

Re: Researchers discover how a high-fat diet causes type 2 diabetes

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Source: <http://sci.tech-archive.net/Archive/sci.med.cardiology/2006-09/msg00274.html>

- *From:* "SEO Learner" <oncemailme@xxxxxxxxx>
 - *Date:* 20 Sep 2006 05:28:28 -0700
-

its nice news

but try to see this one

<http://www.medical-health-care-information.com/encyclopedia/Asthma/asthma.asp>

Matti Narkia wrrohit ote:

On Wed, 20 Sep 2006 14:09:58 +0300, Matti Narkia <mna@xxxxxxxxx> wrote:

On Wed, 20 Sep 2006 03:31:21 +0300, Matti Narkia <mna@xxxxxxxxx> wrote:

When I fed lipotoxicity to google, the first hit was

Sivitz WI.

Lipotoxicity and glucotoxicity in type 2 diabetes. Effects on development and progression.

Postgrad Med. 2001 Apr;109(4):55-9, 63-4. Review.

PMID: 11317469 [PubMed - indexed for MEDLINE]

<http://www.postgradmed.com/issues/2001/04_01/sivitz.htm>

It seems to define lipotoxicity as the diabetogenic effect of increased circulating free fatty acids or increased cellular fat content. The excess circulating free fatty acids seem mostly arise

from obesity. A few citations:

"Lipotoxicity is the diabetogenic effect of increased circulating

free fatty acids or increased cellular fat content. This condition

is manifest in several tissues, most notably the liver, muscle, and pancreatic islet

[...]

It also is thought that excess fuel in the form of fat may be

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responsible for raising blood glucose concentrations to those seen in diabetes. The association between diabetes and obesity is well established.

[...]

The prevalence of obesity among diabetic patients and observations that plasma levels of free fatty acids are elevated in most obese persons suggest that free fatty acids themselves might induce hyperglycemia."

Other related articles:

Below some citations from these articles.

Diabetes & Free Fatty Acids, on MedicineNet.com
<<http://www.medicinenet.com/script/main/art.asp?articlekey=52045>>>

"So what are free fatty acids? During the process of lipolysis — the breakdown of fat stored in fat cells — free fatty acids are released into the bloodstream and circulate throughout the body. Naturally, people who are obese have larger reservoirs of fat cells that can potentially become free fatty acids. When free fatty acid levels are too high, there's evidence they cause a number of problems.

[...]

High free fatty acid levels decrease the ability of the liver to store sugars — keeping sugars in the blood and away from muscles that use them for energy. They may also directly affect the functioning of beta cells in the pancreas, the cells that produce insulin. How free fatty acids do this is the subject of some debate.

One widely accepted hypothesis that goes back 40 years is that an excess of free fatty acids in the bloodstream blocks the normal absorption of glucose by other cells. However, that idea, called the Randle hypothesis, has been under scrutiny recently.

A different hypothesis is that an excess of fat cells results in fat being stored in places that it shouldn't, such as in the

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liver, skeletal muscles, and in the beta cells. This improper storage could result in insulin resistance. Another potentially complimentary hypothesis is that the excretion of other endocrine hormones -- such as leptin and resistin -- from fat tissue could have a marked effect on the body's metabolism, causing dysfunction."

Koutsari C, Jensen MD.

Thematic review series: patient-oriented research. Free fatty acid

metabolism in human obesity.

J Lipid Res. 2006 Aug;47(8):1643-50. Epub 2006 May 9.

PMID: 16685078 [PubMed - in process]

<<http://www.jlr.org/cgi/content/short/R600011-JLR200v1>> (abstract)

<<http://www.jlr.org/cgi/reprint/R600011-JLR200v1>> (full text PDF)

"Adipose tissue lipolysis provides circulating free-fatty acids (FFA) to meet the body's lipid fuel demands. FFA release is well-regulated in normal-weight individuals, however, in upper-body obesity excess lipolysis is commonly seen. This abnormality is considered a cause for at least some of the metabolic defects (dyslipidemia, insulin resistance) associated with upper-body obesity. "Normal" lipolysis is sex-specific and largely determined by the individual's resting metabolic rate. Women have greater FFA release rates than men without higher FFA concentrations or greater fatty acid oxidation, indicating they have greater non-oxidative FFA disposal, although the processes and tissues involved in this phenomenon are unknown. Therefore, women have the advantage of having greater FFA availability without exposing their tissues to higher and potentially harmful FFA concentrations. Upper-body fat is more lipolytically active than lower-body fat in both women and men. FFA released by the visceral fat depot contributes only a small percentage of systemic FFA delivery. Upper-body subcutaneous fat is the dominant contributor to circulating FFA and the source of the excess FFA release in upper-body obesity. We believe abnormalities in subcutaneous lipolysis could be more important than those in visceral lipolysis as a cause of peripheral insulin resistance. Understanding the regulation of FFA availability will help to discover new approaches to treat FFA-induced abnormalities in obesity."

Here's another interesting sstudy with selected citations:

Sandu O, Song K, Cai W, Zheng F, Uribarri J, Vlassara H. Insulin resistance and type 2 diabetes in high-fat-fed mice are linked to high

glycotoxin intake.

Diabetes. 2005 Aug;54(8):2314-9.

PMID: 16046296 [PubMed - indexed for MEDLINE]

<<http://diabetes.diabetesjournals.org/cgi/content/full/54/8/2314>>

"Dietary advanced glycosylation end products (AGEs) have been linked to insulin resistance in db/db(++) mice. To test whether dietary AGEs play a role in the progression of insulin resistance in normal mice fed high-fat diets, normal C57/BL6 mice were randomly assigned to high-fat diets (35% g fat), either high (HAGE-HF group; 995.4 units/mg AGE) or low (by 2.4-fold LAGE-HF group; 329.6 units/mg AGE) in AGE content for 6 months. Age-matched C57/BL6 and db/db(++) mice fed regular diet (5% g fat, 117.4 units/mg AGE) served as controls. After 6 months, 75% of HAGE-HF mice were diabetic and exhibited higher body weight ($P < 0.001$), fasting glucose ($P < 0.001$), insulin ($P < 0.001$), and serum AGEs ($P < 0.01$) than control mice, while none of the LAGE-HF mice were diabetic despite a similar rise in body weight and plasma lipids. The HAGE-HF group displayed markedly impaired glucose and insulin responses during glucose tolerance tests and euglycemic and hyperglycemic clamps and altered pancreatic islet structure and function compared with those of LAGE-HF mice, in which findings resembled those of control mice. The HAGE-HF group had more visceral fat (by two- and fourfold) and more AGE-modified fat (by two- and fivefold) than LAGE-HF and control mice, respectively. In the HAGE-HF group, plasma 8-isoprostane was higher ($P < 0.01$) and adiponectin lower ($P < 0.001$) than control mice, while in the LAGE-HF group, these were more modestly affected ($P < 0.05$). These results demonstrate that the development of insulin resistance and type 2 diabetes during prolonged high-fat feeding are linked to the excess AGEs/advanced lipoxidation end products inherent in fatty diets.

[...]

Advanced glycation end products (AGEs) as well as advanced lipoxidation end products (ALEs) are prooxidant and proinflammatory compounds that have recently been linked to impaired insulin sensitivity (8). These compounds continuously form in the body from the reaction of reducing sugars and reactive carbonyls with free amino groups (9), while amine-containing lipids are also generators of lipid peroxidation products (10-12). AGEs/ALEs can also originate exogenously, during heat processing of food (13-16), and become incorporated in body components after intestinal absorption (17). It has now become apparent that dietary AGEs represent a significant source of circulating and tissue AGEs, manifesting similar pathogenic properties to their endogenous counterparts (17-24). The restriction of the AGE content in standard mouse diets was found, among other effects, to markedly improve insulin

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resistance in obese db/db(++) mice (8).

Because fat-rich foods are also particularly rich in AGEs/ALEs (16), we postulated that the insulin resistance observed after chronic high-fat feeding (25) is related to the obligatory intake of large amounts of AGEs inherent in these diets. To test this hypothesis, we evaluated glucose and insulin responses, visceral adiposity, pancreatic islet morphology, and type 2 diabetes incidence in mice subjected to long-term feeding on high-fat diets but with either high or low AGE/ALE content. We also measured plasma 8-isoprostane as an index of systemic oxidant stress and plasma adiponectin as a molecule that has been found to be inversely correlated with insulin resistance.

[...]

The studies presented demonstrate that in normal mice exposed to a high-fat diet, the metabolic changes, which lead to weight gain, glucose intolerance, insulin resistance, and type 2 diabetes are linked to the AGEs/ALEs present in the diet. In addition, the studies illustrate that visceral adiposity and systemic indicators of oxidative stress or inflammation, such as 8-isoprostane and adiponectin, can be differentially linked to the ingested AGEs beyond the excess of fat. Furthermore, pancreatic islet structure and function, which are affected negatively during prolonged exposure to a fat-rich diet, appear to be linked to the dietary content of glycoxidants and can thus be spared by a diet comparatively low in AGEs, even if it is fat rich. These observations differ significantly from previous observations on the role of dietary AGEs in genetically type 2 diabetes-prone mice (8), the key difference here being the induction of insulin resistance and type 2 diabetes in normal mice exposed to excess fat, a dietary condition resembling that of many healthy humans.

In the present studies, high dietary fat intake by normal mice for the period between 1 and 7 months of age led to an increase in body weight of both high- and low-AGE groups, which was modest yet significantly higher in the HAGE-HF than in the LAGE-HF mice. Interestingly, a major proportion (~75%) of the mice fed a HAGE-HF diet were diabetic by the end of the study compared with none of those exposed to the LAGE-HF diet, based on a fasting blood glucose level >130 mg/dl. The AGE-rich fatty diet resulted in a pattern of profound abnormalities in glucose tolerance, glucose disposal rate, and insulin responses closely resembling those of the diabetic db/db(++) mice (8). In contrast, exposure to the low-AGE fatty diet led to a pattern comparable with the normal metabolic profile associated with the standard (low-fat) diet. These findings suggest that dietary factors other than high fat content contribute to these

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metabolic changes.

[...]

In summary, during prolonged high-fat feeding, the AGE/ALE content of food may exert significant influence on the regulation of insulin secretion and action and visceral adiposity and may ultimately lead to type 2 diabetes. These results, taken together with previous work (8) on the effects of a high-in-AGE-but-low-in-fat diet on insulin resistance support the view that in addition to the fat, the high AGE/ALE content of food is significantly linked to the insulin-resistant state. While the mechanisms linking AGEs and the related deleterious metabolic effects are likely to be complex, the evidence indicates that lowering AGE/ALE content in fatty foods might be an intervention to control insulin resistance and prevent diabetes. Further long-term studies in humans are needed."

Matti Narkia