and, particularly, the adrenal cortex and kidney have a local RAS[5,6]. Although the role of locally generated Ang II is not established, it may modulate the growth and function of the adrenal cortex and vascular smooth muscle[5,6].

Ang II is also a potent growth modulator and proinflammatory peptide. In addition, this peptide degrades bradykinin, a vasodilator[7]. A chemically related enzyme, ACE-related carboxypeptidase, also known as ACE2, has recently been cloned and identified by two different groups[8,9]. ACE2 has 42% homology with ACE at the metalloprotease catalytic domain[4-6] but differs from ACE in having only one enzymatic site. In humans, ACE2 transcripts have been identified in the heart, kidney, and testis[8,10]. Shiota *et al*[11] suggests that ACE2 might prevent both glomerular and tubulointerstitial injury in diabetic nephropathy.

The possible role of RAS has been studied for changes in intraglomerular hemodynamics[7] as well as structural changes in the diabetic kidney at both the glomerular and tubulointerstitial levels[7,12].

PATHOPHYSIOLOGY OF DIABETIC NEPHROPATHY

Diabetic nephropathy starts with glomerular hyperperfusion and renal hypertrophy causing increase in GFR[5,6]. Subsequently, microalbuminuria develops which if not checked will progress to macroalbuminuria and a decline in GFR will result.

During the disease process the increased Ang II activity causes hypertrophy of mesangial cells and tubular epithelial cells[13]. It also promotes production of the prosclerotic cytokine transforming growth factor-beta (TGF-β) which has been identified as one of cause for glomerular sclerosis[13,14].

Some groups of researchers have found that tubular epithelial cells in diabetes induce kidney monocyte chemoattractant protein-1 (MCP-1) production which is regulated by RAS[15,16]. This MCP-1 is responsible for macrophage recruitment resulting in renal fibrosis and indirect promotion of extracellular matrix formation. By observing the role of MCP-1 in the pathophysiology of diabetic nephropathy we can undoubtedly say that it is a promising therapeutic target for treating diabetic nephropathy[15,16].

Oxidative stress-sensitive nuclear factor κB (NFκB) activation and up-regulation of the proinflammatory genes MCP-1 and regulated on activation, normal T-cell expressed and secreted (RANTES)[17] have been observed to be related to proteinuria and interstitial cell infiltration, adding further insult to the kidney. Zhernakova *et al* also found that in type 1 diabetes, RANTES, a T-helper type 1 (Th1) chemokine, promotes activation and proliferation of T-cells[17,18]. Cortical tubular epithelial cells, podocytes, and some renal mononuclear cells have also shown NFκB activity.

ROLE OF ANG II

During inflammation, macrophages and lymphocytes can generate reactive oxygen species and Ang II[19]. Diabetic nephropathy being an inflammatory condition, Ang II levels have been found to be elevated[19]. This rise activates immune cells and causes production of chemokines[20] leading to further renal damage. The increased ACE and Ang II expression in tubular, interstitial and fibroblast-like cells has been seen with immunostaining. These, together with high glucose and inflammatory mediators, target tubular cells causing deranged kidney functions in diabetes[21]. Ang II has also been shown to activate and upregulate NFκB and related genes[20].

As discussed earlier, Ang II is a major hormone of the RAS and contributes to a variety of renal and cardiovascular physiologic and pathologic mechanisms. Some authors have found that Ang II in the kidney generates reactive oxygen species (ROS) and promotes podocyte autophagy by enhancing podocyte expression of autophagic genes, LC3-2 and beclin-1[22].

Ang II causes renal vascular vasoconstriction *via* AT1R. The role of AT2R has been discussed by various investigators and shown to be favorable for vascular health. The beneficial effects include decrease in blood pressure, inhibition of cell growth, apoptosis[23], antiproliferative and anti-inflammatory actions[24]. AT2R has been seen to be upregulated by insulin and insulin like growth factor-1 (IGF-1)[25,26] and downregulated by Ang-II, epidermal growth factor (EGF), platelet derived growth factor (PDGF)[27] and in diabetes[23,28]. AT2R has also been seen

to be upregulated in various clinical conditions such as Na$^+$ depletion, renal ischemia reperfusion[29]. Although the exact regulation mechanism of AT2R in diabetic nephropathy is unknown, immunohistochemistry (IHC) has shown low expression of AT2R in diabetes mellitus[23].

Recently, Siragy demonstrated the role of AT2 receptors in vasodilation, nitric oxide and cGMP production[30] which is beneficial in curbing damage. He therefore suggested the development of specific AT2R agonists to add to the treatment regimen for diabetic nephropathy. Though AT1 and AT2 receptors usually have opposite effects they are actually similar in inhibiting renin production with AT2 achieving this *via* bradykinin-nitric oxide-cGMP vasodilatory pathway[30-32].

ROLE OF POLYMORPHISM

The distribution of ACE insertion/deletion (I/D) polymorphism in type-2 diabetes mellitus (DM) has been studied by various investigators[33,34]. The II genotype has a better response to ACE inhibitors particularly at normoalbuminuria or microalbuminuria levels[35]. In DD genotype patients with overt nephropathy, antirenin angiotensin therapy was shown to be effective whereas in males having nondiabetic proteinuric nephropathies ACE inhibitors were effective[35]. An older study including 2890 patients with type 1 diabetes associated nephropathy showed them to be predisposed to coronary artery disease[34] while relatively new research by Marre *et al*[36] with 494 subjects revealed no such association with ACE polymorphism.

Angiotensinogen (AGT) polymorphism also has effects on the RAS system. Some researchers have found association of methionine 235 with threonine (M235T), a T to C base substitution at position 702 on exon 2 with consequent replacement of M235T, with progression of diabetic nephropathy[37,38], in agreement with data from 95 nephropathy patients taken by Fogarty *et al*[39]. However, studies by Tarnow *et al*[40] (195 nephropathy patients) and Doria *et al*[41] (305 patients having either microalbuminuria or proteinuria) found no relation of AGT polymorphism with diabetic nephropathy. More studies need to be conducted to consolidate the role of AGT polymorphism in diabetic nephropathy.

BLOCKADE OF RAS IN DIABETIC NEPHROPATHY

The importance of RAS has been highlighted time after time and this system has a central role in the pathophysiology of diabetic nephropathy. Hypertension usually accompanies diabetes mellitus, early in type 2 and delayed in type 1. Worsening of diabetic nephropathy is rapid when there is progression from normoalbuminuria to macroalbuminuria, a transition which takes about ten years. With increasing albumin excretion the risk of renal and cardiovascular disease deepens[42,43]. In patients with diabetic nephropathy, lowering of blood pressure and urinary albumin excretion significantly decreases the risk of progression to ESRD, myocardial infarction and stroke[44].

ACE inhibitors decrease the production of Ang II, which is a potent vasoconstrictor, leading to lower intraglomerular pressure and reduced glomerular hypertension. They also decrease the glomerular permeability to urinary albumin leading to decreased proteinuria[45].

ARBs act by blocking Ang II type 1 receptors (AT1 receptors). This AT1 blockade may lead to further increase in synthesis of Ang II which binds to intrarenal AT2 receptors, resulting in decreased blood pressure[46] and reduced renal interstitial fibrosis[47].

Proteinuria better responds to ARBs than ACE inhibitors[48,49]. Treatment with captopril and olmesartan has been shown to be beneficial in experimental models of diabetic albuminuria and podocyte injury[50,51]. In children also, addition of ARBs further reduces renal injury without affecting blood pressure[52]. The diabetics exposed to telmisartan and enalapril (DETAIL) study concluded that telmisartan is non-inferior to enalapril in renoprotection and is associated with a low incidence of mortality[53].

Combined therapy with both ACE inhibitors and ARBs has been shown by some to be more beneficial in terms of reducing proteinuria, blood pressure and cardiovascular morbidity and mortality[54-57]. In contrast, the recently concluded ongoing telmisartan alone and in combination with ramipril global endpoint trial (ONTARGET, 25 620 patients) and the telmisartan randomised assessment study in ACE intolerant subjects with cardiovascular disease (TRANSCEND, 5926 patients) studies came to different conclusions[58,59].

ONTARGET trial found marginal reduction in systolic blood pressure with combination therapy. No significant benefit in terms of myocardial infarction (MI), hospitalization for heart failure or death from cardiovascular or non-cardiovascular causes was detected[58].

The TRANSCEND study again observed slight reduction of blood pressure with telmisartan but the differences in the primary end-point of MI, stroke, hospital admission with heart failure were not statistically significant compared to placebo[59]. A review by Shinichiro Ueda again highlighted the unsolved question of whether dual blockade of RAS will benefit patients[60].

Recently a direct renin blocker has been invented that blocks RAS (Aliskiren), thus allaying the fear of reactive elevation of renin encountered while using ACEI or ARBs. Aliskiren's reno-protective properties have been observed in patients with diabetic as well as non-diabetic nephropathy[61]. Aliskiren in the evaluation of proteinuria in diabetes (AVOID) study observed that aliskiren, in addition to optimising blood pressure treatment in hypertension, also reduces the mean urinary albumin-to-creatinine ratio in patients with type 2 diabetes and nephropathy[62].

CONCLUSION

Diabetes is a multisystem disorder and involvement of the kidney is a major cause of hospitalization and in-

firmity among the diabetic population. RAS has been proved to be the torch bearer in pathogenesis of diabetic nephropathy. Various other factors including polymorphism, inflammatory mediators and cytokines combined with patient unawareness and non-compliance results in serious damage to renal functions in diabetes.

To date, various trials have shown arrest of the disease process and improvement in the condition of patients in the disease population through blockade of RAS although none achieved complete block. Further trials should be conducted at the molecular and genetic level to find better ways to stop insult caused by RAS to the diabetic kidney.

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REVIEW

Role of bile acid sequestrants in the treatment of type 2 diabetes

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Abstract

Cholestyramine is a first-generation bile acid sequestrant (BAS) and antihyperlipidemic agent that currently has limited use because of its relatively weak effect on lowering low density-lipoprotein (LDL)-cholesterol (C) and poor tolerability. The current first choice drugs for hyper-LDL-cholesterolemia are 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (statins) because of their strong LDL-C lowering effects and efficacy in prevention of cardiovascular disease. However, after lowering the target levels of LDL-C in very high risk patients, combination therapy with statins and other antihyperlipidemic drugs may become more important for treatment of hyper-LDL-cholesterolemia. Second-generation BASs such as colesevelam and colestimide have a glucose-lowering effect and improved tolerance, which has led to re-evaluation of their utility in combination with statins or antidiabetic agents.

Key words: Bile acid; Bile acid sequestrant; Type 2 diabetes

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INTRODUCTION

Bile acid sequestrants (BASs) were one of the first classes of drugs to show that cholesterol-lowering therapy decreases the risk of cardiovascular disease (CAD)[1,2]. However, use of first-generation BASs such as cholestyramine and colestipol has been limited by poor tolerability and a relatively weak effect on lowering of low-density lipoprotein cholesterol (LDL-C)[1,2]. Currently, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins are the first choice for treatment of hyper-LDL-cholesterolemia based on their stronger LDL-C lowering effect and prevention of cardiovascular events[3-6]. However, co-administration of BASs with statins may produce lower LDL-C levels[7,8]. Second-generation BASs such as colesevelam (used clinically in the USA since 2000[9-11]) and colestimide (also called colestilan, and used clinically in Japan since 1999[12]) have improved tolerability. BASs also have a glucose-lowering effect[9-16], and are currently being re-evaluated for their potential use in combination with statins or antidiabetic agents.

MECHANISMS UNDERLYING THE LDL-C LOWERING EFFECT OF BILE ACID SEQUESTRANTS

Biliary excretion of cholesterol as a component of bile is

an important excretion pathway for hepatic cholesterol. Conversion of cholesterol to bile acids in the liver and excretion into the intestine *via* the biliary duct and gall bladder also facilitates excretion of cholesterol. Over 95% of bile acids excreted in bile from the gall bladder are reabsorbed in the terminal ileum and transferred to the liver *via* the portal vein in a recycling pathway. BASs, which are not themselves absorbed from the gut, absorb bile acids in the intestine and inhibit enterohepatic circulation of bile acids by preventing their reabsorption. This causes a significant increase of bile acids bound to BASs in feces. The decrease in bile acids transferred to the liver *via* the portal vein leads to upregulation of hepatic cholesterol cytochrome P450 7 alpha1 (CYP7A1), the rate-limiting enzyme for conversion of cholesterol to bile acids, promoting compensatory conversion and, thereby resulting in a decrease of intrahepatic cholesterol. In turn, this activates the hepatic LDL receptor, which then binds circulating LDL-C and results in a decrease in the level of circulating LDL-C[17]. BASs also inhibit cholesterol absorption by preventing formation of micelles composed of bile acids in the intestinal lumen, which may also contribute to the LDL-C lowering effect.

MECHANISMS UNDERLYING THE GLUCOSE-LOWERING EFFECT OF BILE ACID SEQUESTRANTS

Many clinical studies have shown that BASs improve glycemic control in patients with type 2 diabetes[9-16]. The mechanisms underlying this effect remain unclear, but several have been proposed. Bile acids such as cholic acid (CA) and chenodeoxycholic acid (CDCA) are natural ligands for the farnesoid X receptor (FXR)[18-19], and activation of FXR in liver may increase the production of small heterodimer partner (SHP)[20], a protein that plays a central role in lipid and glucose metabolism *via* regulation of various downstream molecules[21,22]. The increase in SHP due to FXR activation increases glucose metabolism by inhibiting production of phosphoenolpyruvate carboxykinase (PEPCK)[22], an enzyme associated with gluconeogenesis (although conversely FXR activation has been shown to increase PEPCK activity and glucose levels[23]). FXR activation also represses glucose levels in a diabetic rat model[24]. Bile acids can also increase glucose metabolism by regulating energy homeostasis *via* activation of the G protein-coupled receptor 5 (TGR5)-cAMP-type 2 iodothyronine deiodinase (D2) pathway in brown adipose tissues or skeletal muscles independently of FXR[25]. These observations suggest that BASs might worsen glycemic control because of potential deactivation of hepatic FXR through a decrease of bile acids in liver, in contrast to the established beneficial effects of BASs for glucose metabolism. However, there is a report showing that BAS treatment does not change the level of total bile acids in serum, but increases the absolute level of CA as well as the CA level relative to total bile acids[26]. The

relative increase in circulating CA may itself influence glucose metabolism through a decrease of glucose levels *via* the TGR5-cAMP-D2 pathway. However, even if this mechanism occurs it is unlikely to improve overall glycemic control because the level of CDCA relative to total bile acids may be decreased by BAS treatment, and CDCA has similar effects on TGR5 to those of CA[25].

The most plausible mechanism for the glucose-lowering effect of BASs may be associated with effects on the liver X receptor (LXR), as proposed by Bay *et al*[27]. LXR is a nuclear transcription factor that mainly regulates lipid metabolism, and its natural ligands are oxysterols such as 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, and 27-hydroxycholesterol[28,29]. Reduction of bile acid flux in the portal vein by BAS treatment decreases FXR activity in liver, and this decreased FXR activity may induce an increase of LXR activity due to decreased SHP production[20]. LXR activation in liver results in improved glucose sensitivity by preventing gluconeogenesis based on inhibition of the activity of PEPCK and G6Pase[30]. LXR activation may also improve glucose metabolism by promoting expression of glucokinase and glucose transporter 4 (GLUT4) in adipocytes[31] or by promoting insulin secretion in β cells in the pancreas[32]. However, LXR activation may simultaneously increase circulating triglyceride levels by promoting production of stimulating sterol regulatory element-binding protein 1c (SREBP1c) in liver[33]. On the other hand, decreased FXR activity in liver may itself promote PEPCK or SREBP1c production *via* reduction of SHP[19,22]. Therefore, FXR deactivation and resulting LXR activation may have competitive effects on molecules such as PEPCK. However, it is likely that regulation of glucose or lipid metabolism by LXR activation probably overcomes the effects of FXR deactivation[34]. These mechanisms suggest that in liver both activation of FXR by FXR agonists such as CA and CDCA, and deactivation of FXR by BASs improve glycemic control, although these changes have opposite effects on TG production *via* SREBP1c (decreased by FXR agonists and increased by BASs).

BAS-induced secretion of glucagon-like peptide-1 (GLP-1) in the ileum may be another important mechanism. Bile acids can increase GLP-1 secretion in L cells in the intestine *via* TGR5[19]. However, a recent report[35] showed that colesevelam also induced the release of GLP-1 and improved plasma glucose levels and insulin resistance in the diet-induced obesity (F-DIO) rat fed a high fat/high sucrose (HF) diet. In contrast, administration of SC-435, an inhibitor of the apical sodium-dependent bile acid transporter (ASBT), did not change GLP-1, glucose levels, and insulin sensitivity in F-DIO rats fed the HF diet, compared to untreated F-DIO rats fed the same diet[35]. Addition of both colesevelam and SC-435 reduced the total concentration of bile acids in portal blood and increased CYP7A1 mRNA expression in liver, which reflects FXR deactivation[35]. These findings suggest that colesevelam can improve glycemic control by increasing GLP-1 levels in the circulation independently of an

Figure 1 Possible mechanisms of the effects of bile acids and bile acid sequestrants on glucose and lipid metabolism. Bile acids activate farnesoid X receptor (FXR) activity in liver, which leads to increased small heterodimer partner (SHP) production that inhibits phosphoenolpyruvate carboxykinase (PEPCK) and therefore inhibits gluconeogenesis in liver. Bile acids also promote energy metabolism in brown adipose tissue and skeletal muscle *via* the G protein-coupled receptor 5 (TGR5) activation, and increase glucagon-like peptide-1 (GLP-1) secretion *via* TGR5 activation in L cells in the intestine. On the other hand, bile acid sequestrants (BASs) may decrease FXR activity in liver, and the resulting decrease in SHP production may cause activation of liver X receptor (LXR) activity. LXR activation inhibits PEPCK and therefore inhibits gluconeogenesis. BASs can also increase circulating GLP-1 levels. These mechanisms may explain the glucose-lowering effects of bile acids and BASs. Because bile acids decrease sterol regulatory element-binding protein 1c (SREBP1c) production due to increased SHP, bile acids decrease triglyceride (TG) levels. In contrast, indirect LXR activation by BASs can increase SREBP1c production and circulating TG levels. In the figure, solid and dotted lines respectively show promoting and inhibitory effects. CA: cholic acid; CDCA: chenodeoxycholic acid.

effect on FXR in liver. A clinical study also showed that colestimide decreased postprandial plasma glucose levels, but increased GLP-1 in patients with type 2 diabetes[36]. It is clear that the mechanisms underlying the glucose-lowering effect of BASs are complicated and other mechanisms may also be involved. The possible mechanisms are summarized in Figure 1.

EFFECTS OF BASS ON GLUCOSE AND LIPID METABOLISM IN PATIENTS WITH TYPE 2 DIABETES

The glucose-lowering effect of first-generation BASs such as cholestyramine was shown in the 1990s[13], but there was little subsequent interest in this effect for several years. In a small randomized, double-blind, crossover trial in 21 patients (20 men and 1 women) with type 2 diabetes complicated with dyslipidemia treated with glibenclamide or insulin, cholestyramine administered at 16 g/d for 6 mo significantly decreased the mean plasma glucose and LDL-C levels by 13% and 28%, respectively, compared with placebo. A decrease of glycated hemoglobin from 8.8% to 8.3% (not significant) also occurred. The glucose lowering-effect of second-generation BASs such as colesevelam and colestimide has attracted more attention. A pilot study of the effect of colesevelam on glucose levels (Glucose-Lowering effect of WelChol Study: GLOWS) showed that addition of colesevelam at 3.75 g/d in 65 patients with type 2 diabetes that was not fully controlled with sulfonylurea or metformin, alone or in combination significantly decreased HbA1c by 0.5% from a baseline level of 7.9% and LDL-C by 11.7% compared with placebo after 12 wk[14]. Interestingly, the extent of the reduc-

tion was greater in patients with HbA1c ≥ 8.0% (1.0% reduction *vs* placebo). Based on the positive results for glycemic control in the GLOWS study, three phase Ⅲ randomized, double-blind placebo-controlled trials with a 2 wk single blind placebo run-in were performed, in which colesevelam was added to sulfonylurea-, metformin-, and insulin-based therapy, respectively[9-11].

In a 26 wk study in 461 patients with type 2 diabetes treated with sulfonylurea as monotherapy or in combination with other oral antidiabetes drugs, colesevelam (3.75 g/d) significantly reduced HbA1c (baseline 8.2%) by 0.54% in all patients and by 0.79% in a subgroup treated with sulfonylurea monotherapy, and reduced fasting plasma glucose (FPG) by 13.5 mg/dL in all patients, compared with placebo[9]. The reduction of HbA1c in a subgroup with HbA1c > 8.0% at baseline was 0.58% *vs* placebo. Colesevelam also significantly reduced LDL-C by 16.7% compared with placebo, while an insignificant elevation of HDL-C (+0.1%) and a significant elevation of triglyceride (TG) (+17.7%) were observed. In a 26 wk study in 316 patients with type 2 diabetes treated with metformin as monotherapy or in combination with other antidiabetes drugs, colesevelam (3.75 g/d) significantly decreased HbA1c (baseline 8.2%) by 0.54% in all patients and by 0.47% in a subgroup treated with metformin monotherapy, and reduced FPG by 13.9 mg/dL in all patients, compared with placebo[10]. The reduction of HbA1c in a subgroup with HbA1c > 8.0% at baseline was 0.60% *vs* placebo. LDL-C was significantly reduced by 15.7%, with insignificant increases in HDL-C (+0.9%) and TG (+4.7%). In a 16 wk study in 287 patients with type 2 diabetes treated with insulin as monotherapy or in combination with other antidiabetes drugs, colesevelam (3.75 g/d) significantly decreased HbA1c (baseline 8.3%)

Table 1 Studies showing glucose-lowing effect of bile acid sequestrants

	n	Duration (wk)	Therapy	Baseline (g/d)	HbA1c (%)	ΔHbA1c	ΔLDL-C	Others
Garg and Grundy	21	6	cholestyramine	16.00	no description	-0.50%[a]	-28.00%	
Zeive *et al*	65	12	colesevelam	3.75	7.90%	-0.50%	-11.70%	
Fonseca *et al*	461	26	colesevelam	3.75	8.20%	-0.54%	-16.70%	ΔCRP-11.2%
Bay *et al*	316	26	colesevelam	3.75	8.20%	-0.54%	-15.90%	ΔCRP-14.4%[c]
Goldberg *et al*	287	16	colesevelam	3.00	8.30%	-0.50%	-12.80%	ΔCRP-12.2%
Yamakawa *et al*	70	12	colestimide	3.00	7.70%	-0.90%[b]	-23.00%	
Takebayashi *et al*	40	12	colestimide	3.00	7.90%	-0.50%	-14.00%	Δ8-isoPGFα-32%[c]
Kondo and Kadowaki	183	12	colestimide	4.50	8.00%	-0.90%	-22.50%	

ΔHbA1c (change of hemoglobin A1c) is shown as the difference between BAS and placebo except for b. [a]Glycated hemoglobin; [b]Change from baseline. ΔLDL-C: change of low density-lipoprotein cholesterol; ΔCRP: change of C reactive protein by treatment ([c]statistical significance); Δ8-isoPGFα: change of urinary 8-iso-prostaglandin F2α (a marker of systemic oxidative stress) by treatment ([c]statistical significance).

by 0.5% in all patients and by 0.59% in a subgroup treated with insulin monotherapy, compared with placebo[11]. The reduction of HbA1c in a subgroup with HbA1c > 8.0% at baseline was 0.57% *vs* placebo, with an insignificant reduction of FPG (-14.6%). LDL-C was significantly reduced (-12.8%), TG was significantly increased (+21.5%), and HDL-C showed a small and insignificant decrease (-0.9%).

The mean percentage compliance in the three studies with sulfonylurea, metformin, and insulin was high: 93.3%, 92.3%, and 92.7% in the colesevelam group, with similar rates in the placebo group. The results of these studies suggest that colesevelam can reduce HbA1c levels by approximately 0.5% in all type 2 diabetic patients when added to sulfonylurea-, metformin-, or insulin-based therapy. The effect on glycemic control of colesevelam as monotherapy or in combination with other antidiabetes drugs in patients with type 2 diabetes is less clear. However, given the possible effect of BASs on GLP-1, as described above, it will be interesting to investigate the effects of coadministration of colesevelam with a dipeptidyl peptidase IV (DPPIV) inhibitor, which improves glycemic control by preventing degradation of circulating GLP-1.

An effect of colestimide on glycemic control in patients with type 2 diabetes has also been reported. Yamakawa *et al* randomly assigned patients with type 2 diabetes complicated by hyperlipidemia to colestimide (3.0 g/d) or pravastatin (10 mg/d) treatment groups, and investigated the effect of these drugs on lipid and glucose metabolism[15]. In both groups, 33 of 35 patients received monotherapy with oral antidiabetic drugs or insulin, or combination therapy with these agents. Colestimide and pravastatin significantly decreased LDL-C levels by 23% and 17%, respectively, but only colestimide produced a significant decrease in HbA1c (0.9% reduction from a baseline level of 7.7%) after 3 mo of therapy. In our study of colestimide (3.0 g/d; *n* = 20) compared to rosuvastatin (2.5 mg/d; *n* = 20) in patients with type 2 diabetes complicated with hyper-LDL-cholesterolemia, HbA1c decreased by approximately 0.6% from a baseline level of 7.9%, with a treatment difference of 0.5% between colestimide and rosuvastatin after treatment for 3 mo[16]. LDL-C was decreased by rosuvastatin and colestimide by 39% and 14%, respectively. All except 3 patients in the colestimide group

had already taken other antidiabetic drugs. Kondo and Kadowaki also recently reported an effect of high dose colestimide therapy (4.5 g/d) on glycemic control in a randomized double-blind placebo-controlled study (*n* = 183 at the start of randomization)[12]. Colestimide was generally administered as monotherapy, except in a few patients. After 3 mo, a 0.9% reduction of HbA1c and a decrease in FPG of 22 mg/dL were observed in the colestimide group (*n* = 86) compared with the placebo group (*n* = 86). In subgroups of patients with HbA1c 8.0 to < 9.0% and ≥ 9.0%, colestimide decreased HbA1c by 1.0% and 1.5%, respectively, compared to placebo. Based on these reports, the HbA1c-lowering effect of colestimide appears to be somewhat stronger than that of colesevelam. It is important to note that the colestimide trials were all performed in Japan, and that the clinical characteristics of the patients differed from those in trials of colesevelam. A trial with direct comparison of the effects of colesevelam and colestimide on glycemic control has yet to be performed. Co-administration of colestimide with DPPIV inhibitors has also not been studied. Studies showing glucose-lowing effect of bile acid sequestrants are summarized in Table 1.

SAFETY, TOLERABILITY, AND DRUG INTERACTIONS IN BAS TREATMENT

As mentioned above, cholestyramine, a first-generation BAS, was shown to lower LDL-C before the clinical use of statins, and was one of the first drugs to show that lowering cholesterol could decrease the risk of CAD[1,2]. However, after the appearance of statins, use of cholestyramine has been limited because of its relatively weak LDL-C lowering effect compared with statins, and because of poor compliance due to a high frequency of side effects, high dosage, requirement for suspension in water, and unpleasant taste[1,2]. Colestipol, another first-generation BAS, was better tolerated by patients than cholestyramine, but its effects were still not satisfactory[37]. The main side effect of BASs is gastrointestinal symptoms including dyspepsia, nausea, and particularly constipation, while systemic severe side effects are rare. Regarding the mechanism of constipation induced by BAS, CDCA in feces promotes secretion of water and electrolytes into

the intestine by activating adenyl cyclase and increasing intracellular cAMP in colonic mucosa cells[38,39]. BAS absorbs bile acids, which causes a decrease in the level of intratubular bile acids and this may induce constipation.

Colesevelam and colestimide are second-generation BASs with reduced side effects, including constipation. For WelChol® (colesevelam hydrochloride)[40], the frequency of adverse reactions is relatively low, with 11.0%, 8.3%, and 4.2% of patients developing constipation, dyspepsia, and nausea, respectively, compared to 7.0%, 3.5%, and 3.9%, respectively, with placebo. Myalgia was found in 2.1% of patients treated with colesevelam compared to 0.4% with placebo. The frequency of constipation with colestimide has been reported to be 3.6%[41]. Both colesevelam and colestimide can be administered as tablets (the latter is also formulated as a granulated powder). The tablet size is still somewhat large, but the drug compliance is better than that for cholestyramine. In addition, BASs can be used safely in children, in pregnant women, and in patients with liver and renal disease because they are not absorbed systemically.

Drug interactions are also an important concern in BAS administration. Cholestyramine has many drug interactions since it increases the absorption of common drugs including digoxin, diuretics, estrogens, hydrocortisone, propranolol, thyroxine, and warfarin, and may also interfere with fat-soluble vitamins such as vitamins A, D, E and K[17]. Therefore, it is recommended that other drugs are taken at least 1 h before or 4 h after cholestyramine treatment. In contrast, colesevelam does not influence the bioavailability of digoxin, fenofibrate, lovastatin, metoprolol, quinidine, valproic acid, pioglitazone, and warfarin[40]. Drugs with a known interaction with colesevelam include glyburide, levothyroxine, and oral contraceptives containing ethinyl estradiol and norethindrone, and it is recommended that these drugs should be taken at least 1 hour prior to colesevelam administration[40]. In summary, severe side effects of BASs are rare, and second-generation BASs have improved tolerability and reduced drug interactions compared to first-generation BASs.

BASS IN THE TREATMENT OF TYPE 2 DIABETES: CURRENT ROLE AND FUTURE PERSPECTIVES

The main role of BASs in treatment of diabetes appears to be as second-line drugs in combination with other antidiabetic agents. The glucose-lowering effect of BASs is moderate to mild, and BAS monotherapy for diabetes has only been examined in one study of colestimide[12]. In fact, colesevelam is only currently approved as adjunct therapy for glycemic control in type 2 diabetes in the USA (since 2008), and colestimide has yet to be approved for treatment of type 2 diabetes alone. As discussed above, BASs can decrease HbA1c by 0.5% to 0.9%[9-16], and the glucose-lowering effect of BASs may be stronger in patients with higher baseline HbA1c levels[9-12,14,16]. BASs rarely cause body weight gain or increase hypoglycemia[9-11], and

second-generation BASs have improved drug compliance due to reduced side effects of constipation or dyspepsia[9-11,41]. Systemic severe side effects of BASs are rare. These characteristics support the utility of BASs as additional drugs for treatment of diabetes.

It is apparent that BASs are more suitable for treatment of patients with type 2 diabetes complicated with hyper-LDL cholesterolemia, rather than patients with type 2 diabetes alone, because there is evidence that reduction of LDL-C by cholestyramine decreases the risk of CAD[1,2]. However, statins are now established as the first choice treatment for hyper-LDL cholesterolemia due to their strong LDL-C lowering effect and prevention of cardiovascular events[3-6]. The beneficial effect of rosuvastatin for prevention of cardiovascular events even extends to apparently healthy men and women with baseline LDL-C levels < 130 mg/dL, but high-sensitivity C reactive protein (CRP) of ≥ 2 mg/L[5]. A beneficial effect of atorvastatin for prevention of cardiovascular events has also been shown in patients with type 2 diabetes with relatively low LDL-C levels (≤ 160 mg/dL)[4].

The target LDL-C level in very high-risk patients (those with cardiovascular disease with diabetes, cigarette smoking or factors associated with metabolic syndrome) has recently been lowered to ≤ 70 mg/dL[42]. This suggests that combination therapy will become more important in patients who cannot achieve the target levels, even with high dose statins, or cannot tolerate high dose statins because of side effects such as myalgia. In addition, a recent meta-analysis suggested that most statins, including rosuvastatin and atorvastatin, are weakly but significantly associated with new onset of type 2 diabetes[43]. This potentially deleterious effect of statins on glucose metabolism may become more apparent when they are used at a high dose[44]. Therefore, combination therapy of statins with other antihyperlipidemic drugs may be appropriate, and addition of BASs to statin therapy may be suitable, especially for type 2 diabetes with hyper-LDL-cholesterolemia. It should be noted that it is still unclear whether statins worsen glycemic control after onset of type 2 diabetes. Regarding the effects of BASs, colesevelam monotherapy can decrease LDL-C by 15% to 21%[17,40,45,46] and by a further 10% in combination with statins[8]. However, care is required with use of BASs in patients with high TG levels because of a potential TG elevation effect[47]. Anti-inflammatory and anti-oxidative stress effects of BASs have also been reported in patients with type 2 diabetes[8,16].

The above findings suggest that BASs are especially suitable for patients with type 2 diabetes complicated by hyper-LDL cholesterolemia, since these patients often fail to achieve target levels of HbA1c and LDL-C with use of other antidiabetes drugs and statins. However, there is still no evidence to show that addition of second-generation BAS such as colesevelam and colestimide reduces the risk of cardiovascular events in these patients.

CONCLUSION

Second-generation BASs such as colesevelam and coles-

timide are generally well tolerated and severe systemic side effects are rare. When BAS is coadministered with antidiabetes drugs such as sulfonylurea, metformin and insulin, a reduction in HbA1c of approximately 0.5% to 0.9% can be expected without increased hypoglycemia or weight gain. The LDL-C lowering effect of BASs is relatively mild, but coadministration of a BAS with statins is likely to produce a further decrease of LDL-C. BAS treatment may be especially beneficial for patients who have not reached target HbA1c and LDL-C levels using other antidiabetic drugs and statins. Further studies are required to determine whether addition of a BAS in these patients will reduce mortality and the risk of cardiovascular events.

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Efficacy and safety of vildagliptin/pioglitazone combination therapy in Korean patients with diabetes

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Abstract

AIM: To assess the efficacy and safety of vildagliptin/pioglitazone combination therapy in Korean patients with type 2 diabetes mellitus (T2DM).

METHODS: This was a *post hoc* analysis in Korean patients, from a 24-wk, randomized, active-controlled, double-blind, parallel-group, multicenter study. Eligible patients were aged between 18 and 80 years, drug naive, and had been diagnosed with T2DM [hemoglobin A_{1c} (HbA$_{1c}$): 7.5%-11.0% and fasting plasma glucose (FPG): < 270 mg/dL (< 15 mmol/L)]. Patients were randomized (1:1:1:1) to receive the vildagliptin/pioglitazone combination at 100/30 mg q.d. (high-dose) or 50/15 mg q.d. (low-dose), vildagliptin 100 mg q.d., or pioglitazone 30 mg q.d. monotherapies. The primary outcome measure was change in HbA$_{1c}$ from baseline to endpoint.

RESULTS: The distribution of baseline demographic and clinical parameters was well balanced between treatment groups. The overall mean age, body mass index, HbA$_{1c}$, FPG, and duration of disease were 50.8 years, 24.6 kg/m^2, 8.6%, 10.1 mmol/L, and 2.2 years, respectively. Adjusted mean changes (± standard error) in HbA$_{1c}$ from baseline (~8.7%) to week 24 endpoint were -2.03% ± 0.16% (high-dose, N = 34), -1.88% ± 0.15% (low-dose, N = 34), -1.31% ± 0.21% (vildagliptin, N = 36), and -1.52% ± 0.16% (pioglitazone, N = 36). The high-dose combination therapy demonstrated greater efficacy than monotherapies [vildagliptin (P = 0.029) and pioglitazone (P = 0.027)]. Percentage of patients achieving HbA$_{1c}$ < 7% and ⩽ 6.5% was the highest in the high-dose group (76% and 68%) followed by low-dose (58% and 47%), vildagliptin (59% and 37%), and pioglitazone (53% and 28%) groups. The overall incidence of adverse events was comparable.

CONCLUSION: In Korean patients, first-line treatment with high-dose combination therapy improved glycemic control compared to pioglitazone and vildagliptin monotherapies, consistent with results published for the overall study population.

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INTRODUCTION

Diabetes is emerging as a global epidemic, imposing enormous humanitarian and economic burdens on society. According to a WHO projection, by 2030, approximately 190 million people will be affected in the Asia-Pacific region alone. Over 3 million of these people are expected to be from Korea[1].

Evidence suggests that patients with type 2 diabetes mellitus (T2DM) increasingly require multiple pharmacological combinations to reach treatment goals. This is specially relevant for diabetic patients in Korea, where only 37.3% achieve glycosylated hemoglobin A_{1c}(HbA$_{1c}$) < 7% with the currently available therapies[2]. Clinical inertia, with failure to advance therapy despite persistently elevated HbA$_{1c}$ levels above target, has become a major problem for the stepwise approach to treatment[3]. Initial combination therapy using two oral anti-diabetic drugs (OAD) with complementary mechanisms of action is an alternative approach that may provide better or more sustained glycemic control. It may also allow the use of lower doses of the component OADs and thus minimize any dose-related adverse events (AEs).

Probably because of different genetic characteristics, diet habits and lifestyle, diabetic patients from Korea show a different clinical profile than Caucasians[4,5]. More than 70% to 80% of Korean patients with T2DM are non-obese, with a body mass index (BMI) below 25 kg/m^2. This finding is in sharp contrast to the patients from the West, where diabetes and obesity are frequently concurrent in the population[5,6]. Although impairment of early phase insulin secretion is reported to be the initial abnormality in the development of glucose intolerance in Koreans, the contribution of increased insulin resistance in the pathophysiology of diabetes is also becoming significant[7].

Vildagliptin is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor that improves pancreatic islet function, evidenced from improved ability of α-cells and β-cells to sense and respond to glucose after treatment[8]. In addition, vildagliptin inhibits hepatic glucose production during meals as well as during the overnight post-absorptive period. DPP-4 inhibition by vildagliptin sup-

presses endogenous glucose production and enhances islet function after single-dose administration[9]. On the other hand, pioglitazone is an agonist for peroxisome proliferator-activated receptors (PPARs) in target tissues for insulin action that regulates transcription of insulin-responsive genes involved in controlling glucose production, transportation, and utilization, thereby enhancing tissue sensitivity to insulin[10]. We recently reported results of a multi-center, international study which indicate that first-line treatment of diabetic patients with vildagliptin/pioglitazone combination therapy provides better glycemic control than the corresponding monotherapies and has a comparable tolerability profile[11].A large proportion of the study population were Korean providing an opportunity to conduct an exploratory analysis to evaluate the efficacy and tolerability of vildagliptin/pioglitazone combination therapy compared with corresponding monotherapies in Korean patients with T2DM. Results of this analysis are presented here.

MATERIALS AND METHODS

Study design

This is a Korean sub-group analysis of a 24-wk, randomized, active-controlled, double-blind, double-dummy, parallel-group study conducted at 145 centers in eight countries, the results of which have been published previously[11]. Participating centers were located in the United States, Europe, and Asia (Korea, India, and Taiwan). In Korea, the study was conducted at 15 centers.

The study was conducted in accordance with the ICH-Good Clinical Practice Guidelines, the Declaration of Helsinki, and the local laws and regulations. The protocol was approved by the independent ethics committee/institutional review board at each study site.

Study population

Eligible patients were aged between 18 and 80 years and had been diagnosed with T2DM (HbA$_{1c}$: 7.5%-11.0%, BMI: 22-45 kg/m^2, and fasting plasma glucose (FPG): < 270 mg/dL (< 15 mmol/L). The patients had not received any treatment for at least 12 wk prior to screening and no oral anti-diabetic agent for more than three consecutive months in the past.

Patients were excluded if they had a history of type 1 or secondary forms of diabetes, acute metabolic diabetic complications, myocardial infarction, unstable angina, or coronary artery bypass surgery within the previous 6 mo, congestive heart failure, liver disease such as cirrhosis or chronic active hepatitis, or any contraindications and warnings according to the country-specific label for pioglitazone. Patients with any of the following laboratory abnormalities were also excluded: alanine aminotransferase or aspartate aminotransferase > 2.5 times the upper limit of normal (ULN); direct bilirubin > 1.3 times the ULN; serum creatinine levels > 220 mmol/L, clinically significant abnormal TSH, or fasting triglycerides (TGs) > 7.9 mmol/L.

Table 1 Baseline demographics and background characteristics of Korean patients (randomized population)				
Mean ± SD	Vilda/Pio 100/30 mg q.d.	Vilda/Pio 50/15 mg q.d.	Vilda 100 mg q.d.	Pio 30 mg q.d.
N	34	34	36	36
Males, n (%)	23 (67.6)	25 (73.5)	32 (88.9)	30 (83.3)
Age (years)	52.9 ± 10.6	51.3 ± 10.3	49.8 ± 10.0	49.2 ± 9.4
BMI (kg/m^2)	24.7 ± 2.8	24.7 ± 2.5	24.7 ± 2.2	24.3 ± 2.3
HbA$_{1c}$ (%)	8.4 ± 0.8	8.8 ± 0.9	8.6 ± 0.9	8.7 ± 0.9
FPG (mmol/L)	9.4 ± 2.0	10.1 ± 2.0	10.9 ± 2.6	9.8 ± 2.6
Duration of T2DM (years)	3.1 ± 3.6	1.6 ± 2.4	1.9 ± 2.5	2.1 ± 2.7

T2DM: type 2 diabetes mellitus; FPG: fasting plasma glucose; HbA$_{1c}$: hemoglobin A$_{1c}$; BMI: body mass index.

Eligible patients were randomized to receive vildagliptin/pioglitazone combination therapy at 100/30 mg q.d. (high-dose, $N = 34$) or 50/15 mg q.d. (low-dose, $N = 34$), or monotherapy with vildagliptin 100 mg q.d. ($N = 36$) or pioglitazone 30 mg q.d. ($N = 36$). All the participants provided written informed consent.

Study assessments
The efficacy variables were change from baseline to endpoint in (1) HbA$_{1c}$; (2) FPG; (3) post-prandial plasma glucose (PPG), glucagon-like peptide-1 (GLP-I), glucagon and insulin levels after a meal test; (4) fasting pro-insulin, pro-insulin/insulin ratio, homeostasis model assessment of β-cell function (HOMA-B), insulinogenic index, HOMA of insulin resistance (HOMA-IR); and (5) changes in body weight. HbA$_{1c}$ reductions in Korean patients were also compared to the non-Korean (all patients from the overall study population, excluding the Korean patients) and non-Asian (all patients from the overall study population, excluding the Indian, Taiwanese, and Korean patient sub-populations) subgroups of patients, and the overall study population.

A standard breakfast meal (500 kcal; 60% carbohydrates, 30% fat, and 10% protein) was provided at baseline (week 0) and at week 24 to the subset of patients (44.6%) who had volunteered to participate in the meal challenge test. Samples for measurement of PPG, insulin, glucagon, and active GLP-1 levels were obtained at 20 min pre-meal and 0, 15, 30, 60, 90, 120, and 240 min post-meal (provided immediately after the 0-min sample and consumed within 15 min). The areas under curve (AUC) for PPG, insulin, and GLP-1 were calculated with the trapezoidal method.

Standard hematology and biochemistry laboratory assessments were made at each visit except for week 16. HbA$_{1c}$ was quantified using ion exchange high-performance liquid chromatography. All laboratory assessments were made by a central laboratory (Covance-US, Indianapolis, IN, USA) with standardized and validated procedures according to Good Laboratory Practice.

Safety and tolerability were evaluated by physical examination, measurement of vital signs, recording of electrocardiograms, and safety laboratory measurements. All AEs were monitored throughout the study and evaluated by the investigators for level of severity, duration, outcome, and relationship to study drug.

Statistical analysis
Data for this *post hoc* analysis were summarized with respect to demography, efficacy, and safety variables. All efficacy analyses were performed on the intent-to-treat (ITT) population (randomized patients who received at least one dose of study medication and for whom a baseline and at least one post-baseline efficacy assessment was available) using last observation carried forward for patients who discontinued early.

The mean change in each efficacy variable from baseline to endpoint was analyzed using an analysis of covariance (ANCOVA) model, with treatment and pooled center as factors and baseline as the covariate. All ANCOVAs were performed on the set of patients within both treatment arms being compared. Data are presented as mean ± standard error (SE) unless otherwise stated. Statistical significance for subgroup analyses was set at 0.05.

RESULTS
Patient demographics
The demographic and clinical parameters of patients included in this sub-group analysis are summarized in Table 1. These characteristics were generally comparable across treatment arms. The overall mean age, BMI, HbA$_{1c}$, FPG, and duration of disease were 50.8 years, 24.6 kg/m^2, 8.6%, 10.1 mmol/L, and 2.2 years, respectively.

Change in HbA$_{1c}$
Figure 1 represents the time-course of mean HbA$_{1c}$ during a 24-wk treatment period in the four treatment arms. Near-maximal efficacy was reached by week 16, and maintained up to 24 wk, for all treatment groups. The adjusted mean change (AMΔ) in HbA$_{1c}$ from baseline to endpoint was similar between the high-dose and low-dose combination groups (-2.03% ± 0.16% and -1.88% ± 0.15%, respectively); however, the change was greater in patients receiving high-dose combination compared with those receiving monotherapy with vildagliptin (-1.31% ± 0.21%) or pioglitazone (-1.52% ± 0.16%), and the difference between these treatments (high-dose combination *vs* monotherapies) was significant ($P < 0.05$). The mean HbA$_{1c}$ reduction was numerically larger for the low-dose combination compared with pioglitazone monotherapy; however, the difference was not statistically

Figure 1 Mean (± standard error) hemoglobin A₁c during 24-wk treatment with vildagliptin/pioglitazone combination (100/30 mg q.d. circles; 50/15 mg q.d. triangles), vildagliptin 100 mg q.d. (squares), or pioglitazone 30 mg q.d. (diamonds) in a Korean population. HbA_{1c}: hemoglobin A_{1c}.

Figure 2 Mean (± standard error) fasting plasma glucose during 24-wk treatment with vildagliptin/pioglitazone combination (100/30 mg q.d. circles; 50/15 mg q.d. triangles), vildagliptin 100 mg q.d. (squares), or pioglitazone 30 mg q.d. (diamonds) in a Korean population. FPG: fasting plasma glucose.

significant (between-treatment difference, -0.30% ± 0.21%, $P = 0.156$).

A sub-analysis of the primary endpoint was also performed on the basis of initial HbA_{1c} level. In all treatment groups, patients with high HbA_{1c} at baseline (> 8% and > 9%) showed consistently larger reductions in HbA_{1c} than patients with lower HbA_{1c} at baseline. In patients with baseline HbA_{1c} > 9.0% receiving the high-dose combination, the mean change from baseline HbA_{1c} was -3.14% ± 0.32%. In those receiving the low-dose combination, vildagliptin monotherapy, or pioglitazone monotherapy, the mean changes from baseline HbA_{1c} were -2.20% ± 0.31%, -1.48% ± 0.50%, and -2.01% ± 0.28%, respectively.

The percentage of patients achieving target HbA_{1c} level of < 7% and ≤ 6.5%, respectively, was highest in the high-dose combination group (75.8% and 67.6%) compared with the low-dose combination (57.6% and 47.1%), vildagliptin (58.8% and 37.1%), and pioglitazone (52.8% and 27.8%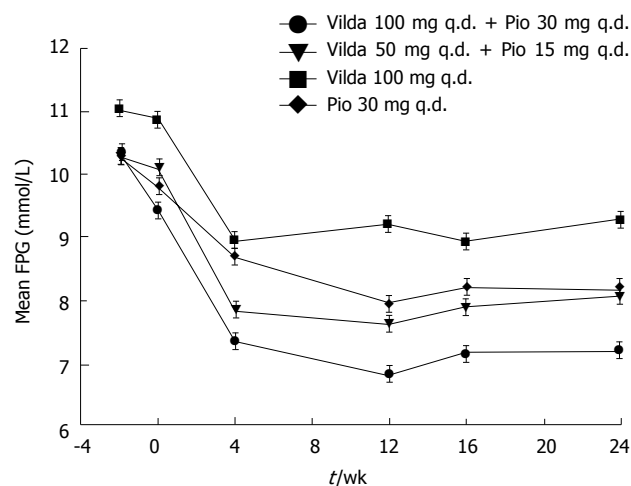) groups. Treatment difference between high-dose combination and pioglitazone monotherapy was statistically significant (< 7%, $P = 0.047$; ≤ 6.5%, P < 0.001). The overall ability of the different therapies to bring about ≥ 1% reduction in HbA_{1c} was comparable for high-dose and low-dose combination therapies (82.4% and 85.3%), and it was lower for the component monotherapies (vildagliptin, 68.6%; pioglitazone, 69.4%).

The adjusted mean change in HbA_{1c} from baseline to endpoint was similar between the high-dose combination groups in Korean (-2.03% ± 0.16%), non-Korean (-1.92% ± 0.11%), non-Asian (-1.93% ± 0.13%), and the overall study population (-1.93% ± 0.09%). However, numerically larger reductions were observed in Korean patients receiving the low-dose combination (-1.88% ± 0.15%) compared with non-Korean (-1.61% ± 0.11%), non-Asian (-1.51% ± 0.14%), and the overall study population (-1.67% ± 0.09%).

Change in FPG
As shown in Figure 2, reduction in the FPG level was observed during the 24-wk treatment period in all the treatment arms. Near-maximal reductions (mmol/L) were observed after 4 wk of initiation of therapy, and were maintained over the next 20 wk (mean reductions of -2.30 ± 0.27, -1.93 ± 0.27, -1.13 ± 0.36, and -1.60 ± 0.26 in the high-dose combination, low-dose combination, vildagliptin, and pioglitazone groups, respectively).

Change in prandial variables
Sixty-two patients (44.6%) volunteered for the standard meal challenge tests (15, 12, 18, and 17 patients in the high-dose and low-dose combinations, vildagliptin, and pioglitazone groups, respectively). Figure 3 shows the AMΔ in the indicated prandial variables across the four treatment groups for these patients.

The adjusted post-prandial plasma glucose $AUC_{0-4\ h}$ (mmol × h/L) was greatly reduced with the high-dose (-9.60 ± 1.03) and low-dose (-9.14 ± 1.66) combinations as well as with vildagliptin monotherapy (-7.55 ± 1.37), in comparison to the reduction with pioglitazone monotherapy (-2.82 ± 0.97). The difference between treatments was statistically significant for combination therapy *vs* pioglitazone monotherapy (high-dose, P < 0.001; low-dose, P = 0.005). Similar reductions were seen in 2-h PPG levels, with the largest reductions observed in the high-dose combination therapy group.

AMΔ in post-prandial active GLP-1 $AUC_{0-2\ h}$ (pmol × h/L) were 14.56 ± 2.87, 6.87 ± 0.99, 4.24 ± 4.80, and -7.95 ± 3.49 in the high-dose combination, low-dose combination, vildagliptin, and pioglitazone groups, respectively. The difference in mean change was statistically significantly higher in both the combination groups (high-dose, 22.51 ± 5.22, $P = 0.012$; low-dose, 11.18 ± 1.35, P = 0.014), compared with pioglitazone monotherapy.

AMΔ in post-prandial glucagon $AUC_{0-2\ h}$ (pmol × h/L)

Figure 3 Mean (± standard error) change in the indicated prandial variables at endpoint, following treatment with vildagliptin/pioglitazone combination (100/30 mg q.d. or 50/15 mg q.d.), vildagliptin 100 mg q.d., or pioglitazone 30 mg q.d., in patients that volunteered for the meal test. [a]Significant difference compared with pioglitazone 30 mg q.d. monotherapy.

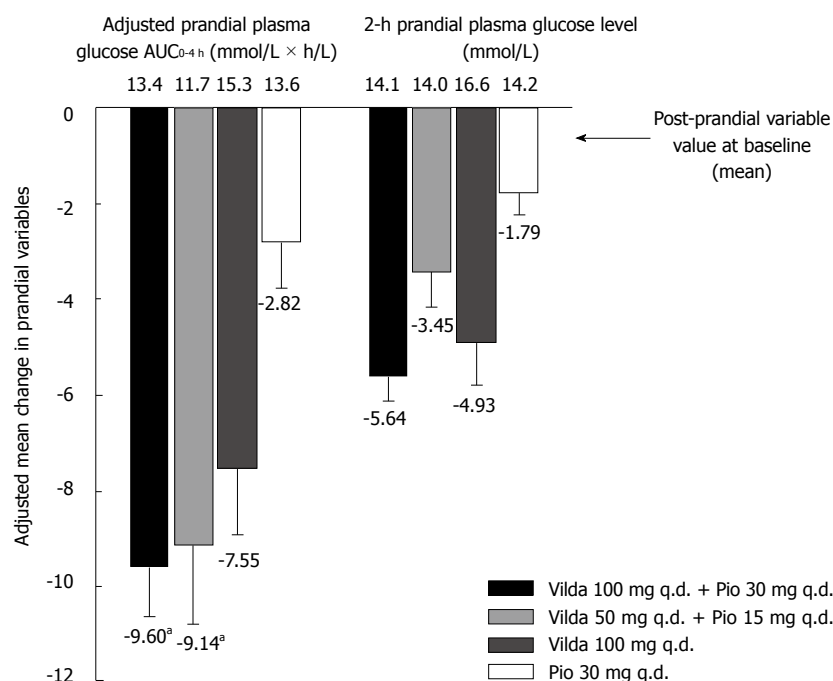were -7.84 ± 1.78, -3.32 ± 1.92, -5.06 ± 2.57, and -3.02 ± 1.67 in the high-dose combination, low-dose combination, vildagliptin, and pioglitazone groups, respectively. The difference in mean change was numerically higher in both the combination groups (high-dose, -4.82 ± 2.44, P = 0.058; low-dose, -0.23 ± 2.52, P = 0.928), compared with pioglitazone monotherapy.

AMΔ in post-prandial plasma insulin $AUC_{0-4 h}$ (pmol × h/L) varied substantially between the treatment groups (high-dose, -30.07 ± 50.02; low-dose, 4.09 ± 53.54; vildagliptin, 144.56 ± 42.37; and pioglitazone, -10.24 ± 46.97).

Change in measures of islet β-cell function and insulin resistance

Fasting pro-insulin levels decreased across all treatment groups. The reductions (pmol/L) were numerically higher and comparable between the high-dose and low-dose combination groups (-9.45 ± 1.74 and -8.68 ± 1.46) than with vildagliptin (-2.43 ± 2.38) or pioglitazone (-7.21 ± 1.64) monotherapy. Correspondingly, small changes in fasting pro-insulin/insulin ratio (-0.19 to -0.27) were also observed across all treatment groups.

HOMA-B increased across all treatment groups. The largest increase was observed in the high-dose combination group, followed by vildagliptin monotherapy, low-dose combination, and pioglitazone monotherapy groups (12.09 ± 2.83, 8.06 ± 2.51, 4.86 ± 1.58, and 4.57 ± 2.84, respectively). However, the difference between combination therapies (high-dose and low-dose) and pioglitazone was not significant.

In both the high-dose and the low-dose combination therapy groups, an increase in insulinogenic index (0-min peak glucose) was observed (0.15 ± 0.06 and 0.42 ± 0.18, respectively) compared with the change in vildagliptin (0.08 ± 0.02) and pioglitazone (0.01 ± 0.07) monotherapy groups.

HOMA-IR decreased for all treatment groups except vildagliptin monotherapy (high-dose combination, -0.45 ± 0.14; low-dose combination, -0.56 ± 0.09; vildagliptin, 0.18 ± 0.18; and pioglitazone, -0.64 ± 0.14). The between-treatment differences in reduction were not significant.

Change in body weight

Increase in weight from baseline to end of study was observed for three treatment groups (2.39 ± 0.49 kg, 1.59 ± 0.47 kg, and 1.54 ± 0.48 kg for high-dose and low-dose combinations, and pioglitazone monotherapy, respectively). No weight gain was observed with vildagliptin monotherapy (0.64 ± 0.30 kg).

Safety and tolerability

During the 24-wk study, all treatments were generally well tolerated. The overall incidence of AEs was comparable across treatment groups (summarized in Table 2). The majority of reported AEs were mild to moderate in severity. The most frequently reported AEs in the study were nasopharyngitis, dizziness, and headache.

The proportion of AEs suspected by the investigators to be study drug-related were relatively higher in the high-dose combination group (17.6%) than in other groups (11.8% in low-dose combination, 2.9% in vildagliptin monotherapy, and 8.3% in the pioglitazone monotherapy group). However, no clustering of specific AEs assessed as drug-related was observed in any treatment group. No hypoglycemic events were reported in this population. AE-related discontinuations were infrequent in all treatment groups, with no meaningful relation to treatment or dose of combination treatment.

A total of 3 AEs were adjudicated by the adjudication committees, with one report each of stroke (low-dose combination), angioedema (vildagliptin monotherapy), and generalized edema (pioglitazone monotherapy).

Table 2 Number (%) of Korean patients with adverse events, SAEs, and discontinuations (safety population)

	Vilda/Pio 100/30 mg q.d. (*N* = 34) *n* (%)	Vilda/Pio 50/15 mg q.d. (*N* = 34) *n* (%)	Vilda 100 mg q.d. (*N* = 35) *n* (%)	Pio 30 mg q.d. (*N* = 36) *n* (%)
Any primary system organ class AE	13 (38.2)	15 (44.1)	13 (37.1)	13 (36.1)
Common AEs				
Nasopharyngitis	0	4 (11.8)	2 (5.7)	3 (8.3)
Dizziness	2 (5.9)	1 (2.9)	2 (5.7)	3 (8.3)
Headache	3 (8.8)	1 (2.9)	0	0
Upper respiratory tract infection	0	0	2 (5.7)	2 (5.6)
Asthenia	1 (2.9)	1 (2.9)	0	2 (5.6)
Constipation	0	0	2 (5.7)	1 (2.8)
AEs leading to discontinuations	2 (5.9)	2 (5.9)	1 (2.9)	1 (2.8)
Headache	1 (2.9)	0	0	0
Hepatitis	1 (2.9)	0	0	0
Cerebral hemorrhage	0	1 (2.9)	0	0
Colon cancer	0	1 (2.9)	1 (2.9)	0
Generalized edema	0	0	0	1 (2.8)
SAEs	1 (2.9)	2 (5.9)	1 (2.9)	0
Thermal burn	1 (2.9)	0	0	0
Cerebral hemorrhage	0	1 (2.9)	0	0
Colon cancer	0	1 (2.9)	1 (2.9)	0

AEs: adverse events.

The overall incidence of other clinically significant AEs was higher with high-dose combination therapy (11.7%) than with other treatments (5.6%-8.8%), primarily because of the higher incidence of mild headache (8.8%) in this group.

No deaths occurred during the study period. Overall, SAEs were observed in 4 patients during the course of the treatment, with no apparent relation to treatment or dose of combination therapy. No major changes or consistent trends were observed for any hematological, biochemical, or urinanalysis parameter or vital signs, and the frequency of treatment-emergent ECG abnormalities was low and comparable in all treatment groups.

DISCUSSION

This *post hoc* analysis suggests that in Korean patients with T2DM, first-line treatment with a vildagliptin/pioglitazone high-dose combination provides, as in the overall population, better glycemic control than the individual component monotherapies. The adjusted mean change in HbA$_{1c}$ from baseline to endpoint was comparable between the high-dose and low-dose combination groups in Korean patients, both numerically larger than that reported in the overall population[11].

In this *post hoc* analysis, 76% of patients achieved the recommended target HbA$_{1c}$ of < 7% in the high-dose combination arm, which is numerically higher than the 65% reported in the overall study population[11]. This may be attributed to pathophysiological differences between Asian and Caucasian diabetic populations. There is some evidence suggesting that small increases in insulin resistance uncover a greater degree of β-cell dysfunction in Asian populations than in non-Asians[7,12]; the therapeutic effect of vildagliptin may then be intensified in patients with greater degrees of β-cell dysfunction.

In the current study, in the sub-population of patients participating in the meal test, treatment with the combination therapy demonstrated substantial reduction from baseline to endpoint in PPG AUC$_{0-4 h}$ and 2-h PPG (≈ -4 mmol/L), as compared to the reduction with pi oglitazone monotherapy. The decrease in PPG levels was associated with concomitantly improved post-meal GLP-1 levels and reduced post-prandial glucagon levels. In addition there was a tendency towards improvement in markers of β-cell function (HOMA-B and insulinogenic index) and insulin resistance (HOMA-IR). All these differences and trends are consistent with previous studies with vildagliptin and its principal mechanism of action to increase the sensitivity of the α- and β-cells to glucose. In keeping with this mechanism is the finding that there was no increased risk of hypoglycemia when vildagliptin was administered in combination with pioglitazone.

Both the combination therapies were well tolerated with an overall similar incidence of AEs and SAEs across treatment groups, and with no discernible relationship with treatment and dose of combination therapy.

The main limitation of this study is that as a *post hoc* analysis, it was not adequately powered to provide answers to some questions. Nevertheless, even with limited number of patients per treatment group the significant difference in the treatment arms indicates the usefulness of the combination therapy in Korean patients, and clears the way for a dedicated study in this specific patient population.

In conclusion, this sub-study indicates that the overall outcomes in Korean patients with T2DM are consistent with results seen in the overall study population. Treatment with vildagliptin and pioglitazone (high-dose combination) improved glycemic control with substantial reductions in HbA$_{1c}$, PPG, FPG, and large HbA$_{1c}$ responder rates at study endpoint compared with that of piog-

litazone monotherapy. Though the results were only statistically significant with the high-dose combination, the trend towards relatively large reductions with the low-dose combination should be explored further in a study specifically designed to investigate this trend in this sub-population. Furthermore, studies comparing the effect of low-dose combination therapy in different ethnic populations are warranted.

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COMMENTS

Background
Evidence suggests that patients with type 2 diabetes mellitus (T2DM) increasingly require multiple pharmacological combinations to reach treatment goals. However, clinical inertia in up-titration of treatment dose and initiation of add-on therapies may contribute to sub-optimal glycemic control rates. Initial combination therapy using two oral anti-diabetic drugs with complementary mechanisms of action is an alternative approach that may provide better or more sustained glycemic control, and allow use of lower doses of the component therapies. Diabetic patients from Korea have differences in genetic characteristics, diet habits and lifestyle, resulting in differences in the clinical profile, as compared to Caucasian patients. Only 37.3% of Korean diabetic patients achieve glycosylated hemoglobin (HbA$_{1c}$) < 7% with the currently available therapies. Thus, specific studies and analyses assessing the efficacy and safety of newer therapies in Korean patients are warranted.

Research frontiers
Vildagliptin is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor that improves pancreatic islet function, evidenced from improved ability of α-cells and β-cells to sense and respond to glucose after treatment. In addition, vildagliptin inhibits hepatic glucose production during meals as well as during overnight post-absorptive period. Pioglitazone is an agonist for peroxisome proliferator-activated receptors in target tissues for insulin action, which enhances tissue sensitivity to insulin. We previously reported results from a multi-center, international study which indicated that first-line treatment of diabetic patients with vildagliptin/pioglitazone combination therapy provides better glycemic control than the corresponding monotherapies and has a comparable tolerability profile. Drug combinations of vildagliptin/pioglitazone 100/30 mg q.d. (high-dose) or 50/15 mg q.d. (low-dose), or component monotherapies (vildagliptin 100 mg q.d. or pioglitazone 30 mg q.d.) were evaluated in this study. Data from an exploratory analysis of these study results in Korean patients with T2DM, to evaluate the efficacy and tolerability of vildagliptin/pioglitazone combination therapy compared with corresponding monotherapies, are presented here.

Innovations and breakthroughs
Results from this *post hoc* analysis suggest that in Korean patients with T2DM, first-line treatment with vildagliptin/pioglitazone high-dose combination provides, as in the overall population, better glycemic control than the individual component monotherapies. Percentage of patients achieving HbA$_{1c}$ < 7% and ≤ 6.5% was highest in the high-dose group (76% and 68%) followed by low-dose (58% and 47%), vildagliptin (59% and 37%), and pioglitazone (53% and 28%) groups. Combination therapy (high-dose) also provided substantial reductions in PPG, FPG, and large HbA$_{1c}$ responder rates at study endpoint compared with that of pioglitazone monotherapy. The combinations were well tolerated with an overall similar incidence of AEs and SAEs across treatment groups, with no added risk of hypoglycemia, and with no discernible relationship with treatment and dose of combination therapy.

Applications
Evidence suggests that patients with T2DM increasingly require multiple phar-

macological combinations to reach treatment goals. An early combination, using two oral anti-diabetic drugs with complementary mechanisms of action is a rational approach that may provide better or more sustained glycemic control with better tolerability. This sub-study indicates that the overall outcomes in Korean patients with T2DM are consistent with results seen in the overall study population. Our approach of earlier aggressive treatment with vildagliptin/pioglitazone combination is a potential treatment option for effective management of diabetes in Korean patients.

Terminology
Glucagon-like peptide-1 (GLP-1) has been shown to increase insulin secretion and suppress glucagon release in a glucose-dependent manner. However, active circulating GLP-1 has a half-life of approximately 1 to 2 min and is rapidly degraded and inactivated by dipeptidyl peptidase-4 (DPP-4). Inhibition of DPP-4 with vildagliptin, a selective DPP-4 inhibitor, results in enhanced active GLP-1 levels *in vivo*.

Peer reviews
This manuscript presents data on the Korean subgroup of an international study investigating the effect and safety of the combination therapy of vildagliptin and pioglitazone in comparison to monotherapies. This is a well written manuscript, focusing on the subgroup of one country. The rational for this analysis is that Korean patients with type 2 diabetes have a different phenotype compared with type 2 diabetics of other nationalities, as they are typically non-obese (BMI less than 25 kg/m^2). Therefore, there is a reasonable case for undertaking this sub-set analysis. Overall, the study design is sound and the question is important in the context of the growing burden of type 2 diabetes in Korea.

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Acknowledgments to reviewers of *World Journal of Diabetes*

Meetings

Events Calendar 2010

January 25-29
Waikoloa, HI, United States
Selected Topics in Internal Medicine

January 28-30
Hong Kong, China
The 1st International Congress on
Abdominal Obesity

March 09-12
Brussels, Belgium
30th International Symposium on
Intensive Care and Emergency
Medicine

March 23-26
Cairo, Egypt
14th Pan Arab Conference on
Diabetes PACD14

May 01-05
New Orleans, LA, United States
Digestive Disease Week Annual
Meeting

June 09-12
Singapore, Singapore
13th International Conference on
Emergency Medicine

June 25-29
Orlando, FL, United States
70th ADA Diabetes Scientific
Sessions

September 12-15
Boston, MA, United States
ICAAC: Interscience Conference
on Antimicrobial Agents and
Chemotherapy Annual Meeting

Instructions to authors

GENERAL INFORMATION

World Journal of Diabetes (*World J Diabetes*, *WJD*, online ISSN 1948-9358, DOI: 10.4239), is a bimonthly, open-access (OA), peer-reviewed journal supported by an editorial board of 323 experts in diabetes mellitus research from 38 countries.

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Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJD* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJD* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJD* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

Aims and scope

The major task of *WJD* is to report rapidly the most recent results in basic and clinical research on diabetes including: metabolic syndrome, functions of α, β, δ and PP cells of the pancreatic islets, effect of insulin and insulin resistance, pancreatic islet transplantation, adipose cells and obesity, clinical trials, clinical diagnosis and treatment, rehabilitation, nursing and prevention. This covers epidemiology, etiology, immunology, pathology, genetics, genomics, proteomics, pharmacology, pharmacokinetics, pharmacogenetics, diagnosis and therapeutics. Reports on new techniques for treating diabetes are also welcome.

Columns

The columns in the issues of *WJD* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Article: To report innovative and original findings in diabetes; (9) Brief Article: To briefly report the novel and innovative findings in diabetes research; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJD*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of diabetes mellitus; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in diabetes mellitus.

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SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

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Personal author(s)
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Electronic journal (list all authors)
15   Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ ncidod/eid/index.htm

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16   **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 200201 03498. 2002 Aug 1

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