

Insulin Sensitizers - An Update

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Unlike insulin dependent diabetes mellitus (IDDM) where there is absolute insulin deficiency, in NIDDM there is only a relative insulin deficiency and infact it is often associated with hyperinsulinaemia. The latter is defined as a situation in which the plasma insulin level is higher than expected for a given glucose concentration. Insulin resistance is a state in which a normal amount of insulin produces a subnormal response.

The pathophysiology of non insulin dependent diabetes mellitus is complex and is characterized by defects in both insulin secretion and insulin resistance¹. Insulin resistance is virtually present in all NIDDM patients and is responsible for the development and progression of diabetes by causing premature beta cell exhaustion due to its demands on insulin secretion². The hepatic and peripheral insulin resistance in NIDDM also contributes to hyperglycaemia and is often associated with dyslipidemia, hypertension and hyperinsulinaemia¹. Thus, drugs which improve insulin sensitivity may be advantageous not only for reducing hyperglycaemia, but may also help postpone beta cell failure by reducing demand on beta cells.

Improvement of insulin sensitivity by regular exercise and avoidance of obesity have shown to reduce the risk of progression to NIDDM, but major changes in life style is difficult and needs a lot of motivation. Therefore, drugs which enhance the action of insulin by ameliorating insulin resistance are of interest in the management of NIDDM.

Drugs used in insulin resistance can be classified as follows :

- i. Insulin action enhancers eg. troglitazone
- ii. Muscle specific glut 4 enhancers
- iii. Supression of glucose production in the liver.
- iv. Inhibitors of insulin receptor kinase production.

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Insulin resistance is virtually present in all NIDDM patients and is responsible for the development and progression of diabetes by causing premature beta cell exhaustion due to its demands on insulin secretion. Troglitazone is effective not only in controlling hyperglycaemia, but also in reversing other metabolic abnormalities such as insulin resistance and dyslipidaemia.

Troglitazone

Troglitazone is a novel thiazolidinedione derivative that appears to lower blood glucose concentrations primarily by enhancing insulin action rather than by altering insulin secretion⁴. The exact mode of action of this agent remains unknown, but it seems to affect insulin signalling at various points in the signalling pathway⁵. In vitro and animal studies indicate that it enhances glucose utilisation through an increase in glycogen synthase activity and reduced hepatic production. Previous studies⁶ have shown that this agent is effective not only in controlling hyperglycaemia, but also in reversing other metabolic abnormalities such as insulin resistance and dyslipidaemia.

Troglitazone treatment has resulted in a decrease in both fasting and postprandial glucose concentrations, insulin mediated glucose disposal measured by the euglycaemia clamp technique, increased upto 59%.

The effects of troglitazone (CS-045) on diabetic metabolic abnormalities were studied in a double-blind clinical trial, by Mimura et al at Kyushu University, Japan⁷.

DURING PRACTICE

A multi-step hyperinsulinaemic euglycaemic clamp study was performed before and after administration of the drug. Following 3 months of treatment with CS - 045, there was significant decrease in the mean levels of fasting plasma and postprandial plasma glucose and there was also reduction in fasting IRI levels. The results are shown in Tables 1 and 2.

Troglitazone treatment was associated with decreased total cholesterol, and triglycerides, with increase in HDL cholesterol.

In patients with impaired glucose tolerance, troglitazone can normalise GTT^a and hence there is scope for prevention

Table - 1 (Ref. No. 7)

	Troglitazone treated		Placebo treated	
	Before	After	Before	After
Fasting plasma glucose (mmol/l)	9.1±0.95	7.7±0.44	10.0±1.19	11.2±1.12
Postprandial plasma glucose (mmol/l)	11.8±1.23	10.3±1.06	11.8±1.26	11.2±0.68

of diabetes mellitus. A multicenter, double blind placebo controlled, parallel group study was conducted in which a total of 51 subjects with IGT between 24 to 77 years of age were enrolled. Patients were randomly assigned to receive either 400 mg of troglitazone or placebo. After 12 weeks of treatment, 80% of the troglitazone treatment group had normalised their glucose tolerance, while only 48% of those on placebo had converted to normal ($P=0.016$). Troglitazone also improves insulin sensitivity in patients with IGT.

Mechanism of action of troglitazone

Troglitazone regulates gene expression by interacting with a family of nuclear receptors.

The precise mechanism of action of these drugs remains unknown. Transcriptional changes are observed in tissue culture cells that enhance insulin action. This regulation of gene expression appears to be mediated by the interaction of thiazolidinediones with a family of nuclear receptors known as the Peroxisome Proliferator Activated Receptors (PPARs)⁹. Three major PPAR family members have been identified. These family members share considerable sequence homology in their activation and DNA - binding and ligand bindings domains. PPAR is known to be a receptor for the fibrate class of lipid lowering drugs, mediating the regulation

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of lipoprotein gene expression. Recent studies have proved that PPAR_α and PPAR_β are the thiazolidinedione activated receptors. PPAR_α is expressed mainly in adipose tissue¹⁰. PPAR_β is found in liver and to a lesser extent in kidney, gut and adipose tissue and PPAR_γ is expressed with significant amounts in liver, fat and muscle¹¹.

Insulin sensitization by thiazolidinediones can be explained by two mechanisms:

- i) The binding of thiazolidinediones to PPAR can induce the interaction of the complex with specific DNA sequences. PPAR can regulate genes such as lipoprotein lipase, which are themselves regulated by insulin, resulting in enhanced transcriptional activity.
- ii) Thiazolidinediones may exert insulinmimetic effects by interacting with sites that overlap with insulin response sequences (IRS). PPAR may induce the expression of genes that encode for proteins that are targets of insulin action, such as glucose transporters.

In addition to enhancing glucose disposal, troglitazone also facilitates insulin dependent inhibition of hepatic glucose output (HGO) by attenuation of gluconeogenesis or by activation of glycolysis¹².

Table - 2 (Ref. No. 7)

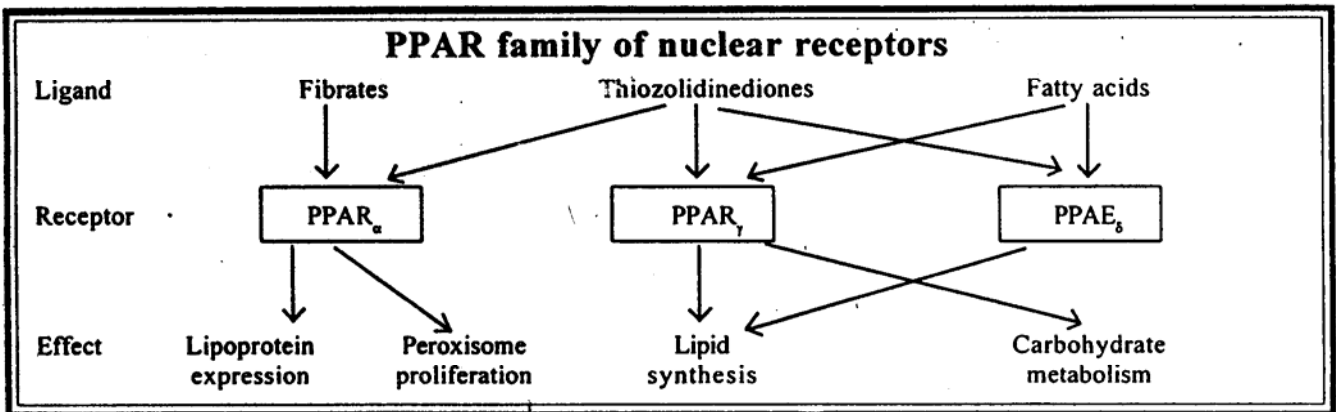
	All in troglitazone treated group		Hyperinsulinaemia patients treated with troglitazone	
	Before	After	Before	After
Plasma insulin (pmol/l)	57±9.6	36.6±4.8	81±7.5	36.6±7.6

Effects of the drug on gene expression were evaluated in HepG2 or H35 cells transfected with glucokinase and PEPCK. Transcription of the glucokinase gene in HepG2 cells was rapidly stimulated by troglitazone, even in the absence of insulin, while PEPCK promoter was unresponsive to troglitazone.

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Insulin Sensitizers...



Troglitazone both prevented and reversed insulin receptor kinase inhibition induced by high glucose levels¹³.

In adipocytes¹⁴ and skeletal muscle, troglitazone increased insulin stimulated 2- deoxyglucose or glucose uptake, insulin binding to plasma membranes and expression of Glut 1 and Glut 4 glucose transporters.

Troglitazone increased glycogen synthase activity in skeletal muscles.

Troglitazone prevented pancreatic islet cell destruction¹⁵ as evidenced by: regranulation of pancreatic beta cells, an increase in pancreatic insulin content and normalisation of islets.

Recommended dosage

Japan : 200 mg twice daily after meals in the morning

and evening.

Europe : 200 - 600 mg once daily.

U.S. : 200-400 mg once daily.

Maximum dose of 600 mg/day, in patients not adequately controlled with insulin.

Adverse effects

The side effects of troglitazone vary in different ethnic groups. In Japanese patients, gastro-intestinal upsets and peripheral oedema were the main side effects.

In European/US patients asthenia, headache, dizziness, nausea, respiratory infections and diarrhoea were the untoward events. The most threatening adverse effect is bone marrow depression.

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Summary

Troglitazone improves all aspects of insulin resistance syndrome (Syndrome X). It has a great role in the treatment of NIDDM and IGT and for prevention of diabetes. It may have a potential to prevent atherosclerosis as it also has additional cardiovascular benefits, but these are obviously areas for future research. Troglitazone is also being investigated for use in a number of other disease states associated with insulin resistance eg. polycystic ovarian syndrome and gestational diabetes.

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