

Thiazolidinedione and cardiovascular risk in type 2 diabetes mellitus

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ABSTRACT

Cardiovascular disorders are the most common complications encountered in patients with type 2 diabetes mellitus (DM). The relationship is likely to be multifactorial and may also involve a specific, though ill-defined, diabetic cardiomyopathy. Patients with heart failure accompanied by DM have a reduced cardiac output compared with patients without DM. Thiazolidinediones (TZDs) are agonists of peroxisome proliferator-activated receptor gamma (PPAR α) and have beneficial effects in the control of blood glucose and cardiovascular parameters, but the ability of these drugs to induce retention of plasma has to be taken into consideration in prescribing them for patients with DM at high risk of cardiovascular disease. The molecular mechanism of fluid retention by TZDs has not been fully elucidated. Available evidence indicate a possible role of epithelial sodium channels (ENaC) in causing the side effects of TZDs. This paper will discuss the mechanism of ENaC in inducing fluid retention and the management to be applied for anticipating these side effects.

Keywords: Thiazolidinedione, heart failure, type 2 diabetes, ENaC

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INTRODUCTION

Epidemiologic studies have shown that around 10% of patients with type 2 diabetes mellitus (DM) experience heart failure. This prevalence rate is 2-4 times higher than that in patients without DM.⁽¹⁻³⁾ Furthermore, approximately 25% of patients in studies of heart failure suffered from DM,⁽²⁾ while only around 0.5% of the general population suffered from both diseases.⁽³⁾ Patients with heart failure

accompanied by DM have a reduced cardiac output compared with patients without DM.

The oral antidiabetic agents called thiazolidinediones (TZDs, or glitazones), consisting of rosiglitazones (RSG) and pioglitazones, are agonists of peroxisome proliferator-activated receptor gamma (PPAR α) that act to increase insulin sensitivity.⁽⁴⁾ In addition to lowering the blood glucose level, TZDs also shows beneficial effects on cardiovascular parameters, such as lipid levels,

blood pressure, biomarkers of inflammation, endothelial functions, and fibrinolytic status.⁽⁵⁾ The beneficial effects of TZDs on blood glucose and cardiovascular risk factors has resulted in the extensive use of these drugs in type 2 diabetic patients at high risk of cardiovascular disease. However, utilization of TZDs is limited by exacerbation of fluid retention. The incidence of peripheral edema following use of TZDs as monotherapy or in combination with other oral antidiabetic drugs is around 5% and may be up to 15% if TZDs are used with insulin.⁽⁶⁾ In extreme cases TZDs can induce expansion of plasma volume such that it causes precipitation or exacerbation of pulmonary edema and congestive heart failure, complications commonly found in patients with type 2 diabetes.⁽¹⁾

The underlying mechanism for the effect of TZDs in inducing plasma volume expansion and edema is still unclear. The molecular targets of TZDs, namely PPAR γ , are diffusely expressed in humans in all organs, including the kidneys.⁽⁷⁾ TZDs have a potential effect on the kidneys that is independent of their effects on glucose and lipid metabolism. In vitro and animal studies have demonstrated the agonist capabilities of PPAR γ in stimulating sodium reabsorption in the distal nephrons by upregulating the expression and translocation of epithelial sodium channels (ENaC) in the collecting ducts.^(8,9)

Fluid retention induced by TZDs is frequently resistant to loop diuretics, but may resolve upon discontinuation of the drug. It may also be possible to counteract expansion of plasma volume due to TZDs by using diuretics that act on the collecting ducts (e.g. spironolactone).⁽¹⁰⁾ A meta-analysis conducted by Nissen et al.⁽¹¹⁾ and Sing et al.⁽¹²⁾ showed that the RSG tend to increase the risk of myocardial infarction by 42% in patients with type 2 diabetes. Other meta-analyses have

confirmed the risk of heart failure on RSG usage.⁽¹³⁾ In contrast to rosiglitazone, pioglitazone in the PPOspective Pioglitazone Clinical Trial in Macro Vascular Events Study (PROactive Study) was capable of reducing macrovascular atherosclerotic risk,⁽¹⁴⁾ recurrent myocardial infarction,⁽¹⁵⁾ and recurrent stroke.⁽¹⁶⁾ The cardiovascular protective effect of pioglitazone is supported by a meta-analysis conducted by Lincoff et al.⁽¹⁷⁾ The difference in ischemic risks of the two drugs is caused by the contrasting effects of these TZDs on lipid profile; pioglitazone causes a reduction in low density lipoprotein (LDL) whereas rosiglitazone raises the LDL concentration.⁽¹⁸⁾

In connection with the potential risk of rosiglitazone in causing myocardial infarction and the risk of fluid retention that may precipitate heart failure when using TZDs drugs, the Food and Drug Administration (FDA) has added a 'black box warning' in the information on prescribing of TZDs.⁽¹⁹⁾

This paper will discuss the mechanism of TZDs in inducing fluid retention in connection with epithelial sodium channels (ENaC), and the management to be applied for anticipating these side effects.

INSULIN RESISTANCE AND ROLE OF PPAR γ

Insulin resistance develops long before the onset of clinical diabetes. The onset of insulin resistance is frequently accompanied by obesity, particularly visceral obesity. Adipose dysfunction leads to the development of resistance to the anti-lipolytic effects of insulin, causing an increased level of plasma free fatty acids (FFA). The latter will induce insulin resistance in the liver and skeletal muscle, resulting in decreased glucose uptake by the tissues and increased gluconeogenesis. Adipose

dysfunction also leads to production of proinflammatory cytokines (e.g. tumor necrosis factor- α (TNF- α), interleukin (IL)-6, and resistin in excessive amounts, which will increase the chances of insulin resistance, inflammation, atherosclerosis, and decrease secretion of insulin-sensitive cytokines, such as adiponectin, produced by adipose tissue.⁽²⁰⁾

PPAR γ receptors are members of the nuclear receptor family that play a role in regulating transcription factors for genes involved in uptake and storage of fatty acids, inflammation, and glucose hemostasis.⁽²⁰⁾ PPAR γ has an important role in the normal differentiation and proliferation of adipocytes, as well as in FFA uptake and storage. Various adipokines, such as adiponectin, TNF α and resistin, are regulated by PPAR γ agonists. Adiponectin is an adipocytokine that is produced exclusively by adipose tissue and enhances insulin sensitivity and anti-atherogenic effects of insulin, whereas TNF α and resistin induce insulin resistance.

Adiponectin levels are low in obese individuals and in those with type 2 DM.⁽²¹⁾

There are several mechanisms of PPAR γ agonists in reducing insulin resistance. Activation of PPAR γ receptors by their agonists can accelerate adipocyte differentiation and FFA uptake from visceral fat, followed by their storage in subcutaneous adipose tissue. This phenomenon results in reduced FFA levels resulting in decreased insulin resistance. Furthermore, activation of PPAR γ by their agonists is thought to enhance expression and translocation of the glucose transporters (GLU), GLUT1 dan GLUT4 to the cell surface, thus increasing glucose uptake by the liver and skeletal muscle and decreasing plasma glucose levels. Another mechanism of PPAR γ agonists in reducing insulin resistance is by reducing proinflammatory cytokines (TNF α , IL-1, resistin)⁽²²⁾ and increasing expression of adiponectin by adipose tissue.⁽²³⁾ The mechanisms of PPAR γ agonists in improving insulin sensitivity are shown in Figure 1.

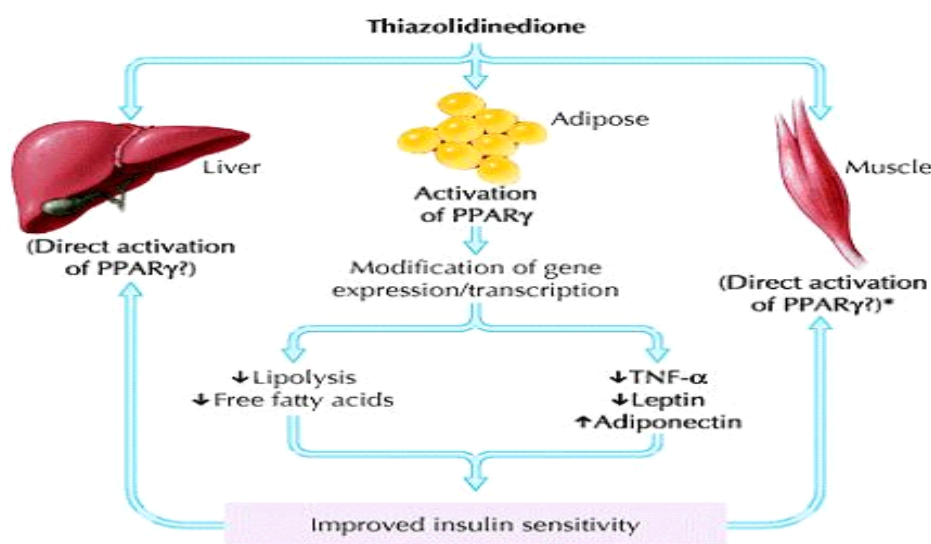


Figure 1. Mechanisms of PPAR γ agonists in improving insulin resistance

PATHOGENESIS OF EDEMA ON TZD USAGE

The mechanisms underlying the ability of TZDs in inducing expansion of plasma volume and edema are still unclear. The role of renal mechanisms in causing induction of edema by TZDs was first demonstrated by the study of Song et al.⁽²⁴⁾ Their study reported that administration of rosiglitazone for 3 days to Sprague Dawley rats significantly reduced urinary volume (up to 33%) and sodium excretion (up to 44%).

In addition the study also reported an increase in concentrations of Na-K-ATPase, Na-K-2Cl cotransporters (NKCC2), sodium hydrogen exchangers (NHE3), aquaporin 2 (AQP2), and aquaporin 3 (AQP3). These findings suggested the occurrence of sodium transport in the proximal tubule and the thick ascending limb.

Other evidence indicating that fluid retention induced by TZDs is based on the activation of sodium transport in the distal nephron is presented here. Firstly, in the kidneys PPAR γ is expressed at substantial concentrations in the collecting duct, and at lower concentrations in the glomerulus, proximal tubule, and the microvasculature. Secondly, in tissue culture of a human cortical collecting duct cell line, PPAR γ agonists increased α ENaC concentrations on the cell surface. This increase in α ENaC occurs in parallel with increased mRNA for serum and glucocorticoid regulated kinase 1 (SGK1), which could be abolished by administration of PPAR γ antagonists before the intervention. This effect is presumably due to binding of PPAR γ to specific response elements in the promoter region of SGK1.⁽⁸⁾ Thirdly, *in vivo* studies indicate that GI262570 (farglizar), a potent PPAR γ agonist, can stimulate water and sodium

reabsorption from the distal nephron of Sprague Dawley rats by stimulating ENaC and Na-K-ATPase.⁽⁹⁾ Forthly, a study conducted on the collecting duct of PPAR γ knockout mice showed the development of resistance to increases in body weight and plasma volume expansion induced by rosiglitazone, as compared with rats expressing PPAR γ in their collecting ducts.⁽²⁵⁾

MECHANISM OF SODIUM REABSORPTION IN THE DISTAL NEPHRON

The main site of sodium reabsorption in the renal tubule is the proximal tubule (>85%), but the distal nephron (particularly the aldosterone sensitive distal nephron) (ASDN), where <10% of sodium reabsorption takes place, plays an important role in the regulation of plasma volume.⁽²⁶⁾ ASDN is located at the end of the distal tubule, including the connecting segment, and the cortical and medullary collecting duct (Figure 2). Sodium reabsorption in the ASDN takes place through the epithelial sodium channel (ENaC). Sodium reabsorption along the whole length of the nephron is controlled by basolateral Na⁺-K⁺-ATPase activity, resulting in decreased intracellular sodium concentrations and intracellular electronegativity. Both conditions lead to an electrochemical difference for sodium influx through the apical membrane.

Sodium transport from the tubular lumen through the apical membrane of epithelial cells is mediated in the proximal tubule up to the thick ascending loop of Henle by the sodium/proton exchanger 3 (NHE3), in the distal tubule and connecting segment by the sodium-chloride cotransporter (NCCT), and in the cortical and medullary collecting duct by the epithelial sodium channel (ENaC).

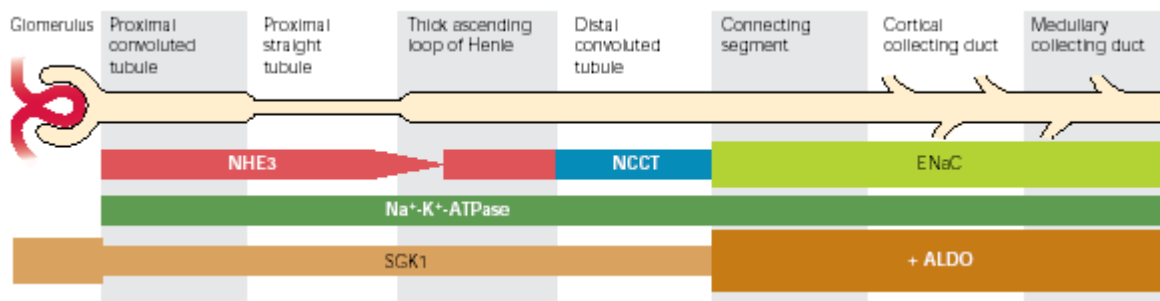


Figure 2. Expression of sodium transporter is specific for the renal segment and SGK1⁽²⁶⁾

The Na⁺-K⁺-ATPase pump transports sodium through the basolateral membrane into the blood. The expression of the aldosterone sensitive distal nephron (ASDN) occurs mainly at the site of ENaC expression. Serum and glucocorticoid regulated kinase 1 (SGK1) is expressed along the whole length of the nephron, and aldosterone potently induces SGK1 activation in the ASDN.

ASDN regulates sodium and water hemostasis through its action on ENaC, a protein with an important role in regulating sodium reabsorption. ENaC consists of three subunits α, β, dan γ (Figure 3), where ENaCα

acts as a functional subunit whose activity is regulated by ENaCα and ENaCβ.⁽²⁷⁾ Sodium reabsorption in the ASDN occurs through expression of ENaC on the apical surface of the renal tubule and is associated with the role of the serum and glucocorticoid regulated kinases (SGK). SGK are a family of protein kinases B (also known as PKB/Akt), that play an important role in survival. Currently there are 3 isoforms of SGK that have been identified as SGK1, SGK2, dan SGK3, whose functions are still not fully understood. These three kinases are said to be potent regulators of ion channel activity, transport, and the transcription process.⁽²⁷⁾

SGK1 has been successfully identified as the key mediator in sodium reabsorption by the renal tubular epithelium. Transcription of SGK1 is stimulated among others by stress or cell shrinkage (in renal epithelium by swelling of the cell), hormones (including mineralocorticoids, glucocorticoids), PPARγ, high glucose levels, and oxidative stress, and is inhibited by heparin.⁽²⁷⁾ SGK1 is expressed at the site of expression of ENaC and mineralocorticoid receptors (MR) (Figure 4). The selective occupation of MR by aldosterone induces expression of SGK1 mRNA. In addition to these mechanisms, activity of SGK1 as well as that of the other members of the PKB/Akt family occurs through activation of the pathways for

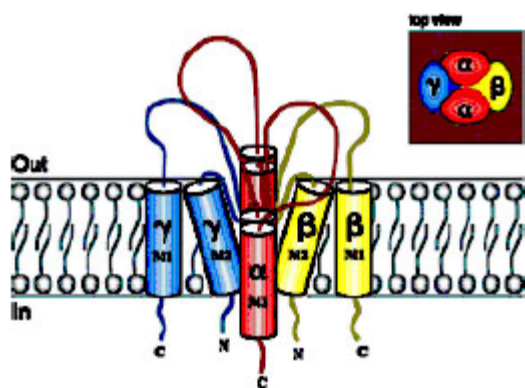


Figure 3. Serum and glucocorticoid regulated kinase 1 (SGK1) as regulator of sodium reabsorption in the kidney⁽²⁶⁾

phosphoinositol 3-kinase (PI3K) signaling and phosphoinositide-dependent protein kinase (PDK1). Insulin itself is also an activator of the PI3K pathway. In synergy with aldosterone, both pathways enhance SGK1 phosphorylation (Figure 3).

SGK1 subsequently integrates the PI3K signaling and mineralocorticoid pathways, leading to expression of ENaC on the ASDN. In addition to aldosterone and insulin, PPAR- γ activation by its agonist may also stimulate transcription and activation of SGK1, which causes an increased expression of ENaC on the surface of the apical membrane of renal tubules.^(26,27)

Activation of ENaC may occur through aldosterone or insulin, and may also be induced by PPAR γ agonists, such as rosiglitazone, through the role of serum and glucocorticoid regulated kinase 1 (SGK1) which induces

ENaC mRNA expression, causing increased translocation of ENaC to the apical membrane. Activation of SGK1 prevents degradation of ENaC by inactivating the ubiquitin ligase neural precursor cell expressed, developmentally down-regulated 4-2 (Nedd4-2). Nedd4-2 interacts with the PY motif in ENaC, causing endocytosis and channel degradation (Figure 4). The ability of SGK1 in inducing ENaC expression is mediated by Nedd4-2, which is closely related to E3 ubiquitin ligase. Interaction between ENaC and Nedd4-2 causes inactivation of ENaC through ubiquitinylation and/ or endocytosis, followed by degradation by lysozyme. SGK1 itself causes phosphorylation of Nedd4-2, which impairs the ability of Nedd4-2 to interact with ENaC. This causes an increased accumulation of ENaC on the plasma membrane leading to increased sodium transport.^(26,27)

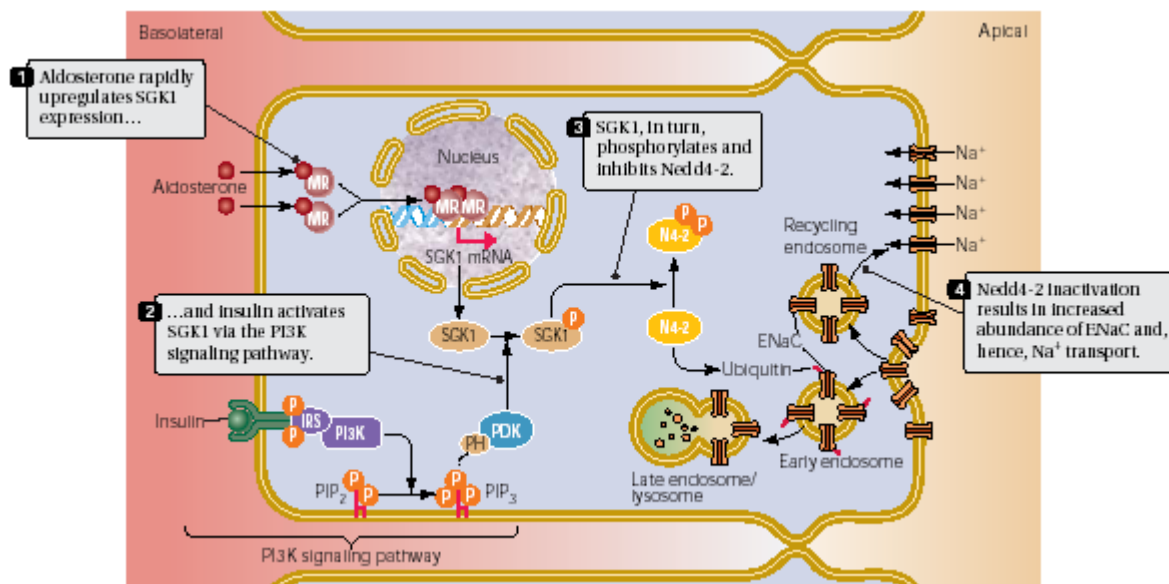


Figure 4. Aldosterone and insulin both stimulate sodium transport in the collecting duct.⁽²⁶⁾

IRS: insulin receptor substrate; PI3K: phosphoinositol 3 kinase; PIP₂: phosphoinositol bisphosphate; PIP₃: phosphoinositol triphosphate.

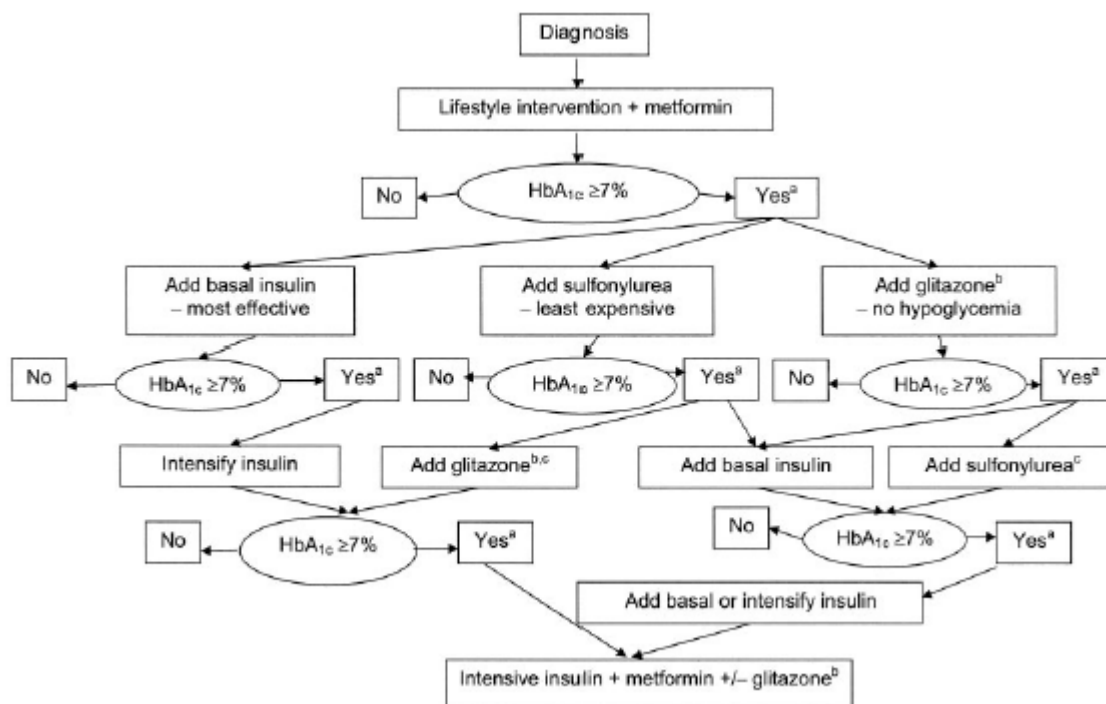


Figure 5. Algorithm for management of type 2 DM⁽³³⁾

The permeability of the cell membrane to water is regulated by water channel proteins aquaporins (AQPs). At present 10 species of AQP have been identified.⁽²⁸⁾ The main aquaporin found in the kidney is AQP1-4. AQP1 and AQP2 function on the apical membrane, while AQP3 dan AQP4 function on the basolateral membrane.⁽²⁹⁾ Collectively these AQPs provide a transcellular pathway for movement of water from the lumen of the collecting duct into the interstitium.⁽³⁰⁾

CLINICAL APPLICATIONS

An update of the consensus statement issued by the American Heart Association and European Association for the Study of Diabetes (2008)⁽³³⁾ currently recommends TZDs as a second line drug in the algorithm for

management of diabetes that cannot be successfully controlled by diet and life style modification or by metformin, as an alternative to insulin (the most effective) and sulfonylureas (the least expensive) for controlling blood glucose in patients with type 2 DM (Figure 5).

In connection with the potential cardiovascular risks (myocardial infarction, heart failure) that may develop on TZDs usage, there are three fundamental concepts that need to be kept in mind by the clinician in prescribing TZDs for patients with type 2 DM.⁽³⁴⁾ First, the high risk of heart failure in patients with DM, because there are multiple cardiovascular risk factors accompanying patients with DM. Second, the difference between true heart failure and heart failure induced by TZDs; and third, the high long-term mortality in patients with DM.

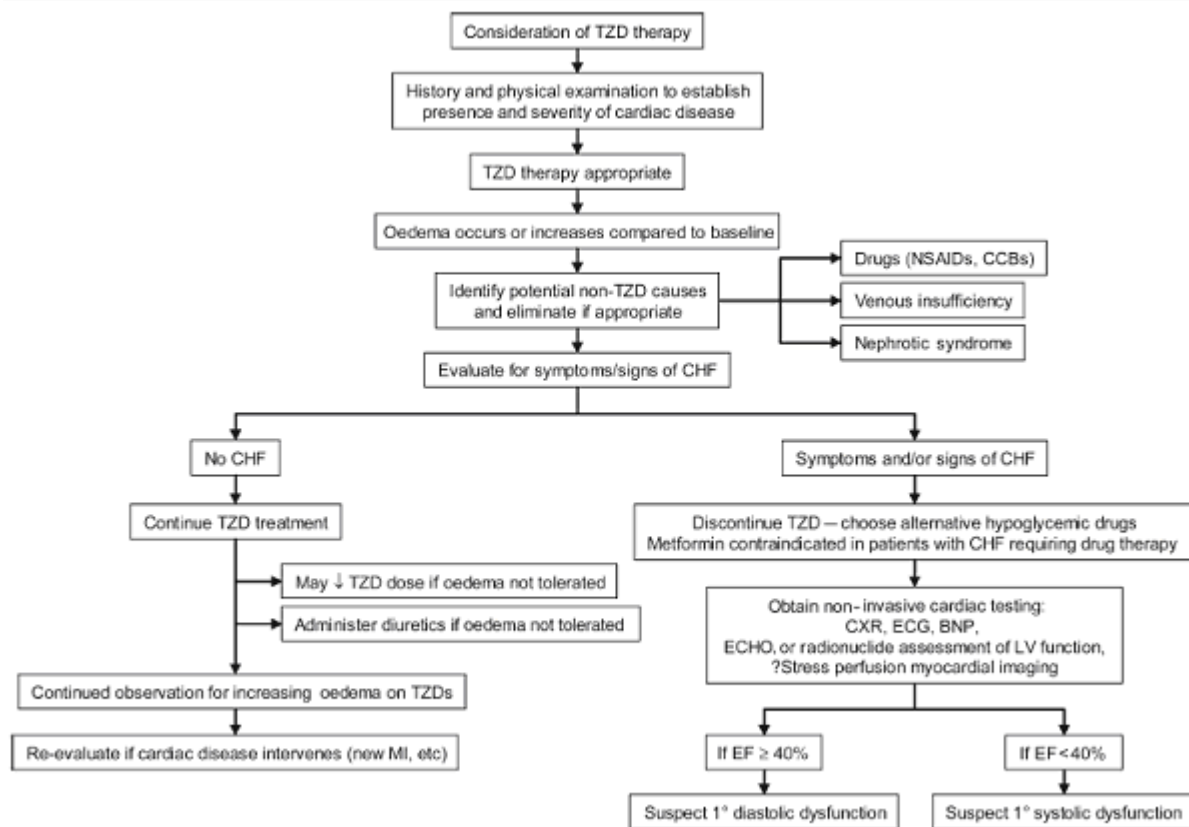


Figure 6. Recommendations in connection with usage of thiazolidinedione and heart failure according to the AHA and ADA.⁽³⁵⁾

In connection with an association between TZDs and risk of heart failure, it is essential to have a potential strategy for minimizing the risk of edema and/or heart failure in patients with type 2 DM on TZDs. Therefore, the consensus of the American Heart Association (AHA) dan American Diabetic Association (ADA)⁽³⁵⁾ may be used as a reference in administering TZDs to patients with diabetes. The concensus recommends that before starting TZDs therapy, a complete evaluation should be performed of risk factors underlying episodes of heart failure, drugs currently taken, and evidence of pre-existing edema or heart failure. The recommendations for TZDs usage in connection with heart failure may be seen in Figure 6.

The recommendation also states that the presence of edema originating from noncardiac causes should not prevent use of TZDs. In addition, there should be adequate monitoring for the presence of edema or heart failure, and the dosage used should be adjusted gradually to attain the hemoglobin A1c (HbA1c) target. Patients experiencing edema when using TZDs should be screened for other causes of edema, including nephrotic syndrome, venous insufficiency, and use of other drugs, such as nonsteroidal anti-inflammatory drugs as well as calcium channel blockers (inhibitors).

In diabetic patients without heart failure TZDs should be prescribed according to the published guidelines. These guidelines do not prohibit use of TZDs in patients with class I/II

functional heart failure according to the New York Heart Association (NYHA), with a lower initial dose than usual for each drug (e.g. rosiglitazone 2 mg/day or pioglitazone 15 mg/day), with the proviso that close monitoring should be performed for fluid retention and that use of TZDs in patients with NYHA class III/IV functional heart failure should be avoided.⁽³⁵⁾

POTENTIAL THERAPY

Use of diuretics in the management of fluid retention induced by TZDs has been evaluated by a number of investigators in case reports,⁽³⁶⁾ and by controlled clinical trials.⁽¹⁰⁾ Most of the case reports state that edema is commonly refractory to loop diuretics (furosemide) and that the symptoms generally resolve when use of TZDs is discontinued.

The clinical trial aiming to determine the efficacy of diuretics in the management of fluid retention induced by RSG was a multicenter parallel group open label randomized study of 381 patients with type 2 DM.⁽¹⁰⁾ The trial used three kinds of diuretics with different mechanisms of action, namely (i) furosemide, which inhibits the Na-K-Cl cotransporter in the thick segment of the ascending limb of Henle, (ii) hydrochlorothiazide (HCT), which inhibits the Na-Cl cotransporter in the distal tubule, and (iii) spironolactone, which is an ENaC inhibitor in the collecting duct. The results of the study showed that spironolactone is equally effective as hydrochlorothiazide in reducing fluid retention, while furosemide did not exhibit any significant effect. The effectiveness of spironolactone in reducing fluid retention may be related to the ability of this diuretic to impair the effects of fluid retention by PPAR γ in the collecting duct. HCT also significantly reduced fluid retention due to rosiglitazone. The site of action of the thiazide diuretics is in the proximal part of the distal tubule, with inhibition of the

Na⁺/Cl⁻ cotransporter as mechanism of action, but this diuretic also inhibits the reabsorption of water and salt in the collecting tubule,⁽³⁷⁾ where PPAR γ is expressed in the nephron.⁽⁷⁾ It is also conceivable that the thiazide diuretics may also antagonize the action of PPAR γ agonists at this site. This is in contrast to the loop diuretics, which do not show a significant effect in reducing fluid retention, presumably because their action is exclusively in the thick segment of the ascending limb of Henle by inhibiting the Na⁺-K⁺ Cl⁻ cotransporter, as this segment does not contain PPAR γ .⁽³⁸⁾ In addition to the ability of spironolactone in antagonizing PPAR γ in the collecting duct, another characteristic of spironolactone is the beneficial effect in ameliorating the left ventricular function and volume.⁽³⁹⁾

CONCLUSIONS

TZDs comprising rosiglitazone and pioglitazone are agonists of peroxisome proliferator-activated receptor gamma (PPAR γ) and have beneficial effects in controlling blood glucose and cardiovascular parameters. In addition to the beneficial effects, the ability of this drug to induce plasma volume expansion should be considered in prescribing TZDs for patients with type 2 DM who also have a high cardiovascular risk. TZDs should not be used in patients newly diagnosed as suffering from type 2 DM. In view of the risk of fluid retention when using TZDs, it is imperative to consider the potential strategies for minimizing the risk of edema and/or heart failure in patients with type 2 DM who are receiving TZDs therapy. The presence of edema due to other causes unrelated to heart failure should not prevent use of TZDs. Adequate monitoring is necessary for signs of edema or heart failure, and increased dosage should be adjusted gradually to attain the expected HbA1c target.

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