Mammalian metabolism appears to have been designed via evolution to function appropriately within a "natural" range of body composition—proportions of fat and muscle similar to those extant during selection (Smith et al., 2004). The current epidemic of insulin resistance reflects, at least in part, an increasing number of individuals with body composition rare in prior mammalian experience (Hathaway and Foard, 1960; Ledger, 1968; Ford and Mokdad, 2008).

The genes and regulatory mechanisms, which integrate carbohydrate ingestion, blood glucose concentration, pancreatic insulin secretion, and glucose clearance, appear to have been selected well over 100 million years ago (Warren et al., 2008; Ebberink et al., 1989) for mammalian predecessors whose body composition anticipated that of contemporary free-living animals (Smith et al., 2004). Although admittedly imperfect indicators of body composition, comparative body mass indices [10 forager groups—the best available Stone Ager surrogates—from five continents (mean BMI = 20.9) (Jenike, 2001), mid-nineteenth century college students (21.1) (Hathaway and Foard, 1960), and contemporary college students (25.8) (Behrens and Dinger, 2003)] suggest that, until recently, proportions of muscle and fat for most humans remained similar to the ancestral pattern, conducive to normal carbohydrate metabolism. Sufficient body fat is adaptive (ovulation, fetal development, food shortage survival, etc.); however, the hyperadiposity (and relative sarcopenia), which have become common during the past 50 years, distort the anatomic arena within which glucose and insulin play their roles.

Based on the skeletal remains of Stone Agers and on the body habitus of recently-studied hunter–gatherers, paleoanthropologists conclude that the physiques of average preagricultural adults resembled those of contemporary superior athletes (Ruff, 2000a,b). For today’s highly trained males, the ratio of skeletal muscle to adipose tissue approximates 5:1 (~50% body weight as muscle, ~10% as fat) (Proctor and Joyner, 1997; Janssen et al., 2000). For current female athletes, the ratio can be as high as 3:1 (~45% muscle, ~15% fat) (Proctor and Joyner, 1997; Janssen et al., 2000), but because elite women athletes often experience ovulatory dysfunction—which would have been selected against—the retrojected tissue proportions...
for Stone Age women are 35%-40% muscle and 20%-25% fat. Today, in
the United States and increasingly all over the world, people with
excess fat (men >25% and women >35%) and reduced muscle (<35%
and <30%, respectively) are common (Janssen et al., 2004). These
are the individuals at high risk for insulin resistance and type 2 diabetes.

The insulin receptors of adipocytes and myocytes are essentially
equivalent. Although there are two insulin receptor isoforms which
differ in their affinity for insulin, similar amounts of both are present
in skeletal muscle and adipocytes (Benecke et al., 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.
For this reason relative tissue proportions largely determine how the
insulin molecules released during any given pancreatic secretory
pulse are distributed. The other major determinant is the proportion
of cardiac output reaching various body regions as discussed below
(Prinzen and Bassingthwaighte, 2000).

Depending on muscle fitness (which is roughly proportional to VO2
max) an insulin molecule activating a muscle insulin receptor induces
7–10 times more glucose clearance than does one reacting with an
adipose tissue receptor (Shulman et al., 1990; Perseghin et al., 1996).
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 had it docked on a myocyte insulin receptor.
Other factors being equal, this means that lean, muscular, fit
individuals exhibit greater insulin sensitivity than do those sarcopenic,
over fat, and unfit:

\[
\text{Insulin Efficacy } \sim \frac{\% \text{Muscle Mass} \times \text{VO}_2\text{max}}{\% \text{Fat Mass}}
\]

Insulin receptor imbalance—too many adipose tissue receptors
relative to myocyte receptors—necessitates extra insulin secretion
for any given carbohydrate load (Fig. 1). In turn, repetitive
hyperinsulinemia activates adaptive intracellular mechanisms (i.e.
gene regulation) which lead to intrinsic insulin resistance (Kahn and
Flier, 2000). Intrinsically resistant tissues (muscle, fat, liver) take up
less glucose than normal despite similar tissue mass, insulin
stimulation, and glucose concentration. Type 2 diabetes development
can therefore be viewed as a two-phase process. The phases are not
sequentially discrete, they overlap, but the initiating phenomenon is
abnormal body composition and associated insulin receptor imbal-
ance. Intrinsic insulin resistance is the secondary, reactive phase.

The anatomic location of adipocytes affects the likelihood that they
will capture circulating insulin molecules. Adipocytes in the liver
occupy a particularly strategic position because they are exposed to all
insulin molecules released from the pancreas into the portal
 circulation. Those insulin molecules docking on hepatic insulin
receptors are “lost” to the remainder of the body; hence more liver
fat means that fewer insulin molecules from any given pancreatic
secretory pulse are available to reach myocyte insulin receptors. This
circumstance may help explain why fat accumulation in the liver has
been found an important determinant of metabolically benign obesity.
Obese individuals who nevertheless have relatively little hepatic fat
tend to be insulin responsive—“fat but fit (Stefan et al., 2008)”.

The apple–pear dichotomy is similarly in keeping with insulin
receptor competition. The intraabdominal (visceral) compartment
receives 25% of cardiac output at rest and 35% during digestion. Skin
and subcutaneous tissue receive only 5% (Williams and 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 five to seven times as many
such molecules as are adipocyte insulin receptors in subcutaneous
adipose tissue (think pear).

Ascertaining the biomolecular details of insulin resistance is
complex, challenging, and fascinating. However, the recent secular
increase in type 2 diabetes prevalence has occurred too rapidly to be
the result of DNA sequence changes or fundamental alteration of gene
regulatory mechanisms. It must reflect altered gene expression
induced by the population’s unprecedented change in body compo-
sition which, in turn, has distorted insulin receptor balance.

There is disagreement about the relative importance of overeating
(gluttony) and physical inactivity (sloth) as causes of obesity and insulin
resistance (Prentice and Webb, 1995). Recently adopted food industry
practices—supersizing, use of high-fructose corn syrup, fast food pricing,
and so on—are clearly contributors. However, ancestral experience
suggests that inadequate physical activity is an equally, if not more,
important factor. Elite athletes, especially competitors in endurance events, consume far more food energy than do average Americans, yet they remain lean. Both the caloric intake and output of today’s superior athletes exceed levels retrodicted for Stone Agers, but if recently-studied hunter–gatherers be accepted as surrogates, our ancestors consumed substantially more food energy than we do [2800 kcal/d vs. 2007 kcal/d (women and men averaged)] (Eaton, 2006). However, their obligatory physical activity [1240 kcal/d vs. 555 kcal/d] determined that greater muscularity and more skeletal robusticity were the result— not hyperadiposity (Eaton and Eaton, 2003).

Health advice based on epidemiological data and mechanistic research has clearly failed to achieve the desired societal impact. This suggests that a new approach, perhaps one integrating physical activity (and nutrition) within an overarching paradigm, deserves consideration. Obesity, type 2 diabetes, many cancers, hypertension, osteoporosis, atherosclerosis, and numerous other disorders conform to the same general rule: deviation from our ancestors’ way of life increases susceptibility, while reincorporating the essentials of that lifestyle reduces risk (Eaton et al., 2002). Hundreds of genes and a myriad of regulatory factors interact with lifestyle to determine whether or not an individual develops complex degenerative disease. Nearly all these genes and also the mechanisms regulating their expression were selected for the circumstances of life in the Paleolithic. An aggressive health promotion campaign based on this rational, easily-understood formulation might energize the public and lead a greater proportion to act on recommendations which have hitherto had disappointingly little effect.

**Conflict of interest statement**
The authors declare that there are no conflicts of interest.

**References**


