A Heavyweight Championship
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For the third world...

Overweight and obesity are among the foremost public health issues that are being tackled on a continuous basis in North America. From government to grass root level, much is being done to increase awareness, promote healthier lifestyle choices and design research to probe into the complexity of this disorder. In developing countries, a huge misconception exists that overweight and obesity are afflictions of affluent populations, who have too many resources, making the common man sluggish. In reality, consumption patterns, tobacco use, and ubiquitous marketing worldwide have resulted in global changes in lifestyle and global health problems. Among these is obesity, cardiovascular disease and diabetes, a related set of dangerous diseases. For the third world, another unfortunate fact is that childhood prevalence of these diseases, including use of tobacco, is rapidly increasing from already striking numbers. The social, economic and health burden is enormous, calling for an urgent response to this epidemic at all levels.

Two major global strategies, the Framework Convention on Tobacco Control (FCTC; adopted in 2003) and the Global Strategy on Diet, Physical Activity and Health (adopted in 2004) are worthy of mention, as they have resulted in documented efforts to improve lifestyles in many countries.

The message to start is simple: Increasing lifestyle physical activity (walking 15-20 minutes a day burns about 100 kcal), reducing portion sizes and saying NO to tobacco, drugs and other addictions. There is a burning need to introduce these messages at all levels of society, from the physician's office, to public health posters, government policies and media. It is up to each society to decide what it is willing to do to help promote healthy living in easy ways.

Are you my brother?

Normal adipose tissue is said to function as an endocrine organ, producing several factors (such as leptin) that affect and regulate metabolism.

Excessive amounts of abdominal visceral fat, sometimes referred to as "bad fat," significantly increase an individual's risk of developing overweight and obesity-related co-morbidities. Fukhara et al. sought to identify new adipocytokines that may preferentially be released by visceral abdominal fat. In an impressively thorough and robust style, they studied samples of subcutaneous and visceral fat, and finally characterized "visfatin," a cytokine that is highly expressed in visceral fat and whose blood levels correlate with obesity. Surprisingly, functional analyses in mice revealed that visfatin has beneficial, insulin-like activity, causing a lowering of blood glucose levels. Even more surprisingly, visfatin was shown to bind to the insulin receptor and activate the insulin signal transduction pathway (although in a manner different from insulin). Vistafin was shown to enhance glucose uptake, suppress glucose release in hepatocytes and induce the expression of genes encoding...
adipose markers. Mice heterozygous for a targeted mutation in the visfatin gene had modestly higher levels of plasma glucose relative to wild-type littermates. An important difference between insulin and vistatin is that plasma vistatin levels do not change significantly in fasting or feeding mice, while insulin levels increase in the fed state and decrease in the fasting state.

This commendable study paves way for new avenues in obesity and metabolic research, even though the precise physiological role of vistatin is yet to be established.


DNA talks!

Telomere length is an important indicator of an individual's age, and factors affecting aging. Promotion of oxidative stress enhances erosion of telomeres with each cell cycle, resulting in a pro-aging effect.

Obesity and cigarette smoking were studied by Valdes et al with regard to their individual and additive effects on telomere length in women. This simple and intriguing study found that telomeres of obese women were 240 bp shorter than that of lean women (translating to 8.8 years of aging) and telomeres of smokers were 200 bp shorter than that of non-smokers (translating to 4.6 years of aging). Each pack-year smoked was equivalent to an additional loss of 5 bp. This study has considerable value for developing countries, where both cigarette smoking and weight problems are increasing simultaneously and rapidly, especially among children.


Let me breathe!

A recent commentary in Nature Immunology by Scott Weiss1 highlights the complex interrelation between obesity and asthma and biological and environmental factors contributing to this paradigm.

The relation between obesity and asthma was overlooked until Camargo and colleagues published their work in 1999. Since then, a large number of epidemiological studies have confirmed this relation, and shown consistently that obesity is associated with both incidence and prevalence of asthma in adults and children, with the effects being greater in females than in males. Moreover, obesity precedes and predicts the development of asthma, not vice versa. The greater the obesity, the more severe the asthma and loss of weight improves asthmatic symptoms.

Physiologically, obesity leads to decreased lung tidal volume and functional residual capacity. These volume changes result in reduced smooth muscle stretch, and contraction ability. The respiratory condition is thus worsened and the individual loses ability to respond adequately to physiological stress (such as exercise). The two diseases share an immunological connection as well, in that both are pro-inflammatory states. The TNF pathway is thought to be upregulated by the presence of both conditions.

Interestingly, genes for obesity and asthma (beta 2 adrenergic receptor gene ADRB2 and the glucocorticoid receptor gene NR3C1) are located on the same chromosome (5 q) and may have pleiotropic or interdependent effects on these complex disorders.

Another interesting avenue for research is the hypothesized effect of the in utero environment on asthma and obesity, where it is thought that these diseases may be a consequence of 'programming' resulting in long-term changes in physiology or metabolism.


Obesity and the Human Clock

A classical study in Science1 deserves mention in a discussion on obesity. The authors studied circadian clock mutant mice and found that these mice have greatly attenuated feeding rhythm, are hyperphagic and obese, and develop the metabolic syndrome (hyperleptinemia, hyperlipidemia, hepatic steatosis, hyperglycemia and hypoinsulinemia).

The study clearly shows that circadian and metabolic processes are linked at multiple levels. Even though locomotor function in clock mutant mice was just somewhat dampened, feeding pattern was severely altered. Additionally, clock mutant mice developed a spectrum of biochemical and tissue abnormalities, which are a hallmark of the metabolic syndrome. Expression of neuropeptides involved in appetite regulation and energy balance were markedly reduced.

This study demonstrates a highly significant principle that feeding rhythmicity and timing (regulated by the circadian clock) are critical in metabolic homeostasis and weight management. In actuality, the clock regulates more than just timing of food intake and metabolic processes, and this presents an exciting area for further research.


Body chemicals haywire

The metabolic syndrome (dyslipidemia, insulin resistance and hypertension) is a well-characterized consequence of overweight and obesity in both animals and humans. For the first time, large prospective studies have
been successfully carried out to study the predictors of metabolic syndrome and its effects of obesity, diuretic use and risk of gout.

Goodpaster and colleagues performed a random, population-based study of over 3000 older men and women (aged 70-79 years) with the objective to determine whether pattern of regional fat deposition is associated with the metabolic syndrome. Their results clearly demonstrate that distribution of body fat is independently associated with the metabolic syndrome. Even in individuals with normal body weight and relatively low total body fat, the metabolic syndrome may still exist due to the amount of adipose tissue located intra-abdominally or interspersed within the musculature. Moreover, visceral and inter-muscular adipose tissue deposits strongly predict insulin resistance and type 2 diabetes. Lower muscle mass (sarcopenia) was not associated with the metabolic syndrome. The authors caution that practitioners should not discount the risk of metabolic syndrome in older patients entirely on the basis of body weight or BMI.

Choi and colleagues collected self-reported data for over 40,000 male participants (health care professionals) over a 12-year period and analyzed the data for correlations between BMI, weight change, hypertension, and diuretic use and incident gout in men with no history of gout. The accuracy of self-reported data has been established earlier in studies on stroke. Strikingly, the results showed that a positive linear relationship exists between BMI and risk of gout, with the magnitude of association becoming larger with increasing BMI. This association was independent of other risk factors for gout, such as age, diet and history of renal failure. Weight loss of greater than 10 lb was found to reduce risk of gout. The authors suggest that higher BMI increases the risk of gout by increasing the serum uric acid level. Hyperuricemia has been associated with obesity via both increased production and decreased renal excretion of urate. Hyperuricemia has also been associated with the insulin resistance syndrome. Hypertension was also strongly associated with the incidence of gout independent of diuretic use and chronic renal failure.


**Weighty heartburn**

In an extensive meta-analysis Hampel et al demonstrated that obesity is a significant risk factor for gastroesophageal reflux disease (GERD), erosive esophagitis and esophageal adenocarcinoma. They reviewed 9 large epidemiological studies published to date and conclude that the risk of these disorders progressively increase, with increasing weight. Thus in overweight patients with symptoms of GERD counseling about weight management should constitute an important therapeutic component.