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Origins of metabolic complications in obesity: adipose tissue and free fatty acid trafficking

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Abstract

Purpose of review—Obesity is associated with a number of serious medical complications that are risk factors for cardiovascular disease (e.g., insulin resistance, dyslipidemia and liver fat accumulation). Alterations in fatty acid trafficking, both between tissues and within cells, represent a key feature in the pathophysiology of the metabolic complications in obese subjects. The ways by which fatty acid “re-routing” may affect metabolic function are summarized in this article.

Recent findings—Ectopic fat accumulation (i.e., fat accumulation in non-adipose tissues) appears to be a key feature distinguishing metabolically healthy from metabolically abnormal subjects. This observation has led to the belief that an imbalance in fatty acid trafficking away from adipose tissue towards non-adipose tissues is a primary cause for the development of metabolic alterations in obese subjects. More recently, however, it has become apparent that fatty acid trafficking within non-adipose tissues cells (i.e., towards storage - in the form of triglycerides - and oxidation) may be equally important in determining risk for development of metabolic disease.

Summary—The pathophysiology of the metabolic alterations associated with obesity is probably multifactorial within a complex network of coordinated physiological responses. Only through the integration of multiple concepts will it be possible to further our understanding in this area and to help prevent the metabolic alterations associated with obesity.

Keywords

Insulin resistance; adipose tissue; ectopic fat; NAFLD

INTRODUCTION

Obesity is associated with a number of serious medical complications, which are often referred to as the “insulin resistance syndrome” because resistance to insulin action in various tissues/organ systems/metabolic pathways is a common underlying feature of these complications [1]. The most common complications involve alterations in metabolic function that are risk factors for cardiovascular disease, namely hyperglycemia, hyperinsulinemia, and glucose intolerance, liver fat accumulation, dyslipidemia (increased serum triglyceride and decreased serum HDL-cholesterol concentrations; a predominance of smaller LDL particles and an increased number of large VLDL particles), and endothelial dysfunction [2–6]. The development of these metabolic alterations is, at least in part, related

to alterations in lipid metabolism rather than excess energy intake because even normal weight subjects (i.e., those with a body mass index [BMI] <25.0 kg/m²) but excessive amounts of body fat), particularly if fat accumulation occurs in the abdominal region, have an increased risk for cardiometabolic alterations and cardiovascular mortality [3–6]. On the other hand, only about 70 % of obese adults develop metabolic abnormalities whereas ~30 % have no obvious metabolic abnormalities [7–10]. Ectopic fat accumulation (i.e., fat accumulation in non-adipose tissues such as in the liver, skeletal muscles, heart, pancreas and intra-abdominally) appears to be a key feature distinguishing metabolically healthy from metabolically abnormal subjects. Fat accumulation in the liver due to non-alcoholic causes (non-alcoholic fatty liver disease, NAFLD) is a robust, independent marker of metabolic dysfunction (insulin resistance in liver, muscle and adipose tissue and dyslipidemia) and an independent predictor of type 2 diabetes whereas obese persons who have normal liver fat content appear to be resistant to developing obesity-related metabolic complications [11–14]. Conversely, insulin resistance is a major independent predictor of ectopic fat accumulation [15]. Increased intramuscular triglyceride accumulation is associated with skeletal muscle insulin resistance [16, 17]. Cardiac steatosis (excess fat accumulation in cardiomyocytes) is a hallmark of obesity and diabetes and is associated with left ventricular dysfunction and premature death [18, 19]. Deposition of fat inside and around the pancreas is associated with impaired β -cell function [20, 21] and increased risk of diabetes [22, 23]. Increased fatty acid flux (i.e., endogenous fatty acids which are released from adipose tissue and meal-derived fatty acids) away from rather than into adipose tissue has therefore been considered the major problem in the progression from health to disease.

Whole body free fatty acid flux relative to lean tissue mass is greater in individuals with abdominal fat accumulation, NAFLD and insulin resistance than in metabolically healthy obese subjects [11, 24, 25]. In addition, triglyceride-derived fatty acid availability is greater because of increased non-adipose tissue uptake of these fatty acids in subjects with insulin resistance [26]*. The mechanistic links between excess fatty acid availability and metabolic alterations associated with obesity have been extensively reviewed [2, 27, 28] and are therefore only briefly summarized here. Experimentally increasing plasma free fatty acid availability, via infusion of a lipid emulsion plus heparin, stimulates hepatic very low-density lipoprotein triglyceride production, leading to dyslipidemia [27, 29, 30], and can reduce insulin action in target tissues/organs via inhibitory serine phosphorylation of IRS1 [14, 28, 31, 32]. More recently, however, it has been recognized that it may not be fatty acid availability and ectopic triglyceride accumulation *per se* but probably more importantly the fate of fatty acids within non-adipose tissues that determines the risk for developing insulin resistance. This concept has its roots in the “athletes’ paradox” [33] because endurance trained athletes are exquisitely insulin sensitive yet their intramuscular triglyceride content matches or even exceeds that of diabetic subjects [34].

The various concepts of how fatty acid trafficking towards the wrong places both at the whole-body level (i.e., away from adipose tissue into non-adipose tissues), including the “visceral fat” hypothesis, the “adipose tissue expandability” or “lipid overflow” hypothesis, and the “sick adipose tissue” hypothesis), as well as fatty acid trafficking within non-adipose tissues cells are summarized below. The major focus of this review will be on intracellular fatty acid trafficking and how it may affect insulin action in non-adipose tissues because it is the most novel of the theories and represents the area in which most new developments have been made in the past couple of years.

The “visceral fat” hypothesis

The fact that it is not obesity *per se* but rather the “masculine type” of obesity (i.e., upper body obesity) that appears to predispose to the development of cardio-metabolic abnormalities was first noticed by Vague in 1956 [35] and was followed by the long-held

view that accumulation of excess visceral fat at the expense of subcutaneous fat results in excess release of fatty acids from visceral adipose tissue stores into the portal system and into the systemic circulation thereby causing dyslipidemia and systemic insulin resistance [36–39]. It has later been recognized that although hepatic insulin resistance and excess glucose and VLDL-triglyceride production and secretion can be explained by this phenomenon, peripheral insulin resistance (i.e., in skeletal muscle) is unlikely to be caused by high rates of visceral adipose tissue lipolysis because visceral fat-derived fatty acids are not the source of excess systemic free fatty acid availability [reviewed in 38, 39]. Thus, visceral fat accumulation is more likely a result, rather than the cause, of systemic insulin resistance.

The “adipose tissue expandability” or “lipid overflow” hypothesis

The “adipose tissue expandability” or “lipid overflow” hypothesis, originally proposed by Roger Unger in 2003 [40], has been the focus of attention for much of the past decade to help explain ectopic fat accumulation [40–43]. According to this hypothesis, the metabolic alterations associated with obesity result from leptin resistance and a failure in the capacity for appropriate adipose tissue expansion and consequently storage of surplus lipids in non-adipose tissues where it results in “lipotoxicity”. Conditions associated with peripheral lipodystrophy are primary examples for this concept [44, 45]. However, these are extreme conditions and unlikely to reflect the slow progression from lean to obese and the concomitant need for progressive adipose tissue expansion. In fact, a major criticism of this theory in the context of obesity is that there is really no evidence for a limit to subcutaneous adipose tissue expansion; moreover, the amounts of triglycerides stored ectopically, even under extreme conditions, seem trivial compared to the size of subcutaneous adipose tissue stores. Although of course it would only take a tiny amount of spill-over over many years to cause ectopic fat stores to expand beyond healthy limits.

The “sick adipose tissue” hypothesis

At the center of this hypothesis, as the name implies, lies dysfunctional adipose tissue which leads to metabolic disease through abnormalities in adipose tissue interaction with other body organs; this condition has been referred to as “adiposopathy” by Harold Bays [46] and has since been reviewed and discussed in detail by Bays [47] and the Adiposopathy Working Group [48]. According to this hypothesis, fat mass gain leads to metabolic disease when it includes excessive fat cell enlargement (adipocyte hypertrophy) due to impaired adipogenesis (creation of new fat cells) and consequently adipocyte dysfunction, which includes hypoxia, endoplasmatic reticulum stress, apoptosis, macrophage infiltration and inflammation, and insulin resistance, which results in excess free fatty acid release and ultimately systemic inflammation and insulin resistance [49–57]*. Indeed, fat cell hypertrophy appears to distinguish metabolically normal from metabolically abnormal obese individuals [58]. Probably included in this list of dysfunctions should be the down-regulation of adipose tissue fatty acid uptake [59, 60], presumably through decreased fatty acid transporter expression [14] and impaired up-regulation of postprandial lipoprotein lipase activity [61], which can also lead to increased fatty acid availability in non-adipose tissues.

Fatty acid trafficking in non-adipose tissues

The “athletes’ paradox” was a first indication that ectopic fat accumulation *per se* is not necessarily a bad thing. Endurance trained athletes are exquisitely insulin-sensitive but have intramuscular triglyceride stores that can match or even exceed, in size, those in diabetic subjects [33, 34]. The apparent paradox of high intramuscular triglyceride content in the context of high insulin sensitivity has also been reproduced in several animal and *in vitro* cell culture models either by stimulating triglyceride synthesis or blocking triglyceride

breakdown through genetic modifications. Transgenic overexpression of diacylglycerol acyltransferase-1 (DGAT-1), a key enzyme in the triglyceride synthesis pathway, in skeletal muscle of mice protects them against fat-induced insulin resistance despite accumulation of intramuscular triglycerides [62–64]. Also, genetic inactivation of triglyceride lipase simultaneously leads to increased ectopic fat accumulation and increased glucose use, glucose tolerance, and insulin sensitivity in mice and human primary myotubes [19, 65]. It has thus been proposed that the protection from insulin resistance in athletes stems from efficient fatty acid trafficking towards net triglyceride synthesis which limits the availability of substrates available for formation and accumulation of more harmful lipid intermediates, such as e.g., diacylglycerides (DAG) and ceramides, which have been implicated as being responsible for fatty-acid induced insulin resistance [66–68]. Consequently, much progress has been made in this area during the last 5 years and a considerable amount of evidence has accumulated that supports this hypothesis. However, there is also good evidence that would argue against this concept, at least as the sole factor responsible for a protective effect.

First off, in rodent models of obesity, the proposed relationship between intramuscular triglyceride synthesis rate and insulin sensitivity (i.e., the greater the rate of synthesis the more insulin sensitive) does not seem to manifest. Both intramuscular triglyceride pool size and intramuscular triglyceride synthesis rates are greater in insulin resistant obese than lean rodents [69, 70]. In fact, Guo [71] used this observation to help explain the development of insulin resistance on the basis of increased rather than decreased intramuscular triglyceride turnover. Importantly, Guo considered both the rate of triglyceride synthesis and breakdown simultaneously, and argued that the accelerated rate of triglyceride breakdown that accompanies the accelerated rate of synthesis in obese rodents provides substrate for excess formation of toxic lipid mediators. This may be particularly true if there is an imbalance in the steps involved in triglyceride breakdown. Badin et al. [65]* recently reported that overexpression of triglyceride lipase, which mediates the conversion of triglycerides to DAGs, in human primary myotubes reduced their triglyceride content but induced insulin resistance; this insulin desensitizing effect was prevented by concomitant hormone sensitive lipase overexpression which completes hydrolysis of DAGs to free fatty acids and glycerol.

Studies in human subjects, on the other hand, appear to confirm the concept of the intramuscular triglyceride pool as a “sink” for excess fatty acids and triglyceride synthesis rate as the “gate-keeper”, responsible for the prevention of insulin resistance. In 2007, Schenk and Horowitz [72] reported that a single bout of exercise prevents fatty acid induced insulin resistance despite an increase in intramuscular triglyceride pool size presumably because exercise increased intramuscular triglyceride synthesis and thereby reduced intracellular ceramide and DAG contents. In 2010, Bergman, Perreault and Eckel and their colleagues confirmed these findings by demonstrating that the intramuscular triglyceride synthesis rate is greater in endurance trained athletes than sedentary control subjects [73]. However, intramuscular DAG concentration was not different in the athletes and control subjects and it was therefore suggested that greater insulin sensitivity in the athletes is probably due to differences in DAG species (less saturated DAGs in the athletes than the control subjects). Although, it is not certain that DAGs and ceramides are in fact the parties responsible for insulin resistance [74–76]. Other potential mediators that could interfere with insulin signaling were not evaluated. Bergman, Perreault and Eckel also demonstrated that pre-diabetic subjects had a slower rate of intramuscular triglyceride synthesis at rest than subjects with normal glucose tolerance [77]. However, pre-diabetic subjects failed to suppress the rate of intramuscular triglyceride synthesis during exercise [77]. Because the higher rate of intramuscular triglyceride synthesis after exercise does not fit the a priori hypothesis, it was concluded that the inflexibility in intramuscular triglyceride synthesis might be the problem. Interpretation of these data appears to be a bit more complicated, though, because the reported triglyceride synthesis rates are expressed relative to the

intramyocellular triglyceride pools size (i.e., as fractional synthesis rate in % per h). In fact, the absolute rate of palmitate incorporation into triglyceride at rest turned out not to be different in the pre-diabetic subjects and subjects with normal glucose tolerance because the intramyocellular triglyceride pools size was ~30 % greater in pre-diabetic subjects and the intramyocellular triglyceride fractional synthesis rate (in % per h) was ~30 % less; although it remained greater in the pre-diabetic than normoglycemic subjects after exercise. Nevertheless, whole-body palmitate rate of disappearance was also less in pre-diabetic than normoglycemic subjects, so that in fact the fatty acid and lipid intermediate precursor pool for the synthesis of insulin signaling inhibitory substrates may not have been different between groups despite the difference in triglyceride synthesis rate. Bucci et al. [78]** also reported similar rates of palmitate incorporation into triglycerides in muscle in obese and lean subjects. The rates of triglyceride breakdown or actual intracellular free fatty acid appearance were not evaluated in these studies (due to the technical challenges involved).

Another way of “getting rid” of fatty acids and their potentially harmful byproducts is, of course, through oxidation. In fact, mitochondrial dysfunction has long been thought to mediate insulin resistance in obese subjects. However, there remains considerable controversy whether mitochondrial dysfunction is a plausible explanation for the development of insulin resistance in muscle as well as other tissues, such as the liver [79–85]. Part of the controversy in this field probably stems from the fact that mitochondrial function is typically assessed by either measuring mitochondrial DNA content or by measuring mitochondrial enzyme (most often citrate synthase) activity *ex vivo*. Although a few months ago, Chomentowski et al. [86] demonstrated that intermyofibrillar mitochondrial content, assessed by using quantitative electron microscopy is significantly reduced (by ~25–40%) in persons with insulin resistance compared with healthy control subjects. Nevertheless, these measurements provide an index of mitochondrial capacity but do not necessarily reflect the ability of mitochondria to oxidize fatty acids *in vivo*. Furthermore, the argument, which seems entirely plausible, has been put forth that mitochondrial deficiency to the extent seen in insulin resistant obese individuals, even those with the most severe form of insulin resistance (type 2 diabetes mellitus), is unlikely to impair the ability of muscle to oxidize fatty acids, because the capacity of muscle to oxidize substrate is far in excess of what is needed to supply energy in the absence of very energy demanding physical activities [84]. In further support of this notion, Irving et al. [87]** have recently demonstrated that nine days of exercise training failed to improve insulin sensitivity in offspring of mothers with type 2 diabetes mellitus despite an increase in skeletal muscle mitochondrial function (i.e., *ex vivo* measured ATP production rate and citrate synthase activity). Furthermore, there is little evidence of impaired fatty acid oxidation in obese insulin resistant subjects when measured *in vivo* by using tracer methodology [71]. The most recent study to have evaluated this issue, and the only one that has actually measured muscle (rather than whole-body or limb) fatty acid oxidation in human subjects, was performed by Bucci et al. [78]**, who report increased rates of fatty acid oxidation in muscle in obese compared with lean subjects. In fact, it was concluded that increased fatty acid oxidation served as the “sink” for excess fatty acid delivery to the muscle because the rate of fatty acid incorporation into muscle triglyceride synthesis was not different in obese and lean subjects. The results from other recent studies have also suggested that hepatic fatty acid oxidation is upregulated in insulin-resistant individuals. Iozzo et al. [88]** reported greater hepatic fatty acid oxidation rates (measured by using PET imaging) in insulin resistant obese compared with lean individuals. And, Hodson et al. [89]** reported greater postprandial ketogenesis in obese than lean individuals. Thus, the “mitochondrial lipid overflow” hypothesis, according to which excess fatty acid supply to mitochondria leads to incomplete oxidation of fatty acids and accumulation of long chain acyl carnitine CoA, which is a precursor for ceramide synthesis, seems more attractive. In this regard, it has been demonstrated that prevention of insulin resistance in muscle through increased trafficking of

fatty acids towards oxidation requires complete β -oxidation to CO_2 whereas mitochondrial fatty acid availability that exceeds the capacity for complete oxidations leads to mitochondrial stress, the depletion of organic acid intermediates of the tricarboxylic acid cycle and accumulation of long-chain acyl carnitine CoA [90]**. Increased mitochondrial fatty acid oxidation to CO_2 through expression of a mutant form of carnitine palmitoyltransferase 1 (CPT1), which is active but resistant to malonyl CoA feedback inhibition, in C2C12 myotubes is also sufficient to protect the cells from palmitate-induced insulin resistance and decreased the content of ceramides and DAGs [91]. Similarly, it has been demonstrated that hepatic overexpression of carnitine palmitoyltransferase 1a (CPT-1A), or its permanently active mutant form CPT1AM, in high-fat diet treated and genetically obese mice, increases liver fatty acid oxidation and improves insulin sensitivity [92]. Furthermore, incomplete oxidation of palmitate was increased in livers of insulin resistant hyperphagic obese Otsuka Long-Evans Tokushima Fatty (OLETF) rats with NAFLD compared with control rats whereas total palmitate oxidation was not different in lean and obese rats [80].

CONCLUSION

There is now plenty of evidence that suggests alterations in fatty acid trafficking, both between tissues and within cells, are probably involved in the development of insulin resistance and the resulting metabolic complications in obese subjects. However, the exact mechanisms by which alternate routing of fatty acids causes metabolic disease are not yet known. Several theories have been developed as working models; each one focuses on a specific aspect of fatty acid metabolism. However, none of the theories are mutually exclusive and in reality, the pathophysiology of the metabolic alterations associated with obesity is probably multifactorial within a complex network of coordinated physiological responses which represent more than the sum of its parts. Only through the integration of multiple concepts will it be possible to further our understanding in this area and to help us prevent the metabolic alterations associated with obesity. The ways by which physical activity and inactivity prevent or increase susceptibility to metabolic disease provide good examples for the complexity of this network of physiological responses and therefore provide good and physiologically relevant working models.

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References

1. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988; 37:1595–607. [PubMed: 3056758]
2. Abumrad NA, Klein S. Update on the pathophysiology of obesity. *Curr Opin Clin Nutr Metab Care*. 2010; 13:357–8. [PubMed: 20574240]
3. Bray, GA.; Bouchard, C. *Handbook of Obesity: Clinical Applications*. Informa Healthcare; 2008.
4. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S. The metabolically obese, normal-weight individual revisited. *Diabetes*. 1998; 47:699–713. [PubMed: 9588440]
5. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Normal weight obesity: a risk factor for cardiometabolic dysregulation and cardiovascular mortality. *Eur Heart J*. 2010; 31:737–46. [PubMed: 19933515]
6. Shea JL, King MT, Yi Y, et al. Body fat percentage is associated with cardiometabolic dysregulation in BMI-defined normal weight subjects. *Nutr Metab Cardiovasc Dis*. (In Press).

7. Brochu M, Tchernof A, Dionne JJ, et al. What are the physical characteristics associated with a normal metabolic profile despite a high level of obesity in postmenopausal women? *J Clin Endocrinol Metab.* 2001; 86:1020–5. [PubMed: 11238480]
8. Wildman RP, Muntner P, Reynolds K, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999–2004). *Arch Intern Med.* 2008; 168:1617–24. [PubMed: 18695075]
9. Bluher M. The distinction of metabolically ‘healthy’ from ‘unhealthy’ obese individuals. *Curr Opin Lipidol.* 2011; 21:38–43. [PubMed: 19915462]
10. Shea JL, Randell EW, Sun G. The prevalence of metabolically healthy obese subjects defined by BMI and dual-energy X-ray absorptiometry. *Obesity.* 2011; 19(3):624–30. [PubMed: 20706202]
11. Fabbrini E, Mohammed BS, Magkos F, et al. Alterations in adipose tissue and hepatic lipid kinetics in obese men and women with nonalcoholic fatty liver disease. *Gastroenterology.* 2008; 134:424–31. [PubMed: 18242210]
12. Korenblat KM, Fabbrini E, Mohammed BS, Klein S. Liver, muscle, and adipose tissue insulin action is directly related to intrahepatic triglyceride content in obese subjects. *Gastroenterology.* 2008; 134:1369–75. [PubMed: 18355813]
13. Deivanayagam S, Mohammed BS, Vitola BE, et al. Nonalcoholic fatty liver disease is associated with hepatic and skeletal muscle insulin resistance in overweight adolescents. *Am J Clin Nutr.* 2008; 88:257–62. [PubMed: 18689359]
14. Fabbrini E, Magkos F, Mohammed BS, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. *Proc Natl Acad Sci U S A.* 2009; 106:15430–5. [PubMed: 19706383]
15. Rossi AP, Fantin F, Zamboni GA, et al. Predictors of Ectopic Fat Accumulation in Liver and Pancreas in Obese Men and Women. *Obesity.* (In Press).
16. Goodpaster BH, Theriault R, Watkins SC, Kelley DE. Intramuscular lipid content is increased in obesity and decreased by weight loss. *Metabolism.* 2000; 49:467–72. [PubMed: 10778870]
17. Pan DA, Lillioja S, Kriketos AD, et al. Skeletal muscle triglyceride levels are inversely related to insulin action. *Diabetes.* 1997; 46:983–988. [PubMed: 9166669]
18. Iozzo P. Myocardial, perivascular, and epicardial fat. *Diabetes Care.* 2011; 34 (Suppl 2):S371–9. [PubMed: 21525485]
19. Haemmerle G, Lass A, Zimmermann R, et al. Defective lipolysis and altered energy metabolism in mice lacking adipose triglyceride lipase. *Science.* 2006; 312:734–7. [PubMed: 16675698]
20. Heni M, Machann J, Staiger H, et al. Pancreatic fat is negatively associated with insulin secretion in individuals with impaired fasting glucose and/or impaired glucose tolerance: a nuclear magnetic resonance study. *Diabetes Metab Res Rev.* 2010; 26:200–5. [PubMed: 20225188]
21. Tushuizen ME, Bunck MC, Pouwels PJ, et al. Pancreatic fat content and beta-cell function in men with and without type 2 diabetes. *Diabetes Care.* 2007; 30:2916–21. [PubMed: 17666465]
22. Lee Y, Hirose H, Ohneda M, et al. Beta-cell lipotoxicity in the pathogenesis of non-insulin-dependent diabetes mellitus of obese rats: impairment in adipocyte-beta-cell relationships. *Proc Natl Acad Sci U S A.* 1994; 91:10878–82. [PubMed: 7971976]
23. Nolan CJ, Madiraju MS, Delghingaro-Augusto V, et al. Fatty acid signaling in the beta-cell and insulin secretion. *Diabetes.* 2006; 55 (Suppl 2):S16–23. [PubMed: 17130640]
24. Fabbrini E, deHaseth D, Deivanayagam S, et al. Alterations in fatty acid kinetics in obese adolescents with increased intrahepatic triglyceride content. *Obesity.* 2009; 17:25–9. [PubMed: 18948971]
25. Jensen MD, Haymond MW, Rizza RA, et al. Influence of body fat distribution on free fatty acid metabolism in obesity. *J Clin Invest.* 1989; 83:1168–1173. [PubMed: 2649512]
- 26*. van Hees, AM.; Jans, A.; Hul, GB., et al. Skeletal muscle fatty acid handling in insulin resistant men. *Obesity.* (In Press) In this study, the authors used sophisticated stable isotope labeled tracer techniques in conjunction with the AV-balance technique to evaluate postprandial trafficking of fatty acids in triglycerides derived from endogenous and exogenous (meal) sources. It was found that muscle extraction of triglyceride-derived fatty acids from endogenous sources (triglycerides secreted from the liver) was greater in subjects with insulin resistance than those without

27. Kirk EP, Klein S. Pathogenesis and pathophysiology of the cardiometabolic syndrome. *J Clin Hypertens*. 2009; 11:761–5.
28. Boden G. Obesity and free fatty acids. *Endocrinol Metab Clin North Am*. 2008; 37:635–46. viii–ix. [PubMed: 18775356]
29. Duez H, Lamarche B, Valero R, et al. Both intestinal and hepatic lipoprotein production are stimulated by an acute elevation of plasma free fatty acids in humans. *Circulation*. 2008; 117:2369–76. [PubMed: 18443237]
30. Lewis GF. Fatty acid regulation of very low density lipoprotein production. *Curr Opin Lipidol*. 1997; 8:146–156. [PubMed: 9211062]
31. Itani SI, Ruderman NB, Schmieder F, Boden G. Lipid-induced insulin resistance in human muscle is associated with changes in diacylglycerol, protein kinase C, and I κ B α . *Diabetes*. 2002; 51:2005–11. [PubMed: 12086926]
32. Petersen KF, Shulman GI. Cellular mechanism of insulin resistance in skeletal muscle. *J R Soc Med*. 2002; 95 (Suppl 42):8–13. [PubMed: 12216329]
33. Goodpaster BH, He J, Watkins S, Kelley DE. Skeletal muscle lipid content and insulin resistance: evidence for a paradox in endurance-trained athletes. *J Clin Endocrinol Metab*. 2001; 86:5755–61. [PubMed: 11739435]
34. van Loon LJ, Koopman R, Manders R, et al. Intramyocellular lipid content in type 2 diabetes patients compared with overweight sedentary men and highly trained endurance athletes. *Am J Physiol Endocrinol Metab*. 2004; 287:E558–65. [PubMed: 15165998]
35. Vague P. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. *Am J Clin Nutr*. 1956; 4:20–34. [PubMed: 13282851]
36. Bjorntorp P. The associations between obesity, adipose tissue distribution and disease. *Acta Med Scand Suppl*. 1988; 723:121–34. [PubMed: 3293356]
37. Larsson B, Seidell J, Svardsudd K, et al. Obesity, adipose tissue distribution and health in men--the study of men born in 1913. *Appetite*. 1989; 13:37–44. [PubMed: 2782865]
38. Jensen MD. Is visceral fat involved in the pathogenesis of the metabolic syndrome? *Human model Obesity*. 2006; 14 (Suppl 1):20S–24S.
39. Jensen MD. Role of body fat distribution and the metabolic complications of obesity. *J Clin Endocrinol Metab*. 2008; 93:S57–63. [PubMed: 18987271]
40. Unger RH. Lipid overload and overflow: metabolic trauma and the metabolic syndrome. *Trends Endocrinol Metab*. 2003; 14:398–403. [PubMed: 14580758]
41. Krssak M, Roden M. The role of lipid accumulation in liver and muscle for insulin resistance and type 2 diabetes mellitus in humans. *Rev Endocr Metab Disord*. 2004; 5:127–34. [PubMed: 15041788]
42. Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. *Science*. 2005; 307:384–7. [PubMed: 15662004]
43. Virtue S, Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome--an allostatic perspective. *Biochim Biophys Acta*. 2010; 1801:338–49. [PubMed: 20056169]
44. Farooqi IS, O'Rahilly S. Leptin: a pivotal regulator of human energy homeostasis. *Am J Clin Nutr*. 2009; 89:980S–984S. [PubMed: 19211814]
45. Sekhar RV, Jahoor F, Pownall HJ, et al. Cardiovascular implications of HIV-associated dyslipidemic lipodystrophy. *Curr Atheroscler Rep*. 2004; 6:173–9. [PubMed: 15068741]
46. Bays HE. Current and investigational antiobesity agents and obesity therapeutic treatment targets. *Obes Res*. 2004; 12:1197–211. [PubMed: 15340100]
47. Bays H, Abate N, Chandalia M. Adiposopathy: sick fat causes high blood sugar, high blood pressure and dyslipidemia. *Future Cardiol*. 2005; 1:39–59. [PubMed: 19804060]
48. Bays HE, Gonzalez-Campoy JM, Henry RR, et al. Is adiposopathy (sick fat) an endocrine disease? *Int J Clin Pract*. 2008; 62:1474–83. [PubMed: 18681905]
49. Wood IS, de Heredia FP, Wang B, Trayhurn P. Cellular hypoxia and adipose tissue dysfunction in obesity. *Proc Nutr Soc*. 2009; 68:370–7. [PubMed: 19698203]

50. Sharma NK, Das SK, Mondal AK, et al. Endoplasmic reticulum stress markers are associated with obesity in nondiabetic subjects. *J Clin Endocrinol Metab.* 2008; 93:4532–41. [PubMed: 18728164]
51. Ozcan U, Yilmaz E, Ozcan L, et al. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. *Science.* 2006; 313:1137–40. [PubMed: 16931765]
52. Ozcan U, Cao Q, Yilmaz E, et al. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. *Science.* 2004; 306:457–61. [PubMed: 15486293]
53. Mollica MP, Lionetti L, Putti R, et al. From chronic overfeeding to hepatic injury: role of endoplasmic reticulum stress and inflammation. *Nutr Metab Cardiovasc Dis.* 2011; 21:222–30. [PubMed: 21277757]
54. Cinti S, Mitchell G, Barbatelli G, et al. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. *J Lipid Res.* 2005; 46:2347–55. [PubMed: 16150820]
55. Weisberg SP, McCann D, Desai M, et al. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest.* 2003; 112:1796–808. [PubMed: 14679176]
- 56*. Kosteli A, Sogari E, Haemmerle G, et al. Weight loss and lipolysis promote a dynamic immune response in murine adipose tissue. *J Clin Invest.* 2010; 120:3466–79. The factors that regulate the accumulation of pro-inflammatory immune cells in adipose tissue are incompletely understood. The results from this study indicate that local lipid fluxes are central regulators of adipose tissue macrophage recruitment. [PubMed: 20877011]
- 57*. Alkhouri N, Gornicka A, Berk MP, et al. Adipocyte apoptosis, a link between obesity, insulin resistance, and hepatic steatosis. *J Biol Chem.* 2010; 285:3428–38. The data from this study complement the ones obtained in reference 56 (Kosteli et al.) and suggest that adipocyte apoptosis is another key event that contributes to macrophage infiltration into adipose tissue. [PubMed: 19940134]
58. Kloting N, Fasshauer M, Dietrich A, et al. Insulin-sensitive obesity. *Am J Physiol Endocrinol Metab.* 2010; 299:E506–15. [PubMed: 20570822]
59. McQuaid SE, Hodson L, Neville MJ, et al. Downregulation of adipose tissue fatty acid trafficking in obesity: a driver for ectopic fat deposition? *Diabetes.* 2011; 60:47–55. [PubMed: 20943748]
60. Potts JL, Coppack SW, Fisher RM, et al. Impaired postprandial clearance of triacylglycerol-rich lipoproteins in adipose tissue in obese subjects. *Am J Physiol.* 1995; 268:E588–94. [PubMed: 7733256]
61. Sadur CN, Yost TJ, Eckel RH. Insulin responsiveness of adipose tissue lipoprotein lipase is delayed but preserved in obesity. *J Clin Endocrinol Metab.* 1984; 59:1176–82. [PubMed: 6386839]
62. Liu L, Zhang Y, Chen N, et al. Upregulation of myocellular DGAT1 augments triglyceride synthesis in skeletal muscle and protects against fat-induced insulin resistance. *J Clin Invest.* 2007; 117:1679–89. [PubMed: 17510710]
63. Liu L, Shi X, Choi CS, et al. Paradoxical coupling of triglyceride synthesis and fatty acid oxidation in skeletal muscle overexpressing DGAT1. *Diabetes.* 2009; 58:2516–24. [PubMed: 19675136]
64. Timmers S, de Vogel-van den Bosch J, Hesselink MK, et al. Paradoxical increase in TAG and DAG content parallel the insulin sensitizing effect of unilateral DGAT1 overexpression in rat skeletal muscle. *PLoS One.* 2011; 6:e14503. [PubMed: 21264296]
- 65*. Badin PM, Louche K, Mairal A, et al. Altered skeletal muscle lipase expression and activity contribute to insulin resistance in humans. *Diabetes.* 2011; 60:1734–42. The projects described in this paper demonstrate that an imbalance in the key steps of adipose tissue triglyceride breakdown and incomplete hydrolysis of triglycerides can contribute to diacylglycerol accumulation and insulin resistance. [PubMed: 21498783]
66. Holland WL, Brozinick JT, Wang LP, et al. Inhibition of ceramide synthesis ameliorates glucocorticoid-, saturated-fat-, and obesity-induced insulin resistance. *Cell Metab.* 2007; 5:167–79. [PubMed: 17339025]
67. Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unravelling the mechanism. *Lancet.* 2010; 375:2267–77. [PubMed: 20609972]

68. Timmers S, Schrauwen P, de Vogel J. Muscular diacylglycerol metabolism and insulin resistance. *Physiol Behav.* 2008; 94:242–51. [PubMed: 18207474]
69. Zhang XJ, Chinkes DL, Wu Z, et al. The synthetic rate of muscle triglyceride but not phospholipid is increased in obese rabbits. *Metabolism.* 2009; 58:1649–56. [PubMed: 19608209]
70. Guo ZK, Jensen MD. Accelerated intramyocellular triglyceride synthesis in skeletal muscle of high-fat-induced obese rats. *Int J Obes Relat Metab Disord.* 2003; 27:1014–9. [PubMed: 12917705]
71. Guo Z. Intramyocellular lipids: maker vs. marker of insulin resistance. *Med Hypotheses.* 2008; 70:625–9. [PubMed: 17766054]
72. Schenk S, Horowitz JF. Acute exercise increases triglyceride synthesis in skeletal muscle and prevents fatty acid-induced insulin resistance. *J Clin Invest.* 2007; 117:1690–8. [PubMed: 17510709]
73. Bergman BC, Perreault L, Hunerdosse DM, et al. Increased intramuscular lipid synthesis and low saturation relate to insulin sensitivity in endurance-trained athletes. *J Appl Physiol.* 2010; 108:1134–41. [PubMed: 20299618]
74. An J, Muoio DM, Shiota M, et al. Hepatic expression of malonyl-CoA decarboxylase reverses muscle, liver and whole-animal insulin resistance. *Nat Med.* 2004; 10:268–74. [PubMed: 14770177]
75. Monetti M, Levin MC, Watt MJ, et al. Dissociation of hepatic steatosis and insulin resistance in mice overexpressing DGAT in the liver. *Cell Metab.* 2007; 6:69–78. [PubMed: 17618857]
76. Wendel AA, Li LO, Li Y, et al. Glycerol-3-phosphate acyltransferase 1 deficiency in ob/ob mice diminishes hepatic steatosis but does not protect against insulin resistance or obesity. *Diabetes.* 2010; 59:1321–9. [PubMed: 20200319]
77. Perreault L, Bergman BC, Hunerdosse DM, et al. Inflexibility in intramuscular triglyceride fractional synthesis distinguishes prediabetes from obesity in humans. *Obesity.* 2010; 18:1524–31. [PubMed: 20035285]
- 78*. Bucci M, Borra R, Nagren K, et al. Human obesity is characterized by defective fat storage and enhanced muscle fatty acid oxidation and trimetazidine gradually counteracts these abnormalities. *Am J Physiol Endocrinol Metab.* (In Press). The authors evaluate skeletal muscle and adipose tissue fatty acid metabolism in human subjects by using positron emission tomography in obese and non-obese subjects. They found that fatty acid oxidation rate was greater and fatty acid esterification rate was reduced in skeletal muscle of obese compared with non-obese subjects. It was suggested that the inability of obese subjects to store fatty acids may have harmful effects on muscle insulin sensitivity. In addition, the results from this study clearly demonstrate that the ability of muscle in obese subjects to oxidize fatty acids is not impaired, despite evidence from other studies (see references 83–86) for reduced muscle mitochondrial capacity.
79. Buchner DA, Yazbek SN, Solinas P, et al. Increased mitochondrial oxidative phosphorylation in the liver is associated with obesity and insulin resistance. *Obesity.* 2011; 19:917–24. [PubMed: 20885388]
80. Rector RS, Thyfault JP, Uptergrove GM, et al. Mitochondrial dysfunction precedes insulin resistance and hepatic steatosis and contributes to the natural history of non-alcoholic fatty liver disease in an obese rodent model. *J Hepatol.* 2010; 52:727–36. [PubMed: 20347174]
81. Patti ME, Corvera S. The role of mitochondria in the pathogenesis of type 2 diabetes. *Endocr Rev.* 2010; 31:364–95. [PubMed: 20156986]
82. Muoio DM. Intramuscular triacylglycerol and insulin resistance: guilty as charged or wrongly accused? *Biochim Biophys Acta.* 2010; 1801:281–8. [PubMed: 19958841]
83. Cheng Z, Tseng Y, White MF. Insulin signaling meets mitochondria in metabolism. *Trends Endocrinol Metab.* 2010; 21:589–98. [PubMed: 20638297]
84. Holloszy JO. Skeletal muscle “mitochondrial deficiency” does not mediate insulin resistance. *Am J Clin Nutr.* 2009; 89:463S–6S. [PubMed: 19056574]
85. Murrow BA, Hoehn KL. Mitochondrial regulation of insulin action. *Int J Biochem Cell Biol.* 2010; 42:1936–9. [PubMed: 20837159]

86. Chomentowski P, Coen PM, Radikova Z, et al. Skeletal muscle mitochondria in insulin resistance: differences in intermyofibrillar versus subsarcolemmal subpopulations and relationship to metabolic flexibility. *J Clin Endocrinol Metab.* 2011; 96:494–503. [PubMed: 21106709]
- 87**. Irving BA, Short KR, Nair KS, Stump CS. Nine days of intensive exercise training improves mitochondrial function but not insulin action in adult offspring of mothers with type 2 diabetes. *J Clin Endocrinol Metab.* (In Press). It is unclear whether reduced skeletal muscle oxidative capacity is responsible for the development of insulin resistance. Irving et al. demonstrated that a short-term intensive exercise training program was equally effective at increasing skeletal muscle oxidative capacity in nondiabetic people and in the offspring of mothers with diabetes. In contrast, the exercise improved insulin sensitivity only in nondiabetic people but not in the offspring of diabetic mothers, revealing a dissociation between improvements in skeletal muscle mitochondrial function and insulin sensitivity.
- 88**. Iozzo P, Bucci M, Roivainen A, et al. Fatty acid metabolism in the liver, measured by positron emission tomography, is increased in obese individuals. *Gastroenterology.* 2010; 139:846–56. 856, e1–6. It has been hypothesized that impaired fatty acid oxidation may be responsible for the development of insulin resistance in obese subjects (see references 83–86). The results from this study indicate that obese individuals have *increased* hepatic oxidation of fatty acids. Thus it is unlikely that the inability to oxidize fatty acids is involved in the pathophysiology of hepatic insulin resistance in obese subjects. [PubMed: 20685204]
- 89**. Hodson L, McQuaid SE, Humphreys SM, et al. Greater dietary fat oxidation in obese compared with lean men: an adaptive mechanism to prevent liver fat accumulation? *Am J Physiol Endocrinol Metab.* 2010; 299:E584–92. In this study, the authors evaluated endogenous and meal-derived fatty acid handling during an entire day. They found that oxidation of dietary fatty acids occurred to a *greater* extent in abdominally obese men. The results from this study clearly demonstrate that the ability of muscle in obese subjects to oxidize fatty acids is not impaired, despite evidence from other studies (see references 83–86) for reduced muscle mitochondrial capacity. [PubMed: 20628024]
- 90**. Koves TR, Ussher JR, Noland RC, et al. Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance. *Cell Metab.* 2008; 7:45–56. It has been suggested that insulin resistance develops secondary to diminished fat oxidation and resultant accumulation of cytosolic lipid molecules that impair insulin signaling. Contrary to this model, this study used targeted metabolomics to find that obesity-related insulin resistance in skeletal muscle is characterized by excessive β -oxidation, impaired switching to carbohydrate substrate during the fasted-to-fed transition, and coincident depletion of organic acid intermediates of the tricarboxylic acid cycle. Furthermore, it was demonstrated that prevention of insulin resistance in muscle through increased trafficking of fatty acids towards oxidation requires complete β -oxidation to CO_2 whereas mitochondrial fatty acid availability that exceeds the capacity for complete oxidations leads to mitochondrial stress, the depletion of organic acid intermediates of the tricarboxylic acid cycle and accumulation of long-chain acyl carnitine CoA. [PubMed: 18177724]
91. Henique C, Mansouri A, Fumey G, et al. Increased mitochondrial fatty acid oxidation is sufficient to protect skeletal muscle cells from palmitate-induced apoptosis. *J Biol Chem.* 2010; 285:36818–27. [PubMed: 20837491]
92. Orellana-Gavalda JM, Herrero L, Malandrino MI, et al. Molecular therapy for obesity and diabetes based on a long-term increase in hepatic fatty-acid oxidation. *Hepatology.* 2011; 53:821–32. [PubMed: 21319201]

KEY POINTS

- The development of the metabolic alterations in obese subjects is, at least in part, related to alterations in fatty acid trafficking both between and within tissues.
- Intracellular fatty acid trafficking in non-adipose tissues affects insulin action by altering substrate availability for the formation and accumulation of potentially harmful lipid intermediates, such as e.g., diacylglycerides (DAG) and ceramide.
- The availability of these fatty acid metabolites appears to depend on a fine-tuned balance between fatty acid delivery, complete fatty acid oxidation, triglyceride synthesis and triglyceride breakdown.