

Oral Hypoglycemic Agents

Drug Class	Common Agents	Daily Dose (mg)	↓Fasting Plasma Glucose (mg/dl)	↓HbA1C (%)	Lipids	Body Weight	Comments
Sulfonylureas Stimulate insulin secretion	Glimepiride Glipizide Glyburide	1 to 8 qd 2.5 to 40 qd, bid 2.5 to 20 qd, bid	60-70	0.8-2.0	No effect	Increase	Glyburide is excreted renally; should be used with caution in patients with renal dysfunction due to risk of hypoglycemia Glipizide and glimepiride are preferred and can be used at low doses with glomerular filtration rate < 50 mL/min May reduce the magnitude of increase in ST segment elevation results in misdiagnosis of MI.
Meglitinides Stimulate insulin secretion	Repaglinide Nateglinide	0.5 to 16 bid-qid 360 bid-qid	65-75	0.8-2.0	No effect	Increase	Dosed 15 minutes before each meal Monitor dose increases in patients with moderate to severe renal dysfunction Better post-prandial glucose control
Alpha-Glucosidase Inhibitors Slows digestion of carbohydrates Delays glucose absorption Reduces increase in postprandial blood glucose	Acarbose Miglitol	75 to 300 tid 75 to 300 tid	25-30	0.7-1.0	No effect	No effect	Taken with first bite of each meal Being with 25 mg per meal and titrate to 2- to 4-week intervals to 100 mg per meal as needed No clinical data regarding use in patients with renal dysfunction
Biguanides Decreases hepatic glucose production Enhances muscle glucose uptake and utilization	Metformin	500 to 2550 bid-tid	50-70	1.5-2.0	↓TG, LDL ↑HDL	Decrease	Contraindicated in renal dysfunction due to risk of lactic acidosis Can be cautiously prescribed in patients with stable creatinine (men <1.5 mg/dL; women <1.4 mg/dL) and normal hepatic function Should be discontinued in cases of transient renal insufficiency acute rejection congestive heart failure radiocontrast agents
Thiazolidinediones Enhance tissue sensitivity to insulin in muscle Suppress hepatic glucose production	Rosiglitazone Pioglitazone	2 to 8 qd or bid 15 to 45 qd	60-80	1.4 -2.6	↓TG, ↑LDL, HDL	Increase	May take six weeks for onset of action and months for peak action Require the presence of insulin (natural or exogenous) Avoid in patients with hepatic dysfunction May cause fluid retention; should be avoided in patients at risk for CHF Use requires monitoring of liver function

THIAZOLIDINEDIONES and INSULIN: Peripheral Edema, Pathophysiology and Clinical Implications

Treatment with TZD has been associated with an increased incidence of edema and congestive heart failure (CHF). All glitazones can cause fluid retention, which can exacerbate or lead to CHF. The incidence of edema seems to be similar with *Avandia* and *Actos* (4.8% and 5%, respectively). The incidence of edema is greater when either drug is used with insulin (16 to 20%), and the use of insulin itself has been associated with CHF. The risk of edema appears to be dose-related

Several factors may account for the development of insulin edema.

- 1) Insulin has been shown to increase sodium retention in the kidney through a decrease in urinary sodium excretion.
- 2) The insulin-induced increase in vascular permeability leads to a loss of intravascular albumin and therefore hypoproteinemic edema.
- 3) Restoration of blood glucose levels to normal levels will decrease or prevent glycosuria, which has a potent diuretic effect.

The pathogenesis of edema with use of the thiazolidinediones seems to be multifactorial; as yet, however, the exact underlying mechanisms have not been fully elucidated.

Among the causes postulated to precipitate edema in patients with diabetes being treated with these agents are the following:

- 1) Increase in plasma volume,
- 2) Increased renal tubular sodium reabsorption,
- 3) Reflex sympathetic activation, alteration of intestinal ion transport
- 4) Increased production of vascular endothelial growth factor (VEGF)—a potent tissue permeability factor

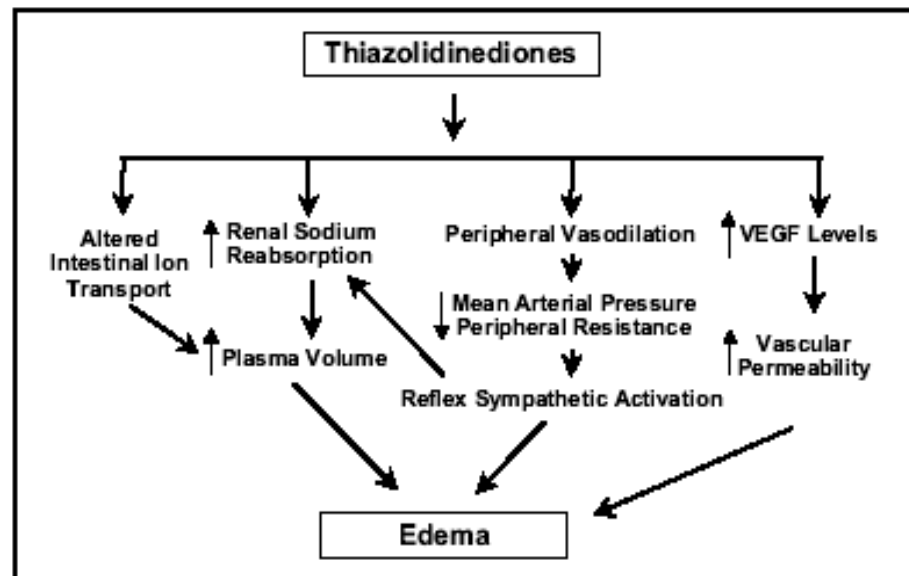


Fig. 3. Potential multifactorial mechanisms of edema formation during treatment with thiazolidinediones. VEGF = vascular endothelial growth factor.