

FREE FATTY ACIDS (FFA), A LINK BETWEEN OBESITY AND INSULIN RESISTANCE

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1. ABSTRACT

Evidence, gained from human studies, is reviewed showing that elevation of plasma FFA levels produce peripheral and probably also hepatic insulin resistance in obese healthy and diabetic subjects. First, plasma FFA levels are elevated in most obese subjects. Second, physiological elevations of plasma FFA inhibit acutely as well as chronically insulin stimulated glucose uptake in a dose dependent fashion. Responsible for this inhibition is a FFA induced defect in insulin stimulated glucose transport and/or phosphorylation which develops after 3-4 hours of raising plasma FFA and a second defect, consisting of inhibition of glycogen synthase, the rate limiting enzyme of glycogen synthesis, which develops after 4-6 hours. FFA induced inhibition of fatty acid oxidation (Randle effect) does not affect insulin stimulated glucose uptake or glycogen synthesis and thus does not cause insulin resistance. Elevated plasma FFA levels also modestly increase insulin suppressed endogenous glucose production (EGP) although this effect has not been found by all investigators. The reasons why it has been difficult to demonstrate unequivocal effects of FFA on EGP include 1) the fact that FFA promote insulin secretion which counteracts its effect on EGP (FFA increase, while insulin decreases EGP); 2) the recognition that FFA induced increase in gluconeogenesis may be compensated by intrahepatic downregulation of EGP (i.e., by a decrease in glycogenolysis).

The FFA induced insulin resistance is physiologically important during starvation by preserving carbohydrate for oxidation in the central nervous system and during pregnancy,

where the well recognized accelerated starvation pattern provides carbohydrate for the growing fetus. In obesity, however, there is no need to spare carbohydrate and the FFA induced insulin resistance may result in type 2 diabetes and other cardiovascular risk factors.

2. INTRODUCTION

Obesity is associated with insulin resistance and hyperinsulinemia, two important cardiovascular risk factors (1,2). The fact that hyperinsulinemia and insulin resistance increase with weight gain and decrease with weight loss (3-6) suggests that this is a cause and effect relationship. What remains uncertain is how obesity produces insulin resistance and hyperinsulinemia. It has recently become clear, however, that FFA play a pivotal role in this process. Plasma levels of FFA are elevated in obesity (7,8) primarily because a greater than normal amount of FFA is released from the expanded adipose tissue mass even though the rate of lipolysis from individual fat cells appears to be normal (9,10). The following is a review of the evidence, gained from studies in human subjects, which shows that elevations of plasma FFA produce peripheral and probably also hepatic insulin resistance in healthy subjects and in patients with Type II diabetes.

3. INSULIN RESISTANCE. DEFINITION

For the purposes of this review, peripheral insulin resistance is defined as inhibition of normal insulin stimulation of whole body glucose uptake. Hepatic insulin resistance is defined as inhibition of normal insulin suppression of hepatic glucose production.

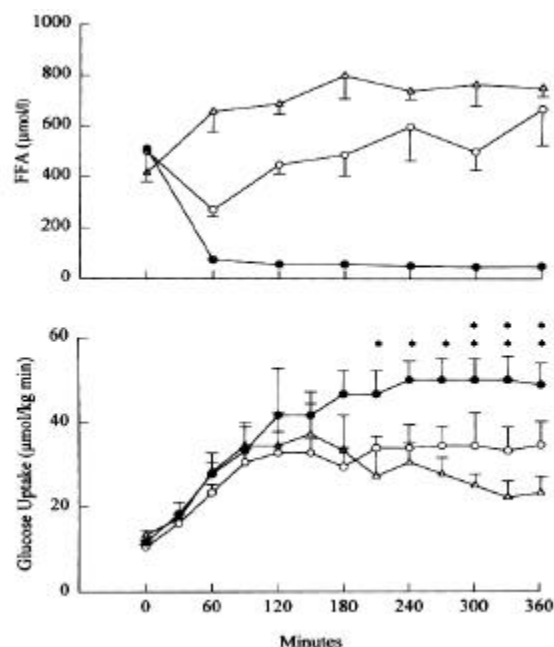


Figure 1: Effect of plasma FFA on insulin-stimulated glucose uptake. Euglycemic-hyperinsulinemic (~ 420 pmol/l) clamping was performed in healthy volunteers for 6 h. High levels of plasma FFA were produced by the infusion of triglycerides ($4.3 \mu\text{mol/min}$) plus heparin ($0.4 \text{ U A kg}^{-1} \cdot \text{min}^{-1}$) (Δ , $n = 4$); intermediate plasma FFA levels, by infusion of triglycerides without heparin (\circ , $n = 4$); and low FFA levels, by infusion of saline alone (\bullet , $n = 6$). Data shown are mean \pm SE. The inhibition of insulin-stimulated glucose uptake became statistically significant ~ 3.5 h after the start of the lipid infusion. * $p < 0.05$; ** $p < 0.01$, comparing high with low FFA. Adapted from Boden *et al.* (14*).

Insulin stimulation of total body glucose uptake and insulin suppression of hepatic glucose production were determined with the hyperinsulinemic clamp technique (11).

4. FFA AND PERIPHERAL INSULIN RESISTANCE

4.1. Effect of FFA on Basal Glucose Uptake

When plasma FFA concentrations were increased acutely by IV infusion of a triglyceride emulsion (Liposyn II, 10% safflower and 10% soybean oil) and heparin (which enhances lipoprotein lipase activity), FFA levels rose 2-3 fold (to between 1.0 and 1.5 mM) but basal rates of glucose uptake did not change (12).

4.2 Effect of FFA on Insulin Stimulated Glucose Uptake

In healthy subjects, acute elevation of plasma FFA by IV lipid/heparin infusion inhibited total body glucose uptake dose dependently after a lag period of 3-4 hours "figure 1". Inhibition of CHO oxidation occurred ~ 2 h earlier than the inhibition of glucose uptake. The latter was reversed ~ 3 hours after discontinuation of lipid/heparin infusions (13) "figure 2".

Other studies showed that the lipid induced inhibition of insulin stimulated glucose uptake was linear (14,15) "figure 3" and occurred similarly in healthy subjects and in patients with Type II diabetes (14-20). The long delay of 3-4 hours between the start of the insulin and lipid infusions and the development of significant insulin resistance was the most likely reason why the inhibitory effect of FFA on glucose uptake was not found in many previous studies (21-25).

The linear relationship between plasma FFA levels and insulin stimulated glucose uptake in healthy controls and patients with Type II diabetes suggested that for every 100 μM increase in plasma FFA, peripheral insulin sensitivity decreased by $\sim 8\%$ "figure 3". It needs to be emphasized, however, that the total range of insulin stimulated glucose uptake was approximately 2 fold higher in healthy controls than in patients with Type II diabetes (15) "figure 4". Thus, FFA could account for maximally 50% of peripheral insulin resistance in patients with Type II diabetes. Several potential problems could affect the interpretation of these results. First, the infused triglyceride emulsion (Liposyn II) contained a considerable amount of glycerol (2.5 grams/100 ml). We have shown, however, that this amount of glycerol did not affect glucose uptake (15). Second, the data showing that elevation of plasma FFA decreased peripheral glucose uptake in response to insulin were all produced in acute experiments. Their relevance relative to the long term effects of elevated plasma FFA, for instance during obesity could, therefore, be questioned. It was, however, shown that lowering of plasma FFA below basal values caused an increase in insulin stimulated glucose uptake (13) "figure 1". This indicated that basal FFA levels exerted long term inhibitory effects on peripheral glucose uptake.

4.3 Cellular Location of FFA Induced Defects

To determine the cellular location of the fat induced inhibition of insulin stimulated glucose uptake, glucose fluxes through all major pathways of intracellular glucose utilization were determined non-invasively. Rates of glucose uptake and glycolysis were estimated with $3\text{-}^3\text{H}$ -glucose and glycogen synthesis was obtained by subtracting glycolysis from glucose uptake. The validity of these methods has been validated (26). CHO oxidation was determined by indirect calorimetry and non-oxidative glycolysis (lactate and alanine formation) by subtracting CHO oxidation from glycolysis. Using these methods, it was found that lipid/heparin infusion inhibited rates of glucose uptake, glycogen synthesis and glycolysis about equally (15). In normal controls, for instance, plasma FFA concentrations of $\sim 600 \mu\text{M}$ inhibited insulin stimulated glucose uptake, glycogen synthesis and glycolysis all by $\sim 50\%$ while in patients with Type II diabetes, a higher plasma FFA concentration of $\sim 1200 \mu\text{M}$ resulted in a $\sim 90\%$ inhibition "figure 5". These results suggested a FFA induced defect at the level of transport and/or phosphorylation (the methods used could not differentiate between these two possibilities). A primary defect at the level of glycogen synthesis or glycolysis, on the other hand, would have produced disproportionate reductions in the flux rates through these pathways.

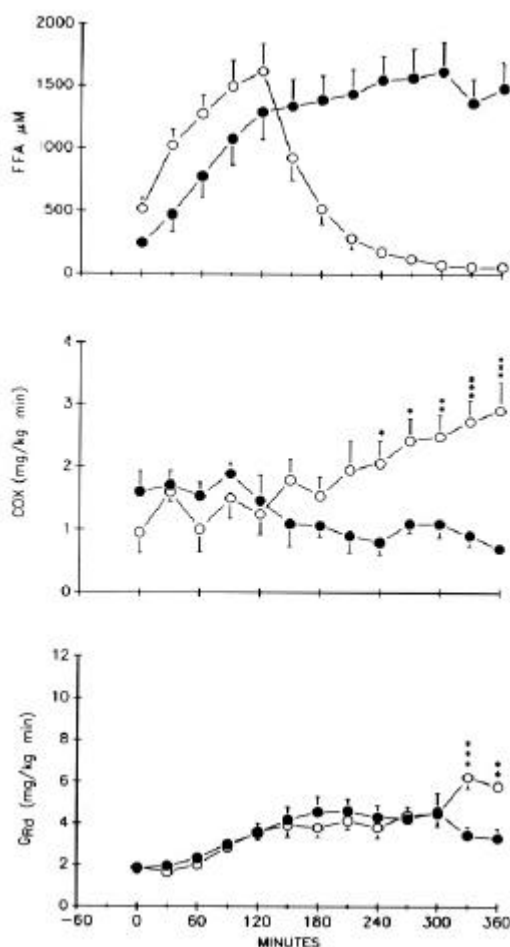


Figure 2. Plasma FFA levels, and rates of CHO oxidation (COX) and glucose disappearance (G_{Rd}) in healthy men during lipid/heparin infusion (solid circles) and during lipid/heparin infusion from 0-120 min followed by saline infusion from 120-360 min (open circles) * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$ comparing the 2 groups. Adapted from Boden *et al.* (13*).

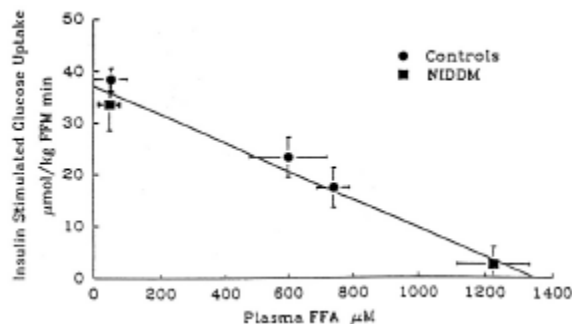


Figure 3. Relationship between insulin stimulated glucose uptake and plasma FFA in 7 patients with NIDDM and in 6 non-diabetic controls. Data from controls were obtained during euglycemic (~ 5 mM)-hyperinsulinemic (~ 450 pM) clamping. Data from patients with NIDDM were obtained during hyperinsulinemic (~ 11 mM)-hyperinsulinemic clamping. Adapted from Boden *et al.* (14,15*).

The conclusion that lipid infusion produced a transport/phosphorylation defect was supported by still another finding. Glycogen synthase activity was normal in muscle biopsies obtained 4 hours after lipid/heparin infusions, i.e., at a time when insulin stimulated glucose uptake was maximally inhibited (14). Since glycogen synthase is the rate limiting enzyme in the glycogen synthesis pathway, these findings suggested that flux through the glycogen synthesis pathway was intact after 4 hours of lipid/heparin infusion. This, however, changed during the ensuing 2 hours, i.e., after 4-6 hours of lipid/heparin infusion, when elevated plasma FFA caused a marked inhibition of muscle glycogen synthase activity associated with an increase in muscle glucose-6-phosphate concentration (14). Thus, elevated plasma levels of FFA produced at least two distinct biochemical defects 1) inhibition of insulin stimulated glucose transport and/or phosphorylation (after 3-4 hours of lipid/heparin infusion) and 2) inhibition of muscle glycogen synthase activity (after more than 4 hours of L/H infusion) "figure 6".

A third defect, namely a FFA mediated inhibition of CHO oxidation, which was first reported by Randle *et al.* in rat hearts (27) developed earlier than the other two defects (Figure 2). This defect, however, did not produce insulin resistance as glucose uptake was not impaired during the initial 3-4 hours of lipid/heparin infusion when CHO oxidation was already severely inhibited. Carbons which had entered the glycolytic pathway and could not be oxidized because of the FFA produced increase in acetyl-CoA (13) and the ensuing inhibition of pyruvate dehydrogenase (28) were shunted into non-oxidative glycolysis (lactate/alanine production) (15).

4.4. Mechanisms

The mechanisms responsible for the FFA induced defects in glucose transport and/or phosphorylation and glycogen synthesis are not known. Putative mechanisms include 1) activation of the hexosamine pathway, 2) inhibition of glucose transporter gene expression and 3) changes in cellular membrane fluidity. Marshall *et al.* have shown in cultured rat hepatocytes that prolonged hyperglycemia produced insulin resistance (glucose toxicity) by activating the hexosamine pathway (29,30). This pathway accounts for only 1-3% of glucose flux under normal conditions and results in the generation of several metabolites which are important substrates for glycoprotein and phospholipid synthesis. Recently, Rossetti's laboratory has shown in rats, that fat induced insulin resistance was associated with accumulation of UDP-N-acetyl glucosamine, an end product of the hexosamine pathway, and that the same degree of insulin resistance could be reproduced by increasing UDP-N-acetyl hexosamine in skeletal muscle (31,32).

Long and Pekala have shown that several long chain fatty acids decreased mRNA levels of the insulin responsive glucose transporter Glut 4 in fully differentiated 3T3-L1 cells by decreasing Glut 4 gene transcription and by destabilizing the Glut 4 message (33). Thus, FFA may cause

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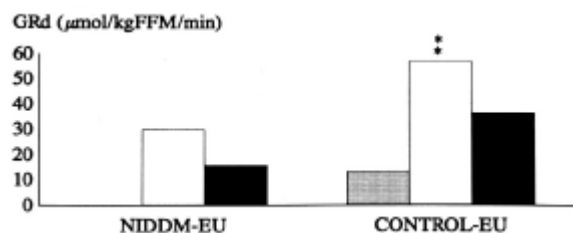


Figure 4. Insulin-stimulated glucose uptake at comparable low plasma FFA ($< 100 \mu\text{mol/l}$) and euglycemia in diabetic and nondiabetic subjects. Shown are insulin-stimulated glucose uptakes before (■) and after (□) 4 h of euglycemic ($\sim 4.8 \text{ mmol/l}$) hyperinsulinemic ($\sim 500 \text{ pmol/l}$) clamping in 7 patients with NIDDM and 6 nondiabetic control subjects. Preclamp glucose uptake could not be obtained in the diabetic patients because insulin was infused to lower their blood glucose concentrations into the normal range. Insulin-stimulated glucose uptake (G_{Rd}) was ~ 2 times higher in nondiabetic than in diabetic individuals (30 vs. $58 \mu\text{mol/kg fat free mass}$, $p < 0.01$). Triglyceride plus heparin infusion (II) decreased insulin-stimulated glucose uptake by $\sim 50\%$ in diabetic and nondiabetic individuals. EU, euglycemia; FFM, fat free mass. Adapted from Boden *et al.* (14,15*).

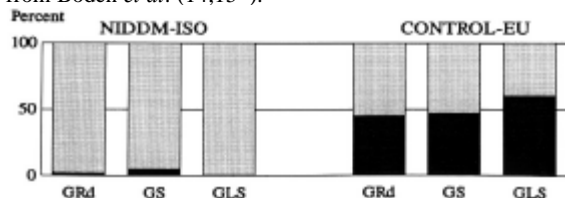


Figure 5. Effects of elevated plasma FFA on rates of glucose uptake (G_{Rd}), glycogen synthesis (GS), and glycolysis (GLS) in 7 patients with NIDDM during hyperinsulinemic ($\sim 900 \text{ pmol/l}$) isoglycemic ($\sim 11 \text{ mmol/l}$) clamping and in 6 nondiabetic control subjects during euglycemic-hyperinsulinemic ($\sim 500 \text{ pmol/l}$) clamping. Total length of bars represent insulin-stimulated G_{Rd} , GS, or GLS, set as 100%. The darkly shaded parts of the bars represent insulin-stimulated G_{Rd} , GS, or GLS after 4 h of elevated plasma FFA ($\sim 1,200 \mu\text{mol/l}$ in NIDDM, $\sim 600 \mu\text{mol/l}$ in controls). FFA inhibited insulin-stimulated G_{Rd} , GS, or GLS similarly in patients with NIDDM and in normal control subjects, regardless of blood insulin and FFA levels. ■, lipid; □, saline. Adapted from Boden *et al.* (14,15*).

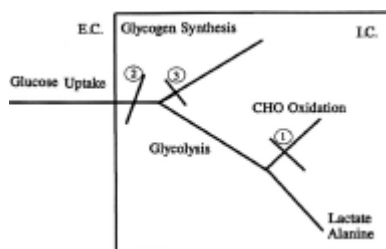


Figure 6. Defects of glucose utilization produced by FFA. The inhibition of carbohydrate oxidation (defect 1) was the earliest demonstrable defect. It developed during the initial 2 h of lipid infusion, but did not inhibit insulin-stimulated glucose uptake or glycolysis. The inhibition of glucose transport and/or phosphorylation (defect 2) developed after 3-4 h, while the inhibition of glycogen synthesis (defect 3) developed after 4-6 h of high plasma FFA. E.C., extracellular; I.C., intracellular.

insulin resistance by inhibiting Glut 4 gene expression in muscle.

Lastly, FFA may induce changes in cell membrane fluidity. Insulin receptors are imbedded in the lipid bilayer of plasma membranes. There is some evidence to suggest that altering the fatty acid content of membranes can alter insulin receptor accessibility, insulin binding and action. For instance, increasing polyunsaturated fatty acid content has been found to increase membrane fluidity, insulin binding and action whereas decreasing their content had the opposite effect (34-37).

5. FFA AND HEPATIC INSULIN RESISTANCE

The issue of whether FFA inhibit insulin suppression of hepatic glucose production (HGP), i.e., causes hepatic insulin resistance remains somewhat controversial. We and others have reported that acute elevation of plasma FFA increased HGP in patients with Type II diabetes and in non-diabetic controls during hyperinsulinemic clamping (14, 38-41) "figure 7". On the other hand, lowering of plasma FFA with nicotinic acid or acipimox, a nicotinic acid analog, has been reported to increase (40) to decrease (42-44) or not to change HGP (45). There are probably two main reasons for these discrepant results. One, while there is good *in vitro* and animal evidence that FFA promote gluconeogenesis (46-50), there is also evidence to suggest that increased gluconeogenesis does not necessarily increase HGP. There appears to be an intrahepatic mechanism which regulates HGP by decreasing glycogenolysis when gluconeogenesis is elevated and vice versa (45,51). Two, FFA are insulin secretagogues. Therefore, elevated plasma FFA levels may increase HGP by stimulating gluconeogenesis, on one hand, but on the other hand, they may raise insulin secretion which will then inhibit HGP. Evidence in favor of a stimulatory effect of FFA on HGP was obtained in overnight fasted normal volunteers in whom plasma FFA were raised acutely by infusing lipid/heparin while insulin was clamped at basal concentrations (by infusing somatostatin and basal insulin replacement) (12). Under these conditions, HGP and plasma glucose levels rose dramatically "figure 8". Therefore, the available human data suggest that FFA can increase HGP but that the extent of the increase is controlled to some extent by the FFA mediated stimulation of insulin secretion.

6. SIGNIFICANCE

The evidence reviewed here indicates that physiological elevations of plasma FFA increases peripheral (and probably also hepatic) insulin resistance in a dose dependent manner. This FFA induced insulin resistance serves important physiological purposes during periods of prolonged starvation and during normal pregnancy. During starvation, rising plasma FFA produce peripheral insulin resistance, which preserves precious carbohydrate resources for oxidation in the central nervous system. Pregnancy, on the other hand, has been characterized as a state of accelerated starvation (52). FFA rise because of an increase

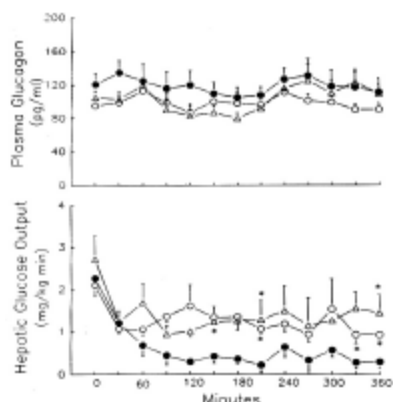


Figure 7. Plasma glucagon and hepatic glucose output (HGO) in healthy men. Effect of euglycemic-hyperinsulinemic clamping at high (open triangles, $n = 4$), medium (open circles, $n = 4$) and low FFA concentrations (filled circles, $n = 6$) on plasma glucagon concentration and on rates of HGO. * $p < 0.05$ comparing high or medium with low FFA concentrations. Adapted from Boden *et al.* (14*).

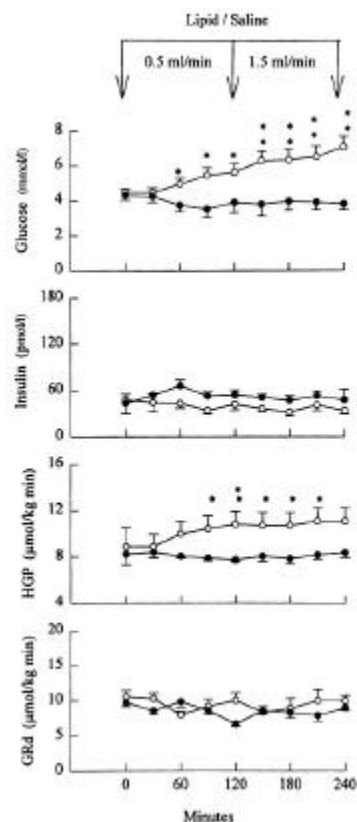


Figure 8. Effect of FFA on plasma glucose and hepatic glucose production (HGP). Triglyceride (Liposyn II, 0.5 and 1.5 ml/min or 2.15 and 4.3 mol/min) plus heparin (0.4 U/min) were infused in 6 healthy volunteers during pancreatic clamping (somatostatin, 305 nmol/h; insulin, 0.33 pmol/kg min; glucagon, 0.25 ng/kg min). FFA produced marked increases in HGP and plasma glucose concentrations. * $p < 0.05$; ** $p < 0.01$ vs. Saline controls. ○, lipid; ●, saline. Adapted from Boden and Jadali (13).

in maternal fat deposition during the early part of pregnancy and as result of increased plasma levels of lipolytic gestational hormones (for instance, human placental lactogen and human chorion gonadotropin) (53). The resulting insulin resistance preserves carbohydrate for the growing fetus. In obesity, however, the FFA induced insulin resistance becomes counterproductive since there is no need to spare glucose. The insulin resistance in obesity is associated with several cardiovascular risk factors including hypertension, dyslipidemia, hyperuricemia and abnormal fibrinolysis (54). Whether or not any these are cause and effect relationships is presently not clear. Moreover, whether or not the FFA mediated insulin resistance will result in deterioration of glucose tolerance depends largely on the ability of the FFA to stimulate insulin secretion. Appropriate insulin secretory responses would largely avoid the need to compensate for the FFA induced insulin resistance with additional, hyperglycemia stimulated insulin secretion. Defective insulin responses, on the other hand, would worsen hyperglycemia.

7. ACKNOWLEDGEMENT

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