GLOBAL SCIENCE LIBRARY

REVIEW

International Journal of Translational Science

How excess dietary saturated fats induce insulin resistance

Steve Blake* and Dustin Rudolph

Director of Nutritional Neuroscience, Maui Memory Clinic, USA

Abstract

Excess dietary saturated fatty acids can increase the risk of and progression of type 2 diabetes. We will explore the mechanisms by which excess saturated fatty acids can reduce insulin sensitivity, suppress insulin production of beta cells through glucolipotoxicity, raise blood glucose, and lessen energy production in cells. Higher dietary saturated fatty acids, especially palmitic acid, can reduce the number of insulin receptors to approximately one-half of their normal number. This contributes to hyperinsulinemia, elevated blood glucose, and reduced mitochondrial energy production. Higher dietary saturated fatty acids also interfere with the signaling between the insulin receptor and the glucose transporter. This reduces the amount of glucose that can enter the cell and increases the risk of elevated blood glucose. Excess dietary saturated fatty acids have been found to suppress insulin production of beta cells and also to stimulate apoptosis of beta cells. Higher dietary saturated fatty acids can reduce the ability of the cells to produce glycogen from glucose, thus lowering energy storage. Finally, higher dietary saturated fatty acids can reduce mitochondrial energy production. Conclusion: Reducing dietary saturated fatty acids may help clear blood of excess glucose in type 2 diabetes.

Keywords: *diabetes; saturated fatty acids; insulin; glucolipotoxicity; palmitic acid; insulin receptors; hyperinsulinemia; elevated blood glucose; beta cells; glycogen; mitochondrial energy production; toll-like receptor-4*

Introduction

Type 2 diabetes has become increasingly more prevalent among the general population, leading to significant morbidity and mortality for those diagnosed, not to mention the undue financial burden it puts on both patients and the healthcare system. We set out to identify the role of dietary saturated fatty acids in the pathogenesis of type 2 diabetes. Reduction of excess dietary saturated fatty acids may be an underutilized treatment for type 2 diabetes mellitus.

Excess dietary saturated fatty acids increase insulin resistance, raise blood sugar levels, and decrease cellular energy production via multiple mechanisms. Excess saturated fatty acids interfere with the transport of glucose molecules into skeletal muscle cells by reducing the total number of insulin receptors available on the cellular membrane by up to one-half. Excess saturated fatty acids can also disrupt the cellular signaling cascade responsible for glucose transport into the cell at the following junctions: insulin receptor substrate phosphorylation, phosphatidylinositol-3-kinase phosphorylation, protein kinase-B phosphorylation, and transport of the glucose transporter-4 to the cellular membrane. This can result in insulin resistance, increased blood glucose levels, and decreased glycogen synthesis. Palmitic acid has been shown to have the strongest effect in reducing insulin sensitivity and decreasing glycogen synthesis.

Excess circulating levels of free saturated fatty acids lead to glucolipotoxicity-induced beta cell insulin resistance and beta cell apoptosis and subsequent drops in pancreatic insulin production. Excessive intake of animal fats can increase circulating free saturated fatty acids, decreasing insulin production by up to 30-60%. Also, increased abdominal fat can be released as free saturated fatty acids into the portal bloodstream, reducing insulin production due to beta cell apoptosis.

Saturated fatty acids interfere with glucose transport into cells by insulin

Insulin promotes glucose uptake in insulin-responsive tissues including liver cells, muscle cells, and adipose tissue. Insulin stimulates a cascade of signaling processes initiated by the binding of insulin to the protruding α-subunit of the insulin receptor on the outer leaf (the plasma side) of the cellular membrane.

1. Insulin binding to the insulin receptor, a transmembrane protein, elicits activation of the β-subunit of the insulin receptor inside the cell.
2. Once activated, the β-subunit of the insulin receptor attracts the insulin receptor substrate, which docks onto the insulin receptor. Saturated fatty acids inhibit activation (tyrosine phosphorylation) of the insulin receptor substrate.
3. The insulin receptor substrate then activates phosphatidylinositol-3-kinase. Phosphatidylinositol-3-kinase is associated with almost all of the metabolic actions of insulin [1]. Excess saturated fatty acids can inhibit phosphatidylinositol-3-kinase phosphorylation [2].
4. Phosphatidylinositol-3-kinase then phosphorylates protein kinase B. Excess saturated fatty acids can decrease protein kinase-B activation [3].
5. Phosphorylated protein kinase B moves glucose transporter-4 vesicles from the cytoplasm to the cell membrane surface,

allowing cellular glucose uptake. The mineral chromium is involved with movement of the glucose transporter-4 to the cell surface [4].

6. Protein kinase B also activates glycogen synthase to stimulate glycogen synthesis from glucose inside the cell. Glycogen synthesis is inhibited by excess saturated fatty acids [3] (Figures 1,2).

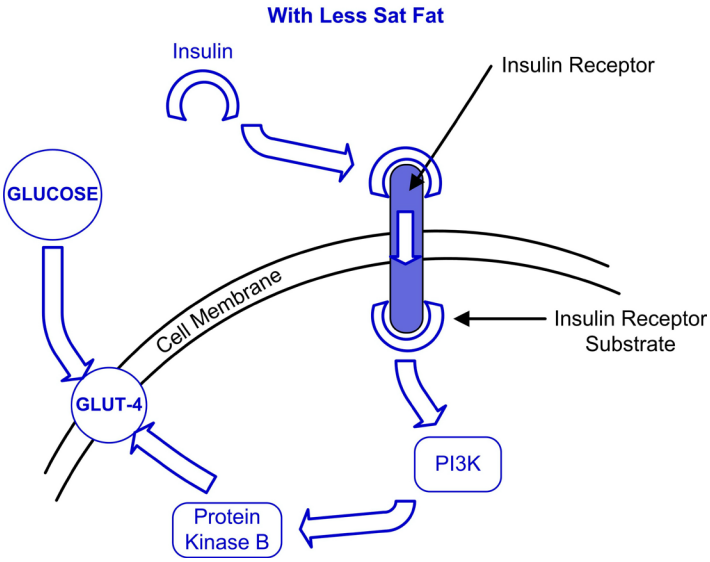

Figure 1: *Removal of glucose from the bloodstream without excess saturated fatty acids.*

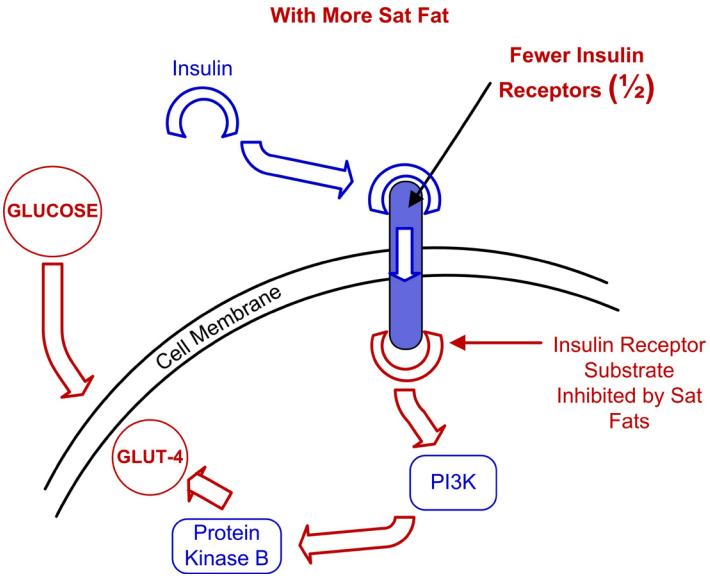

Figure 2: *Impaired removal of glucose from the bloodstream with excess saturated fatty acids.*

Once an insulin molecule has docked onto the cellular receptor and effected its action, it may be released back into the extracellular environment, or it may be degraded by the cell. Degradation normally involves endocytosis of the insulin-receptor complex followed by the action of insulin degrading enzyme. Interestingly, this same insulin-degrading enzyme clears amyloid-beta from the brain—unless it is depleted because of hyperinsulinemia [5]. Most insulin molecules are degraded by liver cells. It has been estimated that a typical insulin molecule is fully degraded about 71 minutes after its initial release into circulation [1].

Saturated fatty acids increase insulin resistance and increase glucose in blood

Saturated fatty acids are associated with insulin resistance and glucose intolerance, which are significant risk factors for type 2 diabetes. Myristic and palmitic acids were positively associated with fasting insulin and increased glucose in blood. Stearic acid was associated with increased glucose, but not increased insulin [6].

The KANWU study included 162 healthy subjects chosen at random to receive a controlled, isoenergetic diet for 3 months containing either a high proportion of saturated or monounsaturated fatty acids. Insulin sensitivity was 12.5 % lower on the saturated fatty acid diet and 8.8 % higher on the monounsaturated fatty acid diet ($p = 0.03$). Insulin secretion was not affected. These effects were only seen at a total fat intake below 37% of total energy intake. Above that level, insulin insensitivity was seen in both groups [7].

Excesses of total fatty acids lead to insulin resistance. Excesses of myristic, palmitic, stearic, and oleic acids have been implicated in interfering with the signaling between the insulin receptor and the glucose transporter GLUT-4. Palmitic acid has been found to be the most powerful in decreasing insulin sensitivity. Interference has been found with the insulin receptor substrate, protein kinase-B, and phosphatidylinositol-3-kinase [8].

Excess dietary saturated fatty acids reduce the number of insulin receptors

Excess dietary saturated fatty acids can lead to a sustained downregulation of the expression of the insulin receptor [2]. Excess dietary saturated fatty acids lead to a lack of the HMGA1 gene, which transcribes a high-mobility group protein. Lack of HMGA1 can suppresses biosynthesis of the insulin receptor [8].

Palmitic acid was shown to decrease insulin receptor expression and activity. A two-fold decrease in the number of insulin receptors in the cellular membrane was found with excess palmitate [2]. Palmitate inhibition of insulin receptor gene expression effectively reduced the amount of insulin receptors in skeletal muscle cells. This is in addition to the well-known interference shown by saturated fatty acids in the signaling between the insulin receptor and glucose transporter-4 [9].

The toll-like receptor-4 may be implicated in some, but not all, routes to insulin resistance

Saturated fatty acids are thought to induce insulin resistance partially through activation of the *toll-like receptor-4*, which in turn transcriptionally activates hepatic ceramide synthesis leading to inhibition of insulin signaling. However, toll-like receptor-4 signaling is not directly required for impairment of insulin-stimulated insulin receptor substrate signaling. Saturated fat-induced insulin resistance may sometimes be independent of TLR-4 activation and ceramides [10]. Toll-like receptor-4 may not

always be involved in saturated fat-induced insulin resistance [11].

Saturated fatty acids stimulated adipose tissue inflammation by a process that involved *toll-like receptor-4*. Toll-like receptor-4 binds bacterial lipopolysaccharides, also known as endotoxins. Lipopolysaccharides come from cooked bacteria and may be found in meat, dairy products, and fish. It has been seen that toll-like receptor-4 deficiency protected against insulin resistance in obesity induced by a diet high in saturated fatty acids. This suggests that toll-like receptor-4 is one link between excess dietary saturated fatty acids and insulin resistance. Less diet-induced insulin resistance and adipose tissue inflammation have been observed in mice with low function of their toll-like receptor-4 [12].

Excess dietary saturated fatty acids decreased the amount of insulin-stimulated glucose uptake. Inflammation may play a role, since saturated fats activated the *nuclear transcription factor-κ*B pathway and induced *interleukin*-6, *tumor necrosis factor*-α , and *monocyte chemoattractant protein*-1 mRNA expressions. The insulin-activated glucose uptake was reduced even though the mice were deficient in Toll-like receptor-4, indicating another mechanism may be involved [11]. However, in another study, saturated fatty acids served as a naturally occurring ligand for toll-like receptor-4, thereby inducing inflammatory changes in both adipocytes and macrophages through *nuclear transcription factor*-κB activation [13].

Saturated fatty acids can suppress insulin production

By the time diabetes is diagnosed, half of the insulin-producing cells may have suffered apoptosis [14]. The remaining beta cells can be inhibited by excess free saturated fatty acids. This can lower their production of insulin. During rapid weight loss (or bariatric surgery), over 8 weeks, these beta cells can start responding again and producing insulin in response to need—relieving high blood sugar [14].

Animal fats can increase circulating levels of free saturated fatty acids. The beta cells that produce insulin in the pancreas can die off from these free fatty acids from animal fats (30-60% decrease) [15]. The beta cells die off principally as a result of damage to the endoplasmic reticulum. There are then less beta cells to make insulin. Oleic acid has been found to be protective, reducing beta cell apoptosis from glucolipotoxicity induced by free saturated fatty acids, diacylglycerols, and ceramides.

Saturated fatty acids released from adipose tissue can also reduce insulin secretion by beta cells in the pancreas. Circulating levels of free saturated fatty acids in the portal system can be increased when there is increased abdominal fat. This abdominal fat can create more free saturated fatty acids in the bloodstream, killing off beta cells that produce insulin [16].

Blood sugar is burned for energy or stored as glycogen in muscle cells. If there is an excess of glucose, liver cells can convert this excess glucose into palmitic acid, a 16-carbon saturated fatty acid. A constant excess of calories can lead to non-alcoholic fatty liver disease. This excess fat in liver cells can later be turned into blood sugar—thus raising fasting blood sugar levels [14].

Saturated fatty acids may impair energy production in the mitochondria

In muscle cells, saturated free fatty acids induced mitochondrial dysfunction. This mitochondrial dysfunction may be associated with impaired glucose metabolism. These saturated fatty acids reduced glucose oxidation and lactate production. Palmitic and stearic acids impaired mitochondrial function as demonstrated by a decrease in ATP generation [3].

Another way that excess free fatty acids may reduce energy production is through a reduction in the number of mitochondria in muscle cells. Exercise can ameliorate this effect of excess free fatty acids in muscle cells by stimulating mitochondrial biogenesis [17]—and burning free fatty acids. Another way to increase the biogenesis of mitochondria is to reduce the amount of excess fatty acids in muscle cells. Reduced excess fatty acids increase the amount of *peroxisome proliferator activated receptor-gamma co-activator 1-alpha* (PGC-1α). Higher amounts of PGC-1α stimulate more mitochondrial biogenesis. Modest over-expression of PGC-1α in muscle increases the glucose transporter GLUT4 expression and increases insulin-stimulated glucose uptake [18].

Palmitic acid may inhibit the biosynthesis of glycogen

Saturated palmitic and stearic acids decreased insulin-induced glycogen synthesis, thus reducing substrates for energy production [3]. Glycogen is produced in the cell by the enzyme *glycogen synthase*. Palmitate was found to impart a dose-dependent inhibition of glycogen synthase activity in cultured muscle cells. Inactivation of glycogen synthase could be the mechanism for saturated long-chain fatty acid inhibition of insulin-mediated carbohydrate storage. The presence of palmitate resulted in a glycogen synthase activity that was 73% of the normal glycogen synthase activity [19].

Chromium assists transport of glucose into the cell

Chromium improves insulin sensitivity in a variety of cellular and animal models of insulin resistance. When sufficient chromium is present, there were enhanced levels of tyrosine phosphorylation of insulin receptor substrate-1. Phosphorylation of protein kinase-B was also increased. Presence of chromium also improved phosphatidlinositol-3-kinase activity. Higher chromium levels also increased levels of the glucose transporter-4 in the plasma membrane [4].

Chromium has been observed to increase the fluidity of the cell membrane by decreasing membrane cholesterol. Chromium has also been shown to cause an up-regulation of sterol regulatory element-binding protein, a membrane-bound transcription factor responsible for controlling cellular cholesterol balance [4].

Summary

Dietary saturated fatty acids play a central role in the development and progression of type 2 diabetes. Reducing excessive dietary saturated fats provides a safe and effective treatment strategy for patients and clinicians wanting to target the root cause of insulin resistance and type 2 diabetes. Without addressing this, it is unlikely that disease reversal is possible. Diet and exercise remain first-line treatment options for type 2 diabetes, and are among the most effective approaches to combatting this disease. The data contained herein underscore the importance of dietary saturated fat intake in the development of insulin resistance, and set the stage for future dietary human interventional studies analyzing the direct effects of saturated fat intake on the development, progression, and potential reversal of type 2 diabetes.

Conflict of interest and funding

The authors declare that there is no conflict of interest and no funding was used.

References

1. Neumann KF, Rojo L, Navarrete LP, Farías G, Reyes P, et al. Insulin Resistance and Alzheimer´s Disease: Molecular Links & Clinical

Implications. *Curr Alzheimer Res*. 2008; 5: 438-447.
2. Dey D, Mukherjee M, Basu D, Datta M, Roy SS, et al. Inhibition of Insulin Receptor Gene Expression and Insulin Signaling by Fatty Acid: Interplay of PKC Isoforms Therein. *Cell Physiol Biochem*. 2005; 16: 217-228.
3. Hirabara SM, Curi R, Maechler P. Saturated Fatty Acid-Induced Insulin Resistance Is Associated With Mitochondrial Dysfunction in Skeletal Muscle Cells. *J Cell Physiol*. 2010; 222: 187-194.
4. Hua Y, Clark S, Ren J, Sreejayan N. Molecular Mechanisms of Chromium in Alleviating Insulin Resistance. *J Nutr Biochem*. 2012; 23: 313-319.
5. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. The Lancet. 2006; 368: 387-403.
6. Ebbesson SO, Tejero ME, López-Alvarenga JC, Harris WS, Ebbesson LO, et al. Individual saturated fatty acids are associated with different components of insulin resistance and glucose metabolism: the GOCADAN study. *Int J Circumpolar Health*. 2010; 69: 344-351.
7. Vessby B, Uusitupa M, Hermansen K, Riccardi G, Rivellese AA, et al. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU study. *Diabetologia*. 2001; 44: 312-319.
8. Bhattacharya S, Kundu R, Dasgupta S, Bhattacharya S. Mechanism of Lipid Induced Insulin Resistance: An Overview. *Endocrinol Metab.* 2012; 27: 12-19.
9. Martins AR, Nachbar RT, Gorjao R, Vinolo MA, Festuccia WT, et al. Mechanisms underlying skeletal muscle insulin resistance induced by fatty acids: importance of the mitochondrial function. *Lipids Health Dis*. 2012; 11: 30.
10. Galbo T, Perry RJ, Jurczak MJ, Camporez JP, Alves TC, et al. Saturated and unsaturated fat induce hepatic insulin resistance independently of TLR-4 signaling and ceramide synthesis in vivo. *Proc Natl Acad Sci U S A*. 2013; 110: 12780-12785.
11. Zhou YJ, Tang YS, Song YL, Li A, Zhou H, et al. Saturated Fatty Acid Induces Insulin Resistance Partially Through Nucleotide-binding Oligomerization Domain 1 Signaling Pathway in Adipocytes. *Chin Med Sci J*. 2013; 28: 211-217.
12. Chait A, Kim F. Saturated Fatty Acids and Inflammation: Who Pays the Toll?. *Arterioscler Thromb Vasc Biol*. 2010; 30: 692-693.
13. Suganami T, Tanimoto-Koyama K, Nishida J, Itoh M, Yuan X, et al. Role of the Toll-like Receptor 4/NF-kB Pathway in Saturated Fatty Acid–Induced Inflammatory Changes in the Interaction Between Adipocytes and Macrophages. *Arterioscler Thromb Vasc Biol*. 2007; 27: 84-91.
14. Taylor R. Reversing the twin cycles of Type 2 diabetes. *Diabet Med*. 2013; 30: 267-275.
15. Cnop M. Fatty acids and glucolipotoxicity in the pathogenesis of Type 2 diabetes. *Biochem Soc Trans*. 2008; 36: 348-352.
16. Estadella D, da Penha Oller do Nascimento CM, Oyama LM, Ribeiro EB, Dâmaso AR, et al. Lipotoxicity: Effects of Dietary Saturated and Transfatty Acids. *Mediators Inflamm*. 2013; 2013: 137579.
17. Jornayvaz FR, Shulman GI. Regulation of mitochondrial biogenesis. *Essays Biochem*. 2010; 47: 69-84.
18. Eckardt K, Taube A, Eckel J. Obesity-associated Insulin Resistance in Skeletal Muscle: Role of Lipid Accumulation and Physical Activity. *Rev Endocr Metab Disord*. 2011; 12: 163-172.
19. Mott DM, Stone K, Gessel MC, Bunt JC, Bogardus C. Palmitate action to inhibit glycogen synthase and stimulate protein phosphatase 2A increases with risk factors for type 2 diabetes. *Am J Physiol Endocrinol Metab*. 2008; 294: E444-E450.

***Correspondence:** Steve Blake, ScD, Director of Nutritional Neuroscience, Maui Memory Clinic, P O Box 81426, Haiku, HI, USA, Tel: (808) 280-6894, E-mail: steve@drsteveblake.com

Rec: 11 Sep 2021; **Acc**: 18 Oct 2021; **Pub**: 22 Oct 2021

Int J Transl Sci. 2021;1(1):104
DOI: 10.36879/IJTS.21.000104