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Review article

Imbalanced insulin action in chronic over nutrition: Clinical harm, molecular mechanisms, and a way forward

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ABSTRACT

The growing worldwide prevalence of overnutrition and underexertion threatens the gains that we have made against atherosclerotic cardiovascular disease and other maladies. Chronic overnutrition causes the atherometabolic syndrome, which is a cluster of seemingly unrelated health problems characterized by increased abdominal girth and body-mass index, high fasting and postprandial concentrations of cholesterol- and triglyceride-rich apoB-lipoproteins (C-TRLs), low plasma HDL levels, impaired regulation of plasma glucose concentrations, hypertension, and a significant risk of developing overt type 2 diabetes mellitus (T2DM). In addition, individuals with this syndrome exhibit fatty liver, hypercoagulability, sympathetic overactivity, a gradually rising set-point for body adiposity, a substantially increased risk of atherosclerotic cardiovascular morbidity and mortality, and – crucially – hyperinsulinemia.

Many lines of evidence indicate that each component of the atherometabolic syndrome arises, or is worsened by, pathway-selective insulin resistance and responsiveness (SEIRR). Individuals with SEIRR require compensatory hyperinsulinemia to control plasma glucose levels. The result is overdrive of those pathways that remain insulin-responsive, particularly ERK activation and hepatic de-novo lipogenesis (DNL), while carbohydrate regulation deteriorates. The effects are easily summarized: if hyperinsulinemia does something bad in a tissue or organ, that effect remains responsive in the atherometabolic syndrome and T2DM; and if hyperinsulinemia might do something good, that effect becomes resistant. It is a deadly imbalance in insulin action. From the standpoint of human health, it is the worst possible combination of effects.

In this review, we discuss the origins of the atherometabolic syndrome in our historically unprecedented environment that only recently has become full of poorly satiating calories and incessant enticements to sit. Data are examined that indicate the magnitude of daily caloric imbalance that causes obesity. We also cover key aspects of healthy, balanced insulin action in liver, endothelium, brain, and elsewhere. Recent insights into the molecular basis and pathophysiologic harm from SEIRR in these organs are discussed. Importantly, a newly discovered oxide transport chain functions as the master regulator of the balance amongst different limbs of the insulin signaling cascade. This oxide transport chain – abbreviated 'NSAPP' after its five major proteins – fails to function properly during chronic overnutrition, resulting in this harmful pattern of SEIRR.

We also review the origins of widespread, chronic overnutrition. Despite its apparent complexity, one factor stands out. A sophisticated junk food industry, aided by subsidies from willing governments, has devoted years of careful effort to promote overeating through the creation of a new class of food and drink that is low- or no-cost to the consumer, convenient, savory, calorically dense, yet weakly satiating. It is past time for the rest of us to overcome these foes of good health and solve this man-made epidemic.

1. The rise of overnutrition, visceral-abdominial obesity, the atherometabolic syndrome, type 2 diabetes mellitus, and their disastrous sequelae

Why not be obese? Extra weight used to indicate prosperity and

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hence attractiveness. But visceral-abdominal obesity associates with a list of seemingly unrelated health problems lumped together as the 'metabolic' or 'atherometabolic' syndrome that increase the age-adjusted risks of major adverse cardiovascular events, type 2 diabetes mellitus (T2DM), certain cancers, and death (Section 2 and Refs. [1–20]).

We have experienced over a century of steady gains in life expectancy in the USA and, more recently, in much of the rest of the world [21,22]. In just the past three decades, however, increasing rates of visceral-abdominal obesity, the atherometabolic syndrome, and T2DM have begun to erode these gains [18,23,24], most disturbingly in terms of quality-adjusted life years [17]. For example, an epidemiologic study to account for the dramatic decrease in age-adjusted deaths in the USA from coronary disease from 1980 to 2000 found that weight gain and diabetes undid 8% and 10%, respectively, of the overall decrease in coronary deaths during that period [25]. The data are worse for young adults [26]. Since the end of the survey period in 2000, obesity and diabetes have continued to increase worldwide [27–30].

Of particular concern, longitudinal surveys indicate that younger birth cohorts exhibit higher obesity-related mortality, even when matched for the same age, body-mass index, sex, and ethnicity as older birth cohorts at time of study [23]. This disturbing phenomenon presumably reflects the burden of earlier-onset metabolic dysregulation in younger birth cohorts. The problem may worsen as these younger cohorts age – and as even younger cohorts are born into our intensely calorie-rich, chair-enticing environment.

On a hopeful note, recent data indicate improving eating patterns [31] and a possible decline in the prevalence of obesity in the very young in the USA [32], where the obesity epidemic began. The prevalences of morbid (BMI > 40 kg/m^2) and extreme (BMI > 50 kg/m^2) obesity in adults continue to rise, but at apparently slower rates [33]. New cases of diabetes mellitus in the USA tripled from 1991 to 2008, but fortunately fell by 16.8% from 2008 to 2014 [34], attributed in large part to modest improvements in the American diet [35]. Further follow-up will be needed to determine if these trends continue to improve or reverse.

Historically, research on visceral-abdominal obesity, T2DM, and related syndromes has focused significant attention on glycemia. But in the modern era, these individuals die mainly from premature atherosclerotic cardiovascular disease [10,19,36].

1.1. Chronic positive caloric imbalance is the cause of obesity – but the underlying reasons for caloric imbalance remain poorly understood

You are what you eat, minus what you burn or malabsorb. The explosion in obesity rates in roughly one generation indicates that the fundamental problem is a recent change in our environment. This environmental change is superimposed upon pre-existing genetic tendencies that cannot have evolved to any significant extent during this brief timescale.

Traditionally, eating has been a highly social and cultural endeavor, and vigorous physical activity has been a requirement for typical daily life. Several factors associated with rising rates of obesity in developed and developing countries disrupt long-standing patterns of dining and movement.

Modern examples that alter eating include rising consumption of simple carbohydrate sweeteners, particularly in the form of sugary beverages; the invention of an evolutionarily unprecedented class of molecules – nonnutritive intense artificial sweeteners – that are widely sold as "diet" aids for weight loss but without convincing evidence that this commercial claim is true [37–42]; recent breeding of domesticated crops and animals to enhance yield and shelf life but without adequate attention to flavor – the common supermarket tomato remains the preeminent example of a healthy food drained of taste and texture [43]; replacement of regular, social meals with unscheduled snacking; agricultural and other governmental subsidies that lower the cost of carbohydrate calories – remarkably, the Food Stamp program in the USA has been estimated to spend nearly US4×10^9 each year to give free sodas and fruit juice to the poor, including children [44,45]; over a half-century of advice from cardiovascular and nutrition societies to avoid dietary fat [46–53], further shifting the public to carbohydrates that strongly associate with population-wide weight gain [54–60]; and the growth of a sophisticated industry that has created a new class of food and drink that is low- or no-cost to the consumer, convenient, savory, calorically dense, yet conspicuously weak in its ability to satiate [59,61–64]. The new foods are the technologic realization of a malicious magical candy from children's literature: "that anyone who had once tasted it would want more and more of it, and would even, if they were allowed, go on eating it till they killed themselves" [65].

Modern examples that diminish physical activity include labor-saving devices, such as washing machines and private cars; widespread use of television – with remote controls – and other electronic entertainment; and the growth of sedentary jobs [66,67] – all of which now associate with worse health outcomes [68–70]. Technologies that generate heat for buildings, vehicles, limited outdoor areas, and even some types of clothing cut down on normal, cold-induced expenditure of biologic energy stores.

Any one of these factors, individually and in moderation, can be highly desirable, particularly the remarkable availability of enough food to sustain a worldwide population of over seven billion people. Yet in combination and in excess, these factors contribute to the disruption of normal physiologic mechanisms that defend body weight and adiposity, leading to chronic positive caloric imbalance and hence the worldwide growth of obesity [71]. Because of difficulties in performing long-term causal studies in humans, the contributions of many of these individual factors to human obesity have been inferred largely or entirely from mere associations, albeit strong ones (e.g., see Section 1.5 on gut microbiota and Section 2.4 on individual macronutrients).

Nevertheless, several points bear emphasis – namely, that sustained reductions in energy intake, though difficult to achieve, reliably produce weight loss and improve metabolic status; bariatric surgery is currently the most effective clinical intervention to reduce energy intake, weight, the rate of T2DM, and premature mortality in appropriately selected obese patients [72–75]; regular exercise improves health even without weight loss; sufficient amounts of purposeful exercise aid long-term weight management; and obese and lean people in sedentary jobs exhibit huge differences in the daily amount of physical activity outside of purposeful exercise – such activity is also known as non-exercise activity thermogenesis or 'NEAT' (these points are reviewed in Refs. [66,76]).

Fig. 1 presents a schematic summary of modern disruptions in caloric intake and expenditure that then cause metabolic deterioriation.

1.2. How much caloric imbalance does it take? Thermodynamically correct mathematical models of human weight change – as well simple arithmetic – indicate that surprisingly small, but sustained, daily caloric imbalance causes obesity

Several groups have examined the relationship between altered energy *intake* and altered energy *balance* in the development of worldwide weight gain and obesity. Long-standing linear models assert that a specified increase in daily caloric intake produces a