

# Free Fatty Acids May be a Target for Therapy

Elevated plasma free fatty acids account for up to 50% of insulin resistance in obese patients with type 2 diabetes.

BY GUENTHER BODEN, MD

It has been widely reported that the increasing rates of obesity in the United States have reached epidemic proportions. It is therefore no surprise that we are also seeing a dramatic increase in the incidence of type 2 diabetes. As I recently wrote in a review article in *Current Opinion in Endocrinology & Diabetes*, elevated plasma levels of free fatty acids (FFA) are a major link between obesity and insulin resistance.

Because FFA are recognized as a major pathogenetic factor in the development of type 2 diabetes, they should be considered as a target for therapy. FFA increases in blood cause insulin resistance in skeletal muscle, liver and endothelial cells, and may be at least partially responsible for vascular diseases in diabetic patients.

Obese people have increased plasma levels of FFA compared with those who are not obese. This is explained by an increased number of fat cells, less FFA

clearance and insulin resistance at the level of adipose tissue resulting in increased lipolysis.

## TARGET TISSUES

It has been shown that FFA can inhibit the action of insulin in several target tissues. When FFA is acutely elevated in skeletal muscle, a dose-dependent inhibition of insulin-stimulated glucose uptake is seen. Insulin resistance also results as a response to chronic elevations of plasma FFA. Research has shown that in obese nondiabetic patients, high plasma FFA was responsible for almost all of their insulin resistance; whereas in patients with type 2 diabetes, FFA was responsible for only about half of their insulin resistance.

In the liver, serum insulin elevations similar to post-prandial levels inhibit endogenous glucose production. Elevations of FFA, following a meal rich in fat, acutely

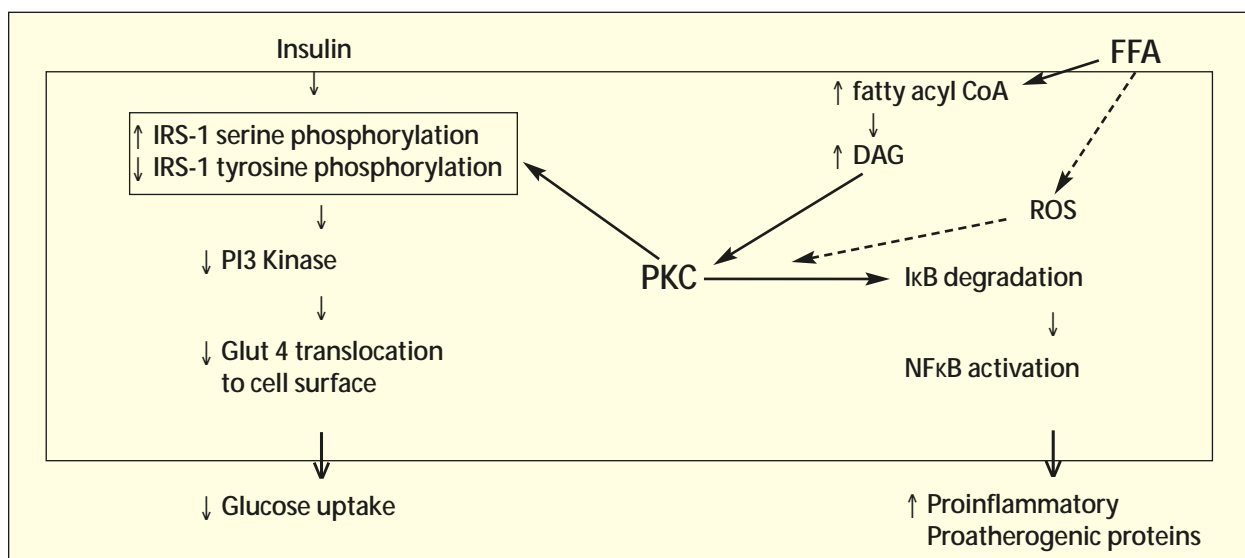


Figure 1. How FFA act on glucose uptake and I $\kappa$ B/NF $\kappa$ B in human muscle. (Figures courtesy of *Current Opinion in Endocrinology & Diabetes*, Lippincott Williams & Wilkins.)

inhibit the endogenous glucose-production-suppressing effect of insulin. This is because of an FFA-induced inhibition of insulin's suppressive action on glycogenolysis.

With regard to endothelial cells, insulin increases peripheral blood flow. Evidence suggests that this is caused by insulin stimulation of nitric oxide production. FFA decreases nitric oxide in endothelial cells, and by doing so, inhibits insulin from increasing blood flow.

FFA elevations after a meal rich in fat acutely inhibit insulin's glucose-production-suppressing effect.

It is widely accepted that acute elevations of plasma FFA stimulate insulin secretion, however, the long-term effects of FFA are the subject of controversy. Evidence is increasing, though, to suggest that in healthy patients' long-term elevations of plasma FFA potentiate glucose-stimulated insulin secretion. Contrasting this is evidence that in prediabetic patients, those with impaired glucose tolerance (IGT) and those with overt type 2 diabetes, FFA elevations do not potentiate and may even inhibit glucose-stimulated insulin secretion.

### FFA-MEDIATED HYPERSECRETION

On the basis of this data, my colleagues and I have proposed that in glucose-tolerant obese patients without a family history of type 2 diabetes, FFA-induced insulin resistance is perfectly matched by FFA-mediated hypersecretion of insulin. In these individuals, hyperinsulinemia and perhaps other metabolic syndrome indicators will be seen, but abnormal blood sugar will be absent.

In contrast to this scenario is the obese patient with a family history of diabetes. In this individual, the FFA-induced insulin resistance cannot be compensated completely by FFA-mediated hypersecretion of insulin. This causes a rise in blood glucose levels and eventual development of type 2 diabetes. We recognize that this hypothesis seems to contradict the concept of beta-cell lipotoxicity, which says that chronically-elevated FFA compromises beta-cell function. We think the beta-cell lipotoxicity hypothesis is difficult to reconcile with the fact that most insulin-resistant obese individuals never develop diabetes.

Studies in human skeletal muscle show that FFA produces a defect in insulin-stimulated glucose transport or phosphorylation, caused by inhibition of insulin signaling. More recently, we and other investigators have shown a

mechanism by which FFA can interfere with insulin signaling. Increased FFA concentrations in plasma create intramyocellular accumulation of triglycerides and other compounds released during triglyceride synthesis. Diacylglycerol (DAG) is one of the compounds that is of particular interest because it is a strong allosteric activator of protein kinase C (PKC). PKC can cause insulin resistance by interrupting insulin signaling at the IRS-1/2 level.

### SIMILAR TO SKELETAL MUSCLE

We do not know much about how FFA cause hepatic insulin resistance. Some animal work suggests that the mechanism may be similar to that seen in skeletal muscle and involves activation of hepatic PKC (Figure 1).

In endothelial cells, insulin stimulates nitric oxide production via the IRS/PI3 kinase pathway. FFA may inhibit the process by interrupting signaling of insulin at the IRS-1/2 level and by activating NADPH oxidase. The activation of NADPH oxidase leads to production of reactive oxygen species (ROS), which may result in the destruction of nitric oxide (Figure 2).

Raising FFA blood levels dramatically lowers the nuclear factor  $\kappa$ B-alpha content in human muscle.  $\kappa$ B is the main physiological inhibitor of nuclear factor  $\kappa$ B, which is a major promoter of inflammation and athero-

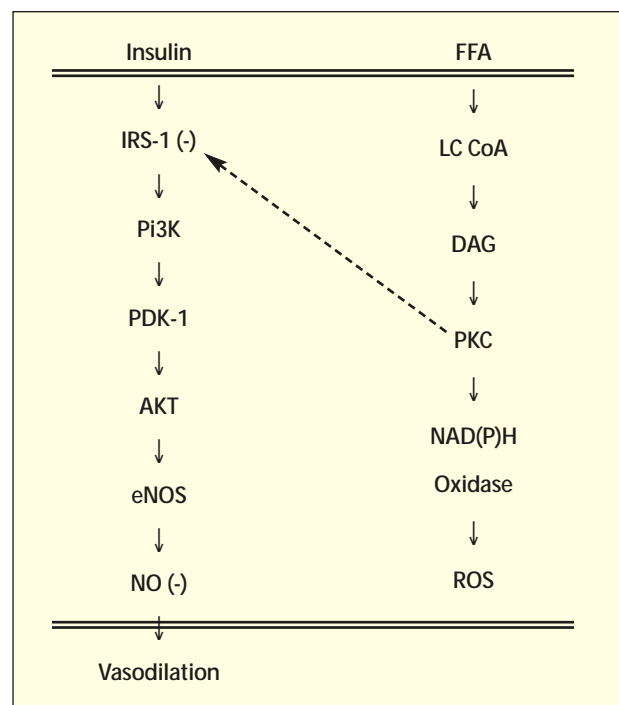


Figure 2. Some of the potential mechanisms of FFA on hemodynamic insulin action are shown.

## FFA AT A GLANCE

- **Elevated plasma levels of FFA are a major link** between obesity and insulin resistance.
- **FFA are a factor in the development of type 2** diabetes, and should be a target for therapy.
- **High plasma FFA was responsible for almost all** of insulin resistance in obese nondiabetic patients, and for only about half of insulin resistance in patients with type 2 diabetes.
- **Acute elevations of plasma FFA** stimulate insulin secretion.
- **Boden and colleagues proposed that in glucose-tolerant obese patients** without a family history of type 2 diabetes, FFA-induced insulin resistance is perfectly matched by FFA-mediated hypersecretion of insulin. However, in obese patients with a family history of diabetes, the FFA-induced insulin resistance is not.
- **It is still unclear how FFA causes hepatic** insulin resistance.
- **New drugs that reduce plasma FFA by 50%** are needed.

sclerosis. Thus, FFA appear to be able to cause not only insulin resistance but atherosclerosis as well. This may explain, at least in part, why there is so much atherosclerotic disease in insulin-resistant patients with diabetes.

## INSULIN SECRETION

Patients develop type 2 diabetes when they are unable to increase insulin secretion sufficiently to compensate for their insulin resistance. Current treatment approaches that are aimed at achieving glycemic control are diet, exercise, sulfonylureas, thiazolidinediones (TZDs) and insulin. Frequently these methods are not entirely successful, and therefore new approaches are needed.

As I have stated, FFA appear to be responsible for most of the insulin resistance in obese nondiabetic patients and for up to 50% of the insulin resistance in patients with IGT or type 2 diabetes. If plasma FFA levels can be normalized, then insulin sensitivity would be enhanced. We hypothesize that FFA normalization may prevent the

development of type 2 diabetes in genetically predisposed patients or improve glycemic control in those who already have diabetes.

Additionally, other manifestations of the metabolic syndrome, such as hypertension and dyslipidemia, may be prevented or improved by lowering plasma FFA, and FFA normalization may reduce the incidence and/or severity of atherosclerotic vascular problems.

Available medications often are not sufficient to normalize FFA levels on obese diabetic or nondiabetic patients. While successful FFA lowering has been seen with nicotinic acid and its analogs, dramatic FFA rebound is a problem. The rebound of FFA levels may also occur with an extended-release nicotinic acid called Niaspan. Niacin and Niaspan both lower glucose tolerance and raise plasma glucose transiently and HbA1c modestly. The preparations' beneficial effects of raising HDL and lowering LDL, triglycerides and C-reactive protein, however, are larger and last longer.

## LOWERING FFA OVER THE LONG TERM

TZDs lower FFA levels over the long term and have shown no rebound or breakthrough. Many investigators believe that the large part of the insulin-sensitizing response to TZDs is due to FFA lowering. Unfortunately, FFA lowering with these drugs is only 15% to 30%, a level not sufficient to normalize plasma FFA in most patients.

What is needed are new drugs that can reduce plasma FFA by  $\geq 50\%$ . We are hopeful that a combination of TZDs and fibrates may achieve this goal; however, this remains to be seen in clinical trials.

We note that therapies directed at normalizing plasma levels of FFA require ways of monitoring FFA concentrations. This could be methods that allow episodic or continuous FFA measurements in blood or interstitial fluids, similar to home glucose monitoring methods.

According to our review of the evidence, it is clear that elevated blood levels of FFA are a major cause of insulin resistance in human skeletal muscle, liver and vascular endothelial cells. They are an important pathogenetic factor in type 2 diabetes development in obese patients. We propose normalizing FFA as an attractive approach to reduce insulin resistance and the risk of type 2 diabetes and the resulting vascular complications. ■

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Boden G. Free fatty acids as a target for therapy. *Current Opinion in Endocrinology & Diabetes*. 2004;11:258-263.