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Insulin Resistance

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Insulin resistance, i.e., the reduced sensitivity of tissues to insulin mediated biologic activity, has been an important clinical and research interest in adult medicine for decades. Even though it was quickly recognized by endocrinologists as being intimately related to the development of type 2 diabetes, interest in insulin resistance greatly expanded among a wide range of medical specialties after it was shown to be potentially etiologically associated, in general, with cardiovascular risk (CV) and, in particular, with obesity, hypertension and dyslipidemia.

The development of the obesity epidemic in pediatrics and evidence that the roots of adult CV risk extend back into childhood has led to a major interest in insulin resistance among pediatric clinicians and researchers, with approximately 600 childhood-related publications between January 2010 and June 2011. Yet there continue to be questions by pediatricians and others involved in the care of children about how to interpret many of these studies, how to apply insulin resistance to clinical care and research in children and adolescents, and how to evaluate methods currently used to measure insulin resistance. As a result, a conference sponsored by the major worldwide pediatric endocrine societies was organized to address issues related to insulin resistance in children, with a broad-based consensus report published in 2010 (1). The goal of this commentary is to expand on the consensus report by focusing on what we believe continue to be the most debated areas of interest, i.e., measurement of insulin resistance, the relation between obesity and insulin resistance, and the relation of insulin resistance to the metabolic syndrome, acknowledging the limitations for an exhaustive review of the literature because of space restrictions.

Measurement of Insulin Resistance

There is considerable clinical, clinical research and basic research interest in measuring levels of insulin resistance, with the goals of measurement differing for each. In order to incorporate insulin resistance into clinical and/or research studies, it is necessary to have a clear understanding of how the methodology and precision of the measurement techniques relate to the specific questions being asked.

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All the direct methods currently used to determine levels of insulin resistance provide a measure of “whole body” insulin resistance and do not single out specific tissues (e.g., muscle, adipose, liver) that are known to be sensitive to the action of insulin. The earliest of the direct measurement methods and the generally acknowledged “gold standard” is the euglycemic hyperinsulinemic clamp (2), in which a steady intravenous infusion of insulin is balanced by an infusion of glucose to maintain a steady glucose level; thus, lower glucose requirements, indicating lower cellular uptake of circulating glucose, are associated with higher levels of insulin resistance. Because over 75% of the infused glucose is taken up by skeletal muscle and only a small percentage by adipose or other tissues (3), and supported by the extremely weak genetic correlation between the clamp measure of insulin resistance and body fatness (4), the value for glucose uptake is adjusted by lean body mass to eliminate the adipose influence on the measurement (5).

Other direct measurement methods have been highly correlated with the clamp and are accepted as valid estimates of insulin resistance. The Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT) requires multiple blood samples for insulin and glucose but has the advantage of being a measure of other aspects of insulin activity (e.g., acute insulin response, disposition index) in addition to insulin resistance (6). The Steady State Plasma Glucose (SSPG) method might be thought of as inverse to the clamp, because it uses a steady state infusion of glucose, with the degree of insulin resistance directly related to the level of plasma glucose rather than glucose uptake (7). The SSPG is not used in children. The Oral Glucose Tolerance Test (OGTT) has been adapted to measure insulin resistance by using a calculation based on fasting glucose and insulin plus steady state glucose and insulin (8). Although it is less highly correlated with the clamp than the FSIVGTT or SSPG, it has the advantage of requiring far fewer blood samples. The FSIVGTT and OGTT also have been shown to be effective estimates of insulin resistance in children (9, 10).

As the interest in measuring insulin resistance grew, particularly in relation to obesity and CV risk, interest also grew for the development of a less burdensome method that could be performed without the need for time consuming invasive procedures and specialized research centers. Although it was known that fasting insulin, itself, was significantly correlated with the clamp and the other direct measures of insulin resistance, a number of surrogate methods for measurement were developed, based on equations using a combination of fasting insulin and fasting glucose, in an attempt to enhance measurement accuracy. It is now clear that no individual surrogate equation (e.g., HOMA, QUICKI, fasting insulin/fasting glucose ratio, $\ln$ fasting insulin + $\ln$ triglycerides, triglyceride/HDL-C ratio) is superior to any of the other surrogate equations (11). Moreover, these equations do not have any advantage over fasting insulin alone, with correlations (r) of >0.95 between fasting insulin and HOMA, the most widely used of the surrogate methods in both children and adults (12, 13), and a genetic correlation of 0.99 (4).

A recurring question related to the measurement of insulin resistance is whether fasting insulin (as representative of the surrogate measures) is a valid estimate in comparison with the direct methods. A number of studies have examined the relation between fasting insulin and either the clamp or FSIVGTT in children, with 1) in general, only modest correlations (12, 14–18), with one exception (19); 2) the largest clamp study in children ($N=300$) showing a r of 0.42 (12) and the largest in adults ($N=1140$) a r of 0.37 (5); and 3) similar results for HOMA and fasting insulin (18). This degree of correlation is not surprising, because studies also have shown only modest genetic correlations between fasting insulin and insulin resistance (4, 20). The correlations are dependent, in part, on fatness, with lower correlations in thin compared with overweight children (12) and adults (11, 21) and in pubertal compared with prepubertal children (14).

An important limiting issue in attempting to diagnose insulin resistance in an individual patient is the absence of standards to define abnormality. This is due to a number of factors, including the well-known lack of a uniform method of insulin measurement; the significant effect of the transitional stages of puberty on insulin resistance (22); significant differences based on ethnicity (23); the naturally occurring effect of biologic development on insulin resistance during the second decade of life (24); and the strong effect of physical activity and exercise, as documented in cohorts of children with normally distributed weight (25) and obesity (26,27). As a result of these issues, it is generally agreed that surrogate measures 1) should not be used to diagnose insulin resistance in individual patients; 2) should not be used in screening for insulin resistance; and 3) are not recommended in populations of thin individuals. However, it is also generally recognized that despite the significant limitations associated with the surrogate measures, these currently are the only feasible methods that reasonably can be used in large epidemiologic or population studies.

Obesity

Peripheral insulin resistance, coupled with obesity, is a major driving force of deteriorating glucose metabolism. The European Group for the Study of Insulin Resistance (EGIR), using euglycemic hyperinsulinemic clamps in 1,146 adult men and women, has shown a significant direct linear relation between insulin resistance and BMI (28). This relation is also present in children (29), and is similar among the Tanner stages (22). Fasting insulin also is correlated with BMI, showing, in particular, a highly significant trend in children (30). Although this trend is, in part, a compensatory response to increased insulin resistance, a component of the hyperinsulinemia associated with obesity is due to insulin hypersecretion that is independent from the obesity related insulin resistance (28). This may help explain the limited precision associated with the use of fasting insulin (or HOMA) as a surrogate measure of insulin resistance.

The statistically significant relation between BMI and both fasting insulin and insulin resistance has led to an assumption that all overweight and obese individuals are insulin resistant and have an insulin associated increase in levels of the CV risk factors. Despite lack of measurement standards for normal vs. abnormal levels of insulin resistance, it has become clear that many overweight/obese individuals are not insulin resistant. In the European study of adults, using an arbitrary definition for insulin resistance based on clamp studies in thin individuals ($\text{BMI} < 25 \text{ kg/m}^2$), only 26% of obese individuals were insulin resistant (28). In a second adult study, restricted to obese individuals, the highest levels of insulin resistance were associated with the highest levels of blood pressure, plasma glucose and lipids (31). This is also true in children. Studies in 300 15 year old adolescents, divided according to median BMI and median insulin resistance, showed significantly greater levels of the CV risk factors in the heavy insulin resistant compared with the heavy insulin sensitive group (32). Although it is clear that obesity in childhood leads to increased risk for adult CV disease and type 2 diabetes, these data suggest that the approach to the obese child would benefit from a better individual accurate assessment of insulin resistance.

To understand the relation of obesity to insulin resistance it will be necessary to clarify the mechanisms associated with patterns of lipid partitioning and adipose biochemistry. Much attention has been given to visceral fat as a key factor in obesity related insulin resistance (33). However, accumulation of fat in the visceral compartment may occur at the expense of a reduced accumulation of subcutaneous fat, and this altered balance between visceral and subcutaneous fat may play a role in the level of insulin resistance (34, 35). The ratio of subcutaneous to visceral fat is significantly lower in obese adolescents with impaired glucose tolerance compared with subjects with normal glucose tolerance (36,37). Alteration of the subcutaneous to visceral fat ratio is consistent with both human and animal models of

lipodystrophy, in which an absence of subcutaneous adipose tissue leads to increased accumulation of lipids in both myocytes and the visceral fat (38,39). Evidence that the degree of subcutaneous fat is linked to insulin resistance is derived from the use of thiazolidinediones, which decrease insulin resistance while increasing subcutaneous abdominal fat and decreasing the visceral and liver fat depots (40).

Visceral fat appears to contribute to fatty liver, based on the higher rates of lipolysis in visceral fat, leading to increased delivery of free fatty acids to the liver via the portal vein, though this theory has been questioned (41). Increases in both hepatic and visceral fat are associated with alterations in glucose and lipid metabolism (42). Studies have shown that, independent of visceral and intramyocellular fat content, obese adolescents with fatty liver have: 1) impaired insulin action in the liver (reduced basal hepatic insulin sensitivity and in response to low dose insulin infusion), in muscle (reduced insulin stimulated glucose disposal) and in adipose tissue (reduced basal adipose tissue sensitivity index); 2) early defects in beta cell function, as shown by the low disposition index, and 3) low adiponectin levels (43). Thus, the liver seems to have a central role in the complex phenotype and pathogenesis of insulin resistance. These findings are consistent with those from studies in adult obese subjects showing that intrahepatic fat, not visceral fat, is linked with the metabolic complications of obesity (44).

Adipose tissue, in general, is now recognized as an active biochemical endocrine system. Expansion of adipose tissue during the development of obesity results in tissue hypoxia, infiltration of inflammatory cells, and alteration in the cytokine profile (45–47). Evidence from animal models (48) and studies in human adults (49) and children (32) have shown an obesity-related oxidative stress and inflammation that likely contribute to increased lipolysis and release of free fatty acids (50) and adipokines (40), all of which influence insulin resistance. In addition, oxidative stress induced lipid peroxidation modifies amino acid side chains (51) in a process called protein carbonylation, resulting in the modification of cellular metabolic processes. Recent data from humans have shown that adipose carbonylation is significantly related to BMI and plasma free fatty acids, with a trend toward insulin resistance (52). Thus, it is clear that complex interactions among adipose biochemistry and lipid storage sites are operative in the well recognized, but mechanistically undefined, relation between obesity and insulin resistance.

Metabolic Syndrome

Insulin resistance has been linked to the metabolic syndrome (i.e., defined by increased waist circumference, dyslipidemia, hypertension and hyperglycemia) since the 1980s when Gerald Reaven suggested it might explain risk factor clustering in patients with cardiovascular disease (53). The linkage has always seemed reasonable, because 1) there is a strong relation between insulin resistance and both obesity and type 2 diabetes; 2) insulin resistance and compensatory hyperinsulinemia are associated not only with hypertension (54) but also with higher levels of blood pressure within the normal blood pressure range (55); and 3) insulin resistance is strongly associated with hypertriglyceridemia and elevated free fatty acids (56).

The relation of insulin resistance to the metabolic syndrome is complex, as recently reviewed (57), either as an independent factor or through an associated hyperinsulinemia. For instance, hypertension may be mediated, in part, via insulin effects on renal sodium reabsorption (58) or sympathetic nervous system activity (59), and hypertriglyceridemia results, in part, from effects of insulin on hepatic lipid metabolism (60). However, insulin also may have its own tissue effect(s) independent from insulin resistance, as shown by the higher prevalence of hyperinsulinemia compared with the prevalence of insulin resistance in

obese subjects in the European Group for the Study of Insulin Resistance (28), and the anti-inflammatory and vasodilator action of insulin on peripheral vasculature, in contrast to the pro-atherosclerotic effects of insulin resistance (61). Thus, the concept of insulin resistance as the unifying pathophysiologic etiology for the metabolic syndrome remains uncertain, and adds to questions raised about the wisdom of focusing on the metabolic syndrome as a disease entity rather than considering each of the components as individual independent risk factors (62).

Attempts have been made to describe a metabolic syndrome in childhood and to link it to insulin resistance. The same risk factors as those included in the adult syndrome have been incorporated into the childhood syndrome, but adjustments to define abnormal childhood levels have been made by using arbitrary cutpoint levels adapted from childhood normal standards (63, 64). However, the utility of the diagnosis in children is far from clear (65). In general, combinations of all five risk factors may be found in adults with the syndrome, but in children obesity, hypertriglyceridemia and HDL-C predominate, with elevated blood pressure or fasting glucose rarely found. Moreover, the syndrome tracks very poorly both during childhood (66, 67) and from adolescence (age 13) into young adulthood (age 22) (68), with obesity being the single factor that is consistently associated either cross sectionally (69) or longitudinally (68) with clustering of risk factors. BMI in childhood is equal to the metabolic syndrome in predicting adult cardiovascular risk (70).

Longitudinal studies have shown that significant changes in blood pressure, triglycerides, HDL-C and insulin resistance occur during the second decade and during puberty (22, 24). It seems reasonable to suggest that these changes could have an inhibiting effect on metabolic syndrome tracking during adolescence, because diagnosis of the metabolic syndrome is dependent on rigid dichotomization of risk factor levels. Despite the failure of the metabolic syndrome at mean age 13 to show a tracking effect, children with the syndrome at age 13 have significantly adverse levels of many of the risk factors at age 22 when compared with individuals at age 13 without the syndrome, and there is a significant correlation between the two ages for a cluster risk score made up of metabolic syndrome variables (48). This is consistent with the fact that the risk factors are continuous variables with graded levels of risk. Thus, despite the generally poor tracking effect of the metabolic syndrome, components of the syndrome should be carefully evaluated in obese children, the group most likely to have abnormal levels (32) and at greatest risk for future metabolic and cardiovascular disease (71). An exception to the results from the childhood tracking studies is the Princeton Lipid Research Clinics Follow-up Study (72) in which 68% of 31 children with the metabolic syndrome at ages 6–19 continued to have the metabolic syndrome 22–31 years later, suggesting that tracking may be more easily identified when observations are extended into later adulthood.

It seems clear from many studies that insulin resistance in childhood is associated with the metabolic syndrome and its component parts (8, 30, 32, 73). A cross sectional study at age 15 reported an interaction between BMI and insulin resistance such that the combination of high BMI and insulin resistance resulted in higher levels of the risk factors than would be expected from the simple addition of each of the two individual effects (30). Persistently elevated plasma insulin levels over an eight-year period beginning in childhood were associated with elevated cardiovascular risk factors (74). Levels of insulin resistance at age 13 predict levels of systolic blood pressure, triglycerides and a risk factor cluster score at age 19 (75), and insulin resistance is present in a high percentage of individuals with the syndrome at ages 13 and 22 (95% and 88%, respectively) (68). Moreover, insulin resistance tracks significantly during adolescence in association with these risk factors (75).

Thus, whether considered in terms of a formal “metabolic syndrome” or obesity with clustering of individual cardiovascular risk factors, there is considerable evidence that insulin resistance has a relevant, although as yet undefined, relation beginning in childhood to the development of cardiovascular disease. Care in choosing methods of measurement that are appropriate to the questions being asked should improve the clarity of results from clinical and research studies.

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References

1. Levy-Marchal C, Arslanian S, Cutfield W, Sinaiko A, Druet C, Marcovecchio ML, Chiarelli F. Insulin resistance in children: Consensus, Perspective and Future Directions. *J Clin Endocrinol Metab.* 2010; 95:5189–5198. [PubMed: 20829185]
2. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol.* 1979; 237:E214–E223. [PubMed: 382871]
3. DeFronzo RA, Bonadonne RC, Ferrannini E. Pathogenesis of NIDDM: a balanced overview. *Diab Care.* 2004; 27:314–319.
4. Rasmussen-Torvik LJ, Pankow JS, Jacobs DR Jr, Steffen LM, Moran AM, Steinberger J, Sinaiko AR. Heritability and genetic correlations of insulin sensitivity measured by the euglycaemic clamp. *Diabet Med.* 2007; 24:1286–1289. [PubMed: 17956454]
5. Ferrannini E, Mari A. How to measure insulin sensitivity. *J Hypertens.* 1998; 16:895–906. [PubMed: 9794728]
6. Bergman RN. Orchestration of glucose homeostasis: From a small acorn to the California oak. *Diabetes.* 2007; 56:1489–1501. [PubMed: 17526912]
7. Greenfield MS, Doberne L, Kraemer FB, Tobey TA, Reaven GM. Assessment of insulin resistance with the insulin suppression test and the euglycemic clamp. *Diabetes.* 1981; 30:387–392. [PubMed: 7014307]
8. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing. *Diab Care.* 1999; 22:1462–1470.
9. Cruz ML, Weigensberg MJ, Huang TTK, Ball G, Shaibi GQ, Goran MI. The metabolic syndrome in overweight Hispanic youth and the role of insulin sensitivity. *J Clin Endocrinol Metab.* 2004; 89:108–113. [PubMed: 14715836]
10. Yeckel CW, Weiss R, Dziura J, Taksall SE, Dufour S, Burgert TS, Tamborlane WV, Caprio S. Validation of insulin sensitivity indices from oral glucose tolerance test parameters in obese children and adolescents. *J Clin Endocrinol Metab.* 2004; 89:1096–1101. [PubMed: 15001593]
11. Ruige JB, Mertens IL, Bartholomeeusen E, Dirinck E, Ferrannini E, Van Gaal LF. Fasting-based estimates of insulin sensitivity in overweight and obesity: A critical appraisal. *Obesity.* 2006; 14:1250–1256. [PubMed: 16899806]
12. Schwartz B, Jacobs DR Jr, Moran A, Steinberger J, Hong CP, Sinaiko AR. Measurement of insulin sensitivity. *Diab Care.* 2008; 31:783–788.
13. Stern S, Williams K, Ferrannini E, DeFronzo RA, Bogardus C, Stern MP. Identification of individuals with insulin resistance using routine clinical measures. *Diabetes.* 2005; 54:333–339. [PubMed: 15677489]
14. Rossner SM, Neovius M, Montgomery SM, Marcus M, Norgren S. Alternative methods of insulin sensitivity assessment in obese children and adolescents. *Diab Care.* 2008; 31:802–804.
15. Cutfield WS, Hofman PL. Simple fasting methods to assess insulin sensitivity in childhood. *Horm Res.* 2005; 64(suppl 3):25–31. [PubMed: 16439841]

16. Brandou F, Brun JF, Mercier J. Limited accuracy of surrogates of insulin resistance during puberty in obese and lean children at risk for altered glucoregulation. *J Clin Endocrinol Metab.* 2005; 90:761–767. [PubMed: 15546909]
17. Giannini C, Santoro N, Caprio S, Kim G, Lartaud D, Shaw M, Pierpont B, Weiss R. The triglyceride-to-HDL Cholesterol ratio. *Diab Care.* 2011; 34:1869–1874.
18. Huang TTK, Johnson MS, Goran MI. Development of a prediction equation for insulin sensitivity from anthropometry and fasting insulin in prepubertal and early pubertal children. *Diab Care.* 2002; 25:1203–1210.
19. Gungor N, Saad R, Janosky J, Arslanian S. Validation of surrogate estimates of insulin sensitivity and insulin secretion in children and adolescents. *J Pediatr.* 2004; 144:47–55. [PubMed: 14722518]
20. Bergman RN, Zaccaro DK, Watanabe RM, Haffner SM, Saad MF, Norris JM, Wageknecht LE, Hokanson JE, Rotter JI, Rich SS. Minimal model-based insulin sensitivity has greater heritability and a different genetic basis than homeostasis model assessment or fasting insulin. *Diabetes.* 2003; 52:2168–2174. [PubMed: 12882937]
21. Kim SH, Abbasi F, Reaven GM. Impact of degree of obesity on surrogate estimates of insulin resistance. *Diab Care.* 2004; 27:1998–2002.
22. Moran A, Jacobs DR Jr, Steinberger J, Hong CP, Prineas R, Luepker R, Sinaiko AR. Insulin resistance during puberty: Results from clamp studies in 357 children. *Diabetes.* 1999; 48:2039–2044. [PubMed: 10512371]
23. Arslanian SA, Saad R, Lewy V, Danadian K, Janosky J. Hyperinsulinemia in African-American children: decreased insulin clearance and increased insulin secretion and its relationship to insulin sensitivity. *Diabetes.* 2002; 51:3014–3019. [PubMed: 12351441]
24. Moran A, Jacobs DR Jr, Steinberger J, Steffen LM, Pankow JS, Hong CP, Sinaiko AR. Changes in insulin resistance and cardiovascular risk during adolescence: Establishment of differential risk in males and females. *Circulation.* 2008; 117:2361–2368. [PubMed: 18427135]
25. Schmitz KH, Jacobs DR Jr, Hong C-P, Steinberger J, Moran A, Sinaiko AR. Association of physical activity with insulin sensitivity in children. *Int J Obesity.* 2002; 26:1310–1316.
26. Nassis GP, Papantakou K, Skenderi K, Triandafillopoulou M, kavouras SA, Yannakoulia M, chrousos GP, Sidossis LS. Aerobic exercise training improves insulin sensitivity without changes in body weight, adiponectin, and inflammatory markers in overweight and obese girls. *Metabolism.* 2005; 54:1472–1479. [PubMed: 16253636]
27. Bell LM, Watts K, Siafarikas A, Thompson A, Ratnam N, bulsara M, Finn J, O'Driscoll G, Green DJ, Jones TW, Davis EA. Exercise alone reduces insulin resistance in obese children independently of changes in body composition. *J Clin Endocrinol Metab.* 2007; 92:4230–4235. [PubMed: 17698905]
28. Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N, Mingone G. Insulin resistance and hypersecretion in obesity. *J Clin Invest.* 1997; 100:1166–1173. [PubMed: 9303923]
29. Sinaiko AR, Jacobs DR Jr, Steinberger J, Moran A, Luepker R, Rocchini AP, Prineas RJ. Insulin resistance syndrome in childhood: Associations of the euglycemic insulin clamp and fasting insulin with fatness and other risk factors. *J Pediatr.* 2001; 139:700–707. [PubMed: 11713450]
30. Weiss R, Dziura j, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, Allen K, Lopes M, Savoye M, Morrison J, Sherwin RS, Caprio S. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med.* 2004; 350:2362–2374. [PubMed: 15175438]
31. McLaughlin T, Abbasi F, Lamendola C, Reaven G. Heterogeneity in the prevalence of risk factors for cardiovascular disease and type 2 diabetes mellitus in obese individuals. *Arch Intern Med.* 2007; 167:642–648. [PubMed: 17420421]
32. Sinaiko AR, Steinberger J, Moran A, Prineas RJ, Vessby B, Basu S, Tracy R, Jacobs DR Jr. Relation of body mass index and insulin resistance to cardiovascular risk factors, inflammatory factors, and oxidative stress during adolescence. *Circulation.* 2005; 111:1985–1991. [PubMed: 15837953]
33. Jensen M. Is visceral fat involved in the pathogenesis of the metabolic syndrome? *Human Model Obesity.* 2006; 14:20S–24S. doi: 10.1038/oby.2006.278.

34. Danforth E Jr. Failure of adipocyte differentiation causes type II diabetes mellitus? *Nat Genet.* 2000; 26:13. [PubMed: 10973236]
35. Shulman GI. Cellular mechanisms of insulin resistance. *J Clin Invest.* 2000; 106:171–176. [PubMed: 10903330]
36. Weiss R, Dufour S, Taksali SE, Tamborlane WV, Petersen KF, Bonadonna RC, Boselli L, Barbetta G, Allen K, Rife F, Savoye M, Dziura J, Sherwin R, Shulman GI, Caprio S. Prediabetes in obese youth: a syndrome of impaired glucose tolerance, severe insulin resistance, and altered myocellular and abdominal fat partitioning. *Lancet.* 2003; 362:951–957. [PubMed: 14511928]
37. Taksali SE, Caprio S, Dziura J, Dufour S, Cali AM, Goodman TR, Papademetris X, Burgert TS, Pierpont BM, Savoye M, Shaw M, Seyal AA, Weiss R. High visceral and low abdominal subcutaneous fat stores in the obese adolescent. *Diabetes.* 2008; 57:367–371. [PubMed: 17977954]
38. Petersen KF, Oral EA, Dufour S, Befroy D, Ariyan C, Yu C, Cline GW, DePaoli AM, Taylor SI, Gorden P, Shulman GI. Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. *J Clin Invest.* 2002; 109:1345–50. [PubMed: 12021250]
39. Kim JK, Gavrilova O, Chen Y, Reitman ML, Shulman GI. Mechanism of insulin resistance in A-ZIP/F-1 fatless mice. *J Biol Chem.* 2000; 275:8456–60. [PubMed: 10722680]
40. Bays H, Mandarino L, DeFronzo R. Role of the adipocyte, free fatty acids and ectopic fat in the pathogenesis of Type 2 Diabetes Mellitus: peroxisomal proliferator-activated receptor agonists provide a rational therapeutic approach. *J Clin Endocrinol Metab.* 2004; 89:463–478. [PubMed: 14764748]
41. Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD. Splanchnic lipolysis in human obesity. *J Clin Invest.* 2004; 113:1582–8. [PubMed: 15173884]
42. Cali AM, De Oliveira AM, Kim H, Chen S, Reyes-Mugica M, Escalera S, Dziura J, Taksali SE, Kursawe R, Shaw M, Savoye M, Pierpont B, Constable RT, Caprio S. Glucose dysregulation and hepatic steatosis in obese adolescents: is there a link? *Hepatology.* 2009; 49:1896–903. [PubMed: 19434725]
43. D'Adamo E, Cali AM, Weiss R, Santoro N, Pierpont B, Savoye M, Caprio S. Central role of fatty liver in the pathogenesis of insulin resistance in obese adolescents. *Diab Care.* 2010; 33:1817–22.
44. Fabbri E, Magkos F, Mohammeda BS, Pietka T, Abumrada NA, Patterson BW, Okunade A, Kleina S. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. *PNAS.* 2009; 106:15430–15435. [PubMed: 19706383]
45. Ye J, Gao Z, Yin J, He Q. Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. *Am J Physiol Endocrinol Metab.* 2007; 293:E1118–E1128. [PubMed: 17666485]
46. Rausch ME, Weisberg S, Vardhana P, Tortoriello DV. Obesity in C57BL/6J mice is characterized by adipose tissue hypoxia and cytotoxic T-cell infiltration. *Int J Obes (Lond).* 2008; 32:451–463. [PubMed: 17895881]
47. Hosogai N, Fukuhara A, Oshima K, Miyata Y, Tanaka S, Segawa K, Furukawa S, Tochino Y, Komuro R, Matsuda M, Shimomura I. Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. *Diabetes.* 2007; 56:901–911. [PubMed: 17395738]
48. Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature.* 2006; 440:944–948. [PubMed: 16612386]
49. Steffes MW, Gross MD, Lee DH, Schreiner PJ, Jacobs DR Jr. Adiponectin, visceral fat, oxidative stress, and early macrovascular disease; the Coronary Artery Risk Development in Young Adults Study. *Obesity (Silver Spring).* 2006; 14:319–326. [PubMed: 16571859]
50. Abdul-Ghani MA, DeFronzo RA. Pathogenesis of insulin resistance in skeletal muscle. *J Biomed Biotechnol.* 2010; 2010:476279. [PubMed: 20445742]
51. Sayre LM, Lin D, Yuan Q, Zhy X, Tang X. Protein adducts generated from products of lipid oxidation; focus on HNE and one. *Drug Metab Rev.* 2006; 38:651–675. [PubMed: 17145694]
52. Frohnert BI, Sinaiko AR, Serrot FJ, Foncea RE, Moran A, Ikramuddin S, Choudry U, Bernlohr D. Increased adipose protein carbonylation in human obesity. *Obesity.* 2011; 19:1735–1741. [PubMed: 21593812]
53. Reaven GM. Role of insulin resistance in human disease. *Diabetes.* 1988; 37:1595–1607. [PubMed: 3056758]

54. Reaven GM. Insulin resistance/compensatory hyperinsulinemia, essential hypertension, and cardiovascular disease. *J Clin Endocrinol Metab.* 2003; 88:2399–2403. [PubMed: 12788834]
55. Ferrannini E, Natali A, Capaldo B, Lehtovirta M, Jacob S, Yki-Jarvinen H. Insulin resistance, hyperinsulinemia, and blood pressure. *Hypertension.* 1997; 30:1144–1149. [PubMed: 9369268]
56. Ginsberg HN. New perspectives on atherosclerosis: Role of abnormal triglyceride-rich lipoprotein metabolism. *Circulation.* 2002; 106:2137–2142. [PubMed: 12379586]
57. Ferrannini E. Is insulin resistance the cause of the metabolic syndrome? *Ann Med.* 2006; 38:42–51. [PubMed: 16448988]
58. DeFronzo RA. The effect of insulin on renal sodium metabolism: A review with clinical implications. *Diabetologia.* 1981; 21:165–171. [PubMed: 7028550]
59. Landsberg L. Hyperinsulinemia: possible role in obesity-induced hypertension. *Hypertension.* 1992; 19(suppl 1):161–166. [PubMed: 1737650]
60. DeFronzo RA. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diab Care.* 1991; 14:173–194.
61. Fonseca V. the effects of insulin on the endothelium. *Endocrinol and Metab Clin No Am.* 2007; 36(suppl 2):20–26.
62. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal. *Diab Care.* 2005; 28:2289–2304.
63. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. *Arch Pediatr Adolesc Med.* 2003; 157:821–827. [PubMed: 12912790]
64. Ford ES, Li C, Zhao G, Pearson WS, Mokdad AH. Prevalence of the metabolic syndrome among U.S. adolescents using the definition from the International Diabetes Federation. *Diab Care.* 2008; 31:587–589.
65. Steinberger J, Daniels SR, Eckel RH, Hayman L, Lustig RH, McCrindle B, Mietus-Snyder ML. Progress and Challenges in Metabolic Syndrome in Children and Adolescents: A Scientific Statement From the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism. *Circulation.* 2009; 119:628–647. [PubMed: 19139390]
66. Goodman E, Daniels SR, Meigs JB, Dolan LM. Instability in the diagnosis of metabolic syndrome in adolescents. *Circulation.* 2007; 115:2316–2322. [PubMed: 17420347]
67. Gustafson JK, Yanoff LB, Easter BD, Brady SM, Keil MF, Roberts MD, Sebring NG, Han JC, Yanovski SZ, Hubbard VS, Yanovski JA. The stability of metabolic syndrome in children and adolescents. *J Clin Endocrinol Metab.* 2009; 94:4828–4834. [PubMed: 19837941]
68. Kelly AS, Steinberger J, Jacobs DR Jr, Hong CP, Moran A, Sinaiko AR. Predicting cardiovascular risk in young adulthood from the metabolic syndrome, its component risk factors, and a cluster score in childhood. *Int J Pediatr Obes.* 2011; 6:e283–e289. [PubMed: 21070100]
69. Goodman E, Dolan LM, Morrison JA, Daniels SR. Factor analysis of clustered cardiovascular risks in adolescence; obesity is the predominant correlate of risk among youth. *Circulation.* 2005; 111:1970–1977. [PubMed: 15837951]
70. Magnussen CG, Koskinen J, Chen W, Thomson R, Schmidt MD, Srinivasan SR, Kivimaki M, Mattsson N, Kahonen M, Laitinen T, Taittonen L, Ronnema T, Viikari JS, Berenson GS, Juonala M, Raitakari OT. Pediatric metabolic syndrome predicts adulthood metabolic syndrome, subclinical atherosclerosis, and type 2 diabetes mellitus-but is no better than body mass index alone: The Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study. *Circulation.* 2010; 122:1604–1611. [PubMed: 20921439]
71. Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, Srinivasan SR, Daniels SR, Davis PH, Chen W, Sun C, Cheung M, Viikari JSA, Dwyer T, Raitakari OT. Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med.* 2011; 365:1876–1885. [PubMed: 22087679]

72. Morrison JA, Friedman LA, Gray-McGuire C. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton lipid research clinics follow-up study. *Pediatrics*. 2007; 120:340–345. [PubMed: 17671060]
73. Lee SJ, Gungor N, Bacha F, Arslanian S. Insulin resistance: link to the components of the metabolic syndrome and biomarkers of endothelial dysfunction in youth. *Diab Care*. 2007; 30:2091–2097.
74. Bao W, Srinivasan SR, Berenson GS. Persistent elevation of plasma insulin levels is associated with increased cardiovascular risk in children and young adults: The Bogalusa Heart Study. *Circulation*. 1996; 93:54–59. [PubMed: 8616941]
75. Sinaiko AR, Steinberger J, Moran A, Hong CP, Prineas RJ, Jacobs DR Jr. Influence of insulin resistance and body mass index at age 13 on systolic blood pressure, triglycerides, and high-density lipoprotein cholesterol at age 19. *Hypertension*. 2006; 48:730–736. [PubMed: 16923995]