

# Treatment Of Insulin Resistance

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## Abstract

Sufficient evidence is available to suggest that reducing insulin resistance may be beneficial, independent of a glucose –lowering effect.

It is uncertain however, when one should start pharmacological treatment of insulin resistance, and for how long it should be prescribed. It is also difficult to assess insulin sensitivity directly in clinical practice. Most tests for insulin sensitivity are invasive or unstandardized, and clinicians are forced to rely on surrogate end points.

In spite of these limitations, however, there is a consensus that insulin resistance should be treated aggressively. This review will focus only on anti diabetic medications in the treatment of insulin resistance.

## CLASSIFICATION: DRUG TREATMENT OF INSULIN RESISTANCE

### 1. ANTI-DIABETIC DRUGS

- a. Non- Pharmacological
- c. diet
- d. exercise
- e. yoga

### 1. Pharmacological

1. Insulin sensitizers
3. metformin
4. thiazolidinediones
6. rosiglitazone
7. pioglitazone

### 1. Incretin – based therapies

#### 3. GLP -1 analogues

#### 5. liraglutide

### 1. DPP (IV) inhibitors

#### 3. vildagliptin

#### 4. sitagliptin

#### 5. saxagliptin

### 1. Alpha glucosidase inhibitors

#### 3. acarbose

#### 4. voglibose

### 1. STATINS

### 2. ANGIOTENSIN CONVERTING ENZYME

### 3. INHIBITORS ARBS

### 4. ANTI-OBESITY DRUGS

## GLITAZONES

Both pioglitazone and rosiglitazone raise HDL cholesterol (1, 2), change small, dense, more atherogenic LDL to larger, less atherogenic particles (3,4), and lower triglycerides (1,2), Rosiglitazone also reduces blood pressure, proportional to its effect on lowering insulin resistance (5).

The drug also lowers plasminogen activator inhibitor -1 levels, C- reactive protein (CRP) (5), E, selectin (7) and matrix –degrading metallo- proteinase (MMP-9)(8).

Pioglitazone lowers CRP in patients who do not exhibit glucose –lowering effect with the drug (6).

Pioglitazone has been shown to decrease intima –media

thickness of the carotid artery (9) and pulse wave velocity (6), irrespective of glycemic –lowering effect. These markers correlate well with atherosclerosis and vascular damage.

Rosiglitazone also improves endothelial function (10) and myocardial blood flow (11), the latter effect being noted only in type 2 diabetes of shorter duration.

Type 2 diabetic patients with coronary stents exhibit a reduced re stenosis rate when prescribed rosiglitazone or pioglitazone, even in the absence of glycemic difference (12, 13).

### **METFORMIN**

The UKPDS showed that metformin is particularly effective in overweight type 2 diabetes subjects, a condition usually characterized by insulin resistance (14). Moreover, in essentially all clinical studies the improvement of hyperglycemia with metformin occurred in the presence of unaltered or reduced plasma insulin concentrations (15, 16). Taken collectively, these findings indicate the potential of metformin as an insulin –mimetic drug.

Metformin has no effect on the pancreatic  $\beta$  - cell stimulating insulin secretion (17). Mild increases in glucose –stimulated insulin secretion after metformin treatment (18) are thought to be the result of reduced glucose toxicity on the  $\beta$  – cell secondary to improved glycemic control (19).

In patients with type 2 diabetes, metformin has been shown to inhibit endogenous glucose production in most studies (20-22). This could be accounted for largely by inhibition of gluconeogenesis (23) , although an additional inhibitory effect of metformin on glycogen breakdown is likely (23,24).

Many (25, 27, 28), but not all, studies (26) using the hyperinsulinemic –euglycemic clamp technique have shown that metformin certainly –induced increase in insulin stimulated glucose disposal in patients with type 2 diabetes (20,22) . Since muscle represents a major site of insulin –mediated glucose uptake (19), metformin certainly have an insulin –like or insulin –sensitizing effect on this tissue.

Requirements of exogenous insulin are reduced (by  $\approx$  30%) by addition of metformin in obese patients with type 2 diabetes (25-26) and in some patients with type 1, diabetes in whom glycemic control was unaltered (21,28).

While metformin improves insulin sensitivity in muscle, it

does not affect the antilipolytic action of insulin on adipose tissue (29). The overall effect of metformin on body weight is attributed to a reduction in caloric intake (25,30) rather than an increase in energy expenditure (31). Since reduction in body weight per se reduces insulin resistance, this may also represent mechanism by which metformin improves insulin resistance.

### **ALPHA GLUCOSIDASE INHIBITORS**

Laube et al, 32 has reported that 12 weeks of acarbose treatment (100 mg three times daily) increased steady –state glucose infusion rate (SSGIR) by 45 %. In addition, Shinozaki et al. (33) treated subjects with IGT with voglibose (0.2mg three times daily), for 12 weeks, and showed that SSPG levels decreased significantly after voglibose treatment. These data suggest that  $\alpha$  –glucosidase inhibitors improve insulin sensitivity in subjects with IGT and hyperinsulinemia possibly secondary to an amelioration of glucose –induced insulin resistance by reducing postprandial hyperglycemia. In contrast to studies in subjects with IGT, studies examining the effect of  $\alpha$  glucosidase inhibitors or insulin sensitivity in patients with type 2 diabetes showed no amelioration of insulin resistance despite decreased postprandial glycemia (34-38). Thus, these data are in support of the notion that  $\alpha$  glucosidase inhibitors improve insulin sensitivity in subjects with IGT but have no effect on insulin sensitivity in subjects with over type 2 diabetes.

### **GLP -1 AGONISTS**

Decline of beta-cell sensitivity to glucose is an early defect of beta –cell function in type 2 diabetes. Liraglutide has been shown to restore beta –cell sensitivity to glucose [39]. The effect of exenatide on beta –cell sensitivity to glucose was assessed by measuring C-peptide levels during a hyperglycemic clamp in a study of 10 insulin– naïve patients with type 2 diabetes [40]. Fasting plasma C-peptide concentrations significantly increased from 0.75nmol/l before treatment  $\approx$  0.83 nmol/l after exenatide treatment ( $p<0.002$ ) following a hyper- glycaemic clamp.

Both liraglutide and vildagliptin ,have been shown to increase insulin sensitivity in obese candy –fit rats. Liraglutide also reduced weight, decreases calorie intake and shifts food preference, but did not reduce energy expenditure in the animals. The weight loss was found to be associated with a change in fat man percentage (41, 42).

In LEAD -3 study, insulin resistance decreased by 0-65 %

with liraglutide 1.2 mg ( $p=0.0249$  vs. glimepiride) and 1.35% with liraglutide 1.8 mg ( $p=0.0011$  vs. glimepiride). This was associated with a reduction of weight in both liraglutide groups (2kg and 2.5 kg and 1.2 mg and 1.8 mg groups). Weight loss was apparent during the first 16 weeks, then remained stable upto 52 weeks, and was not related to nausea. Liraglutide also led to significant reductions in systolic blood pressure [43].

Thus, liraglutide has been shown to improve all components of the insulin resistance syndrome, when given as monotherapy.

Similar results have been reported to authors studying liraglutide in combination with metformin, glimepiride and insulin [44].

No episodes of major hypoglycemia have been reported with liraglutide monotherapy, and the incidence of minor hypoglycemia is low [44].

### CONCLUSION

Many drugs are available for the management of insulin resistance. These drugs have beneficial effect only on glycemic parameters, but also on the other aspects of insulin resistance, such as weight, blood pressure and lipid profile. Metformin has been studied extensively, and remains the drug of choice for management of insulin resistance. Promising results signal a possible shift towards the use of liraglutide and other incretin –based therapies for the multifaceted treatment of insulin resistance.

This review should help treating physicians choose the appropriate therapy for patients with insulin resistance.

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