

SPECIAL TOPICS: COMMENTARY

Physical Inactivity, Obesity, and Type 2 Diabetes: An Evolutionary Perspective

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ABSTRACT

Physical inactivity (and unhealthy nutrition) has distorted body composition and, in turn, reordered the proportions of myocyte and adipocyte insulin receptors. Insulin acting on adipocyte receptors produces less glucose uptake than does comparable interaction with myocyte receptors. Accordingly, in individuals with disproportionate muscle/fat composition, any given glucose load requires greater-than-normal pancreatic insulin secretion for adequate disposal. This hyperinsulinemia then becomes the leading cause of type 2 diabetes (T2DM) as insulin-sensitive tissues become desensitized. Because T2DM is rooted in potentially reversible lifestyle factors, rather than focusing on the intricacies of glucoregulation at the molecular level and on testing new drugs to control blood sugar, this article calls for a new prevention and treatment paradigm, in which exercise and weight control are essential and for which an inexpensive and acceptably accurate measure of body muscle and fat proportions is needed.

KEYWORDS

Body composition; exercise;
fat-muscle index (FMI);
insulin resistance

The past 20 years have seen enormous expenditure on diabetes-related research—\$3 billion in the United States during 2007 alone (Gold & Briefel, 2007). Still, during the same interval, worldwide type 2 diabetes (T2DM) prevalence doubled to 285 million, and global spending on patient care (\$376 billion in 2010) now comprises 12% of all health care costs (P. Zhang et al., 2010). That this preventable condition has assumed epidemic proportions has been termed “a public health humiliation” (*The Lancet*, 2010, p. 2193).

Research has focused on the intricacies of glucoregulation at the molecular level and on testing drugs to control blood sugar. However, this investigational emphasis is now being questioned. Will “increasingly complex and costly treatments . . . being applied to an increasing population . . . result in proportionately improved outcomes?” (Alexander, Sehgal, Maloney, & Stafford, 2008, p. 2088). Because T2DM is rooted in potentially reversible lifestyle factors, medicalization, which disempowers individuals, is unlikely to be the solution. Some believe it is “time to change our approach” (*The Lancet*, 2010, p. 2193).

Recent findings about physical inactivity and health suggest new opportunities for addressing the diabetes epidemic. Both obesity and diabetes are consequences of the mismatch between human biology and contemporary human environments. Evidence increasingly shows that today’s societal conditions promote chronic inactivity

such as prolonged sitting. This relative inaction, together with unhealthy nutrition, is metabolically toxic: It distorts body composition and impairs glucoregulation. As politicians, policymakers, business leaders—and ordinary people—come to understand the actual mechanism whereby inactivity leads to T2DM, preventive campaigns should achieve far greater popular engagement. Here, in the context of physical inactivity and health, we describe such a mechanism.

The public has been told ad nauseum that exercise and weight control are essential for preventing T2DM, but they have not been provided an understandable, convincing link between these factors and T2DM’s biological basis. An evolutionary perspective, together with the concept of insulin receptor competition, may fill that need.

Glucoregulation has been highly conserved throughout evolutionary experience

Genes underlying fundamental aspects of animal life—cell division, intermediary metabolism, embryonic development, tetrapod body structure, physiological control systems, and the like—have been highly conserved during evolution (Sun, Skogerbo, Wang, Liu, & Li, 2008; Woolfe et al., 2005). Glucoregulation falls into this category: Insulin and the insulin receptor are homologous in insects, nematodes, molluscs, and

humans suggesting that these biologically vital molecules were present in a common Archaemetazoan ancestor 500 million years ago (Claeys et al., 2002; Muggeo et al., 1979; Smit et al., 1993). The ancestors of cats, mice, and humans diverged at least 70 million years ago, yet rodents can be used as models for research on T2DM (Rees & Alcolado, 2005) and a diabetes epidemic similar to that in humans afflicts household pets (Klausner, 2011).

Glucoregulation is thus an ancient process, and for nearly all its evolution, it has operated in the context of body composition—proportions of skeletal muscle and adipose tissue—as found in free-living wild-type animals. However, agriculture and the advent of social stratification among humans led to the appearance of elites for whom food acquisition and physical exertion became dissociated. This promoted obesity among the wealthy. More recently, the societal impact of industrialization has made an increasing segment of humanity metabolically affluent. This extraordinary cultural-physiological departure, physical inactivity, has altered the proportions of fat and muscle for many humans (Ford & Mokdad, 2008; Hathaway & Foard, 1960), wealthy or otherwise, and for some of their household pets as well.

Human body composition

The fatness of contemporary wild animals “... is directly correlated with body size from less than 5% in mice to about 35% in blue whales” (Agricultural Board, 1968, p. 53). Many men and women, colloquially termed whales, now have body fat percentages equaling or exceeding that of their oceanic namesakes—even though a blue whale is 1,000 times larger than an average human.

Prevailing paleoanthropological opinion is that throughout evolution, our prehuman and human progenitors exhibited body composition similar to that observed in other naturally living primate species. For wild lemurs, thought to resemble our Eocene ancestors of 50 million years ago, percent body fat varies seasonally from 5.2% to 20.5% (Simmen et al., 2010). For free-living baboons, whose size and lifeways are thought to be analogous to those of Australopithecines, body fat ranges from 1.9% to 23.2% (Altmann, Schoeller, Altmann, Maruth, & Sapolsky, 1993).

Recently studied hunter-gatherers constituted the best available analogues for Stone Age humans and afforded insight into their body composition. Despite its limitations, the body mass index (BMI) can be used to compare hunter-gatherers and affluent Westerners. For 10 forager groups from five continents, BMI averaged 20.9 (Jenike, 2001). In the mid-19th century, college student BMIs were similar (21.1; Hiermeyer, 2010), but the BMIs of contemporary college students (25.8) are

notably higher (Pribis, Burtneck, McKenzie, & Thayer, 2010). Comparative triceps skinfold values (hunter-gatherers, 4.7 mm; recent North American 19-year-olds, 15.5 mm; Eaton, Konner, & Shostak, 1988; McDowell, Fryar, Ogden, & Flegal, 2008) suggest that most of the difference can be attributed to the extra adipose tissue carried by contemporary humans. Accordingly, it seems likely that in recent years, proportions of muscle and fat have deviated from the ancestral pattern—that conducive to normal carbohydrate metabolism.

The bony remains of preagricultural humans indicate that their muscularity was comparable to that of contemporary superior athletes (Mészáros, Soliman, Othman, & Mohácsi, 1998; Ruff, 2000). For today's highly trained male athletes, the ratio of skeletal muscle to adipose tissue approximates 5:1 (~50% body weight as muscle, ~10% as fat; Janssen et al., 2000; Kyle, Genton, Slosman, & Pichard, 2001). For current female athletes, the ratio can be as high as 3:1 (~45% muscle, ~15% fat; Janssen et al., 2000; Kyle et al., 2001), but because elite women athletes often experience ovulatory dysfunction (Warren, 1999)—which would have been selected against during evolution—the retrojected tissue proportions for Stone Age women are 35% to 40% muscle and 20% to 25% fat.

Today, in the United States and increasingly all over the world, people with excess fat (men > 25%; women > 35%; Kyle et al., 2001) and reduced muscle (< 40% and < 30%, respectively; Kyle et al., 2001) have become common. These individuals are at high risk for insulin resistance and T2DM. Their evolutionarily novel but increasingly widespread body compositional pattern alters the physiological conditions from those for which mammalian glucoregulatory mechanisms were originally selected. For such individuals, the proportion of adipocyte insulin receptors is increased relative to those of myocytes.

Adipocyte-myocyte ‘competition’ for insulin molecules

Myocyte and adipocyte insulin receptors are essentially identical. There are two insulin receptor isoforms that differ in their affinity for insulin, but the proportions present in skeletal muscle and adipose tissue are similar (Benecke, Flier, & Moller, 1992). Accordingly, fatty tissue and skeletal muscle engage in a whole-body competition for circulating insulin: Insulin molecules, which dock on adipocyte receptors, are unavailable to muscle insulin receptors, and vice versa (Eaton et al., 2002; Wells, 2010). For this reason, relative tissue proportions play a major role in determining how the insulin molecules released during any given pancreatic secretory pulse are distributed. As will be discussed, two other important determinants are the proportion of cardiac output

reaching various body regions (Williams & Leggett, 1989)—which influences the well-known apple-pear dichotomy—and an individual's cardiorespiratory fitness (Leite, Monk, Upham, & Bergenstal, 2009)—which affects tissue (chiefly muscle) metabolic activity.

While the insulin receptors of adipocytes and myocytes are structurally identical, their biochemical impact differs. In humans, an insulin molecule activating a muscle insulin receptor induces 2.1 times to 3.1 times more glucose clearance than does one reacting with an adipose tissue receptor (Virtanen et al., 2002). In rats, the differential is somewhat greater (2.1 to 8.6; Escriba et al., 1997; Ferré, Leturque, Burnol, Penicaud, & Girard, 1985; Kraegen, James, Jenkins, & Chisholm, 1985). In regard to glucose clearance, insulin molecules interacting with fatty tissue are being utilized inefficiently. That is, an insulin molecule docking on an adipocyte insulin receptor results in less glucose clearance than it would if it had docked on a myocyte insulin receptor. Other factors being equal, it means that lean, muscular, fit individuals exhibit greater whole-body insulin sensitivity than do those sarcopenic, overfat, and unfit individuals. The latter may be considered as suffering from “systemic” or whole-body insulin resistance (Figure 1).

Albert Einstein favored “thought experiments” that helped him to conceptualize physical phenomena and to explicate his conclusions. A similar exercise regarding the impact of body composition on glucose clearance might be:

Suppose a nondiabetic man whose body composition is 50% muscle and 10% fat consumes and absorbs sufficient glucose so that 110 molecules are presented for combined [fat + muscle] uptake. Further, suppose that insulin–myocyte interaction results in uptake of 2 glucose molecules while insulin–adipocyte interaction causes uptake of only 1.

Muscle: $50 \times 2 = 100$ glucose molecules cleared

Fat: $10 \times 1 = 10$ glucose molecules cleared

Total: $100 + 10 = 110$ glucose molecules cleared

Remainder: none

Contrast this outcome with that for a nondiabetic man whose body composition is 35% muscle and 25% fat.

Muscle: $35 \times 2 = 70$ glucose molecules cleared

Fat: $25 \times 1 = 25$ glucose molecules cleared

Total: $70 + 25 = 95$ glucose molecules cleared

Remainder: 15 glucose molecules

In the second man's case, the pancreas would be required to secrete additional insulin to achieve appropriate blood glucose homeostasis.

This thought experiment, though trivial compared with Einstein's, illustrates how insulin receptor imbalance, or too many adipose tissue receptors relative to myocyte receptors, necessitates extra insulin secretion—hyperinsulinemia—for any given carbohydrate load. Individuals in this condition have developed systemic insulin resistance.

Hyperinsulinemia and insulin resistance

Insulin, like other hormones, stimulates its target cells but also resets their responsiveness—thereby decreasing the effect of subsequent hormone exposure. This process, “homologous desensitization,” is widespread. In the case of insulin, persistently elevated levels desensitize target cells (myocytes, adipocytes, hepatocytes, etc.) through multiple intracellular mechanisms (Shanik et al., 2008).

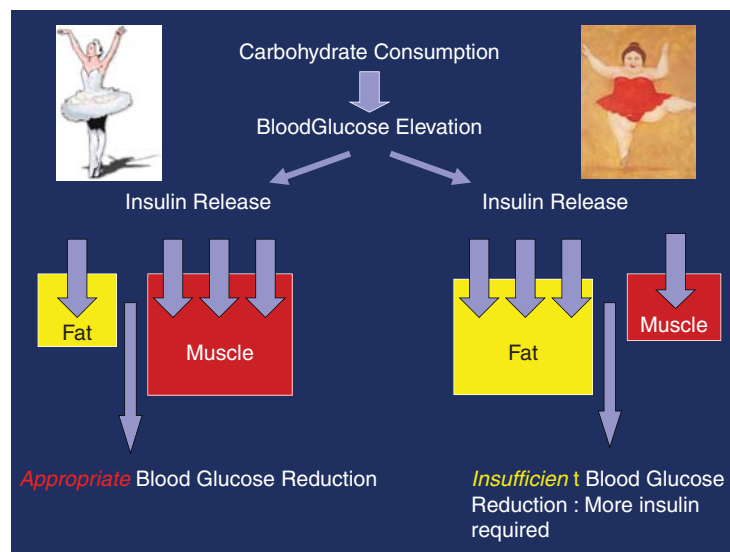


Figure 1. How body composition affects glucoregulation.

These epigenetic regulatory responses to elevated insulin levels typically lead to generalized “intrinsic” insulin resistance (Kahn & Flier, 2000).

Intrinsically resistant tissues (muscle, fat, liver) take up less glucose than normal despite similar tissue mass, insulin stimulation, and glucose concentration. This kind of insulin resistance is ordinarily thought of in connection with T2DM—an inappropriate response of target cells to insulin stimulation. For example, intrinsic skeletal muscle insulin resistance has been called, “... the primary defect in Type 2 Diabetes” (DeFronzo & Tripathy, 2009). However, insulin resistance could be more broadly defined as reduced responsiveness of the whole organism to the insulin concentration to which it is exposed (Shanik et al., 2008). This whole organismal, or “systemic,” reduced responsiveness is readily explained by adipocyte–myocyte imbalance.

As a “primary defect,” intrinsic cellular resistance begs the question as to how it comes about and how it relates to the secular increase in T2DM; extraordinarily rapid genetic evolution seems unlikely. On the other hand, recent changes in body composition as “the primary cause” can be readily understood (although they, in turn, indict sedentism and nutritional overload—both evolutionary novelties—as the true initiating factors). Because adipocyte–myocyte imbalance leads, ultimately, to intrinsic cellular insulin resistance, development of T2DM can be understood as a two-phase process. The phases are not sequentially discrete; rather, they overlap, but the initiating phenomenon is abnormal body composition and associated insulin receptor imbalance. Intrinsic insulin resistance, myocytic or otherwise, is the secondary, reactive phase.

Adipose tissue distribution

The apple-pear dichotomy is similarly in keeping with insulin receptor competition. The intra-abdominal

(visceral) compartment receives 25% of cardiac output at rest and 35% during digestion (Figure 2a). Skin and subcutaneous tissue receive only 5% (Williams & Leggett, 1989). Accordingly, adipocyte insulin receptors within the abdominal cavity (think apple) are favorably placed to compete for insulin molecules because they are exposed to 5 times to 7 times as many such molecules as are adipocyte insulin receptors in subcutaneous adipose tissue (think pear). Even individuals whose BMI is 40 or more may exhibit normal insulin sensitivity if they have relatively little visceral fat and marked muscularity—Sumo wrestlers being an extreme example (Matsuzawa, 1997; Yamauchi, Abe, Midorikawa, & Kond, 2004).

Exercise and insulin sensitivity

Strength training improves insulin sensitivity primarily by increasing muscle mass with less effect or no effect on body fat mass and with a modest effect on muscle metabolism (Miller, Sherman, & Ivy, 1984; Shaibi et al., 2006; van der Heijden et al., 2010). On the other hand, endurance exercise tends to increase insulin sensitivity chiefly by upregulating muscle metabolic activity (Kirwan, Kohrt, Wojta, Bourey, & Holloszy, 1993). Moderate aerobic training has little impact on body composition, but more intense endurance activity tends to reduce body fat mass and can increase leg muscle mass (Ferrara, Goldberg, Ortmeier, & Ryan, 2006; Mårin et al., 1992; Poehlman, Dvorak, DeNino, Brochu, & Ades, 2000; Shepard, Cocks, Tipton, Wagenmakers, & Shaw, 2010).

Further evidence linking body composition and insulin sensitivity

Insulin sensitivity and body composition have been variables assessed in disparate studies, which together cover a broad range of potential influences. The results of these studies have been consistent with the hypothesis that in prediabetic individuals, insulin sensitivity is

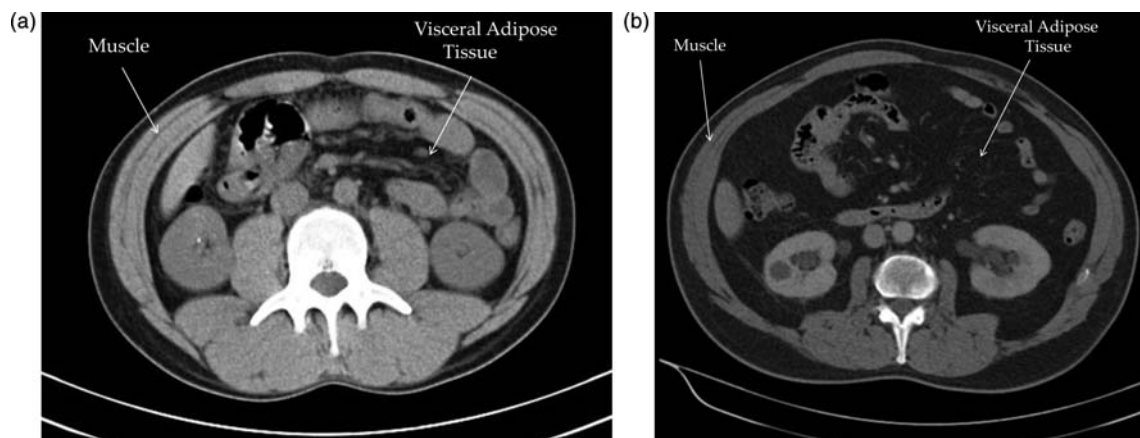


Figure 2. (a) Note paucity of visceral adipose tissue relative to muscle. (b) Note paucity of muscle relative to visceral adipose tissue.

directly related to % lean body mass but is inversely related to % body fat.

Resistive and, to a lesser extent, aerobic exercise (Ferrara et al., 2006; van der Heijden et al., 2010) both shift body composition toward the ancestral pattern (more muscle, less fat) while improving insulin sensitivity (especially aerobic exercise, which has more metabolic impact). Testosterone replacement therapy enhances muscularity and reduces adiposity; it also improves insulin sensitivity (Aversa et al., 2010; Mårin et al., 1992). Aging is typically associated with loss of lean body mass, while fat mass remains stable or increases. These shifts are usually accompanied by diminished insulin sensitivity (Amati et al., 2009; Basu et al., 2003; Coon, Rogus, Drinkwater, Muller, & Goldberg, 1992; Kohrt et al., 1993). Weight loss achieved by dieting generally improves both body composition (i.e., increases the muscle-to-fat ratio) and insulin sensitivity (Goodpaster, Kelley, Wing, Meier, & Thaete, 1999), especially in conjunction with high protein intake (Piatti et al., 1994). Ethnic groups that exhibit diminished insulin sensitivity have, on average, less lean body mass, more total fat mass, and more visceral fat compared with ethnicities that tend to be more insulin sensitive (Ehtisham, Crabtree, Clark, Shaw, & Barrett, 2005; Lear, Kohli, Bondy, Tchernof, & Sniderman, 2009; Wulan, Westerterp, & Plasqui, 2010). Growth hormone treatment produces an immediate decrease in insulin responsiveness—much before its effect on body composition. However, over subsequent months to years, as positive body composition changes toward more muscle and less fat, insulin sensitivity tends to revert toward baseline values. This reversion represents improvement relative to the low point observed early on and occurs even in older individuals who would ordinarily be experiencing diminished insulin sensitivity (Svensson & Bengtsson, 2003). Diabetes-prone but myostatin-deficient (*myst*−) mice become “double-muscle” and exhibit near normal insulin sensitivity compared with their (*myst*+) relatively insulin-resistant conspecifics (McPherron, Lawler, & Lee, 1997; C. Zhang et al., 2011).

In most of these studies, the relation between body composition and insulin sensitivity has not been the investigative focus. Nevertheless, in aggregate, they provide support for the hypothesis that more muscled, less adipose individuals exhibit greater insulin responsiveness.

Conclusion

Throughout the entire evolution of animal life on Earth, energy acquisition and energy expenditure have been inextricably linked and humanity’s recent uncoupling of these vital functions must surely be the ultimate cause of

T2DM. Physical inactivity (and unhealthy nutrition) have distorted human body composition and, in turn, have reordered the proportions of myocyte and adipocyte insulin receptors. Insulin acting on adipocyte receptors produces less glucose uptake than does comparable interaction with myocyte receptors. Accordingly, in individuals with disproportionate muscle/fat composition, any given glucose load must require greater-than-normal pancreatic insulin secretion for adequate disposal. This hyperinsulinemia then becomes T2DM’s proximate cause as insulin-sensitive tissues become desensitized and produce intrinsic insulin resistance.

Current research efforts focused on the detailed biochemistry and molecular biology of T2DM are intellectually challenging for the dedicated, earnest scientists attempting to advance basic biological understanding. They are also attractive for the pharmaceutical concerns that provide much-needed investigational support. A truly successful “magic bullet” for patients with T2DM would likely merit a Nobel Prize, be welcomed by a grateful and ever-growing patient population, and generate substantial financial rewards. Let us all hope for success along these lines.

In the meantime, however, we need to proceed as though a “magic bullet” may not be found. The individual components involved in glucoregulation are so interrelated and have been so highly conserved during evolution that effective pharmacological intervention without serious side effects may be impossible (e.g., biguanides, thiazolidinediones, etc.). Accordingly, the health establishment needs to elicit much more enthusiastic public engagement than it has so far. Health promotion involves marketing as well as science. Regarding this point, economic historian Joel Mokyr’s *The Gifts of Athena* (2002) argues that an understandable, persuasive paradigm is essential for public acceptance of, and compliance with, authoritative recommendations, no matter how sound the basic research on which they are based. Mokyr used the germ theory of disease as an example. The need for personal and household hygiene was a concept as novel in the 19th century as is the need for physical activity in the 21st century. The easily understood germ theory led to widespread changes in popular habits and behavior. Consequently, the incidence of infectious diseases began to downturn well before the introduction of antibiotics. Evolutionary insight and an appreciation of how myocyte/adipocyte insulin receptor imbalance leads to T2DM may be capable of producing comparable benefits today. An inexpensive, acceptably accurate measure of body muscle and fat proportions should become as important a part of routine health exams as are checks of body weight now.

At present, methods for assessing human muscle mass are conspicuously lacking (Lukaski, 2005). Developing a

practical method for measuring body muscle (and fat) proportions should become a technological goal. Recent investigations support an association between the Skeletal Muscle Mass / Visceral Fat Area ratio and metabolic syndrome (Kim et al., 2011), but further studies along these lines are necessary. When the relationship becomes more fully characterized, the much-criticized BMI may well be retired and an individual's fat-muscle index (FMI) may be substituted as a criterion for metabolic health.

Replacing BMI with the FMI may seem mere semantics, but unlike the BMI, the FMI is biologically, not just statistically, meaningful. Also, "fat" and "muscle" have powerful psychological connotations. Hence, an FMI could perhaps evoke a fitness/aesthetic challenge that the BMI has clearly failed to elicit. If so, it might engage the public sufficiently to stem the tide of metabolic illnesses.

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