SAMJ

ENDOCRINOLOGY, METABOLISM AND DIABETES

CONGRESS REPORT

Obesity research — where do we stand?

Special report for SASO

The field of obesity is a rapidly developing area with significant and exciting progress being made with regard to the scientific (basic science) and clinical aspects of this disorder. The emergence of obesity as a disorder reaching epidemic proportions in many countries warrants ongoing efforts in this direction, and the proceedings of the 7th ECO Congress in Barcelona this year were witness to these efforts.

Although increased energy intake and decreased physical activity may be the main causes of obesity, genetic epidemiological studies demonstrate that human obesity may be due in part to genetic inheritance.

The discovery in December 1994 of the ob-gene and its encoded protein termed leptin, uniquely synthesised in fat cells and secreted in the blood, has been of particular interest.

Leptin is a satiety factor and several genetic defects were identified in mice and rats which led to their becoming obese. The so-called ob-mouse had multiple defects in the ob-protein (leptin) due to mutations in the corresponding gene, which could explain the obesity. Treatment of these animals with intact protein normalised body weight, appetite and thermogenesis.

Paul Trayhurn (Scotland) also discussed the subject of the obesity gene and the leptin system. As the ob-gene is expressed in white adipose tissue (WAT) in humans, it appears that the secreted protein (leptin) signals the size of these WAT depots. Although leptin may act centrally as a satiety factor, there is also evidence that it may affect energy expenditure. The ob-gene is expressed in both the subcutaneous and visceral adipose tissue with substantial variation in the level of expression. The expression of the ob-gene is also subject to nutritional regulation; for example, it falls on fasting and vice versa. Acute exposure to cold suppresses expression of the gene.

Obese humans appeared to be overproducing leptin and may therefore be resistant to its signal, perhaps because of impaired suppression of neuropeptide Y produced within the central nervous system. (Neuropeptide promotes hyperphagia and obesity in normal rats.) In addition, TNF-α, a cytokine produced by human adipocytes, may be partly responsible for insulin resistance in obesity.

A further exciting development has been the recent descriptions of a beta-3 receptor in brown adipose tissue that mediates lipolysis and thermogenesis. Although the importance of thermogenesis in the regulation of energy balance in humans remains debatable, **Michael Stock** (London) indicated that there is now general agreement that most animal models of obesity involve a failure to activate thermogenesis. This has led to the development of several compounds with beta-3 receptor agonist activity; these are currently being studied as therapeutic modalities in the treatment of human obesity. The potential benefit of such compounds would be to induce thermogenesis and thereby offset the reduction in metabolic rate associated with dieting, producing a larger overall negative energy balance.

Claude Bouchard (Canada) gave a state-of-the-art address at the Barcelona Congress on the genetics of obesity and highlighted the promising advances as well as the failures. Although obesity is multifactorial, the genetic contribution may account for up to 40% of the individual differences in body fat. Although the single-gene hypothesis does not account for obesity, a major recessive gene could account for up to 25% of the variance. This would put the homozygotes at between 5 - 9% of the population. He emphasised that these numbers are unsubstantiated, as the gene (or genes) have not yet been identified. Looking at the risk of becoming obese in first-degree relatives of an overweight subject, he pointed out that we have not yet been able to establish a level of risk.

Per Bjorntorp (Sweden) summarised the endocrine abnormalities associated with obesity. The studies show that in central obesity there is increased cortisol secretion (as there is in Cushing's syndrome); this is probably caused by factors at a higher level than corticotropin-releasing factor, which will stimulate the hypothalamic pituitary adrenal axis. Secondly, the high waist/hip ratio (WHR) is associated with low levels of sex steroids and growth hormone. The effect of all of these hormonal changes is an accumulation of adipose tissue in the visceral area.

Obesity is also the most prevalent metabolic disease in developed countries and there is overwhelming evidence that obesity constitutes an independent risk factor for cardiovascular disease. Central obesity, and visceral obesity in particular, are strongly associated with metabolic abnormalities such as hyperlipidaemia, insulin resistance, hypertension and increased susceptibility to type II diabetes, commonly known as the metabolic syndrome.

It has been suggested that elevated non-esterified fatty acid (NEFA) concentrations in obesity arise from the increased visceral adipose tissue mass. In fact, impaired suppression of plasma NEFA by insulin is a characteristic of upper-body obesity. This elevated availability of fatty acids could reduce insulin-driven glucose utilisation and lead to glucose intolerance and insulin resistance. Elevated plasma NEFA will also result in hypertriglyceridaemia due to increased very-low-density lipoprotein production and decreased removal of triacylglycerol (TAG)-rich chylomicrons by both an increased supply of NEFA to the liver as well as loss of lipoprotein lipase (LPL) activity in adipose tissue (insulin resistance).

Williamson (USA) reviewed the epidemiological evidence for intentional weight loss and longevity. He noted that in the USA approximately 40% of women and 25% of men are trying to lose weight at any point in time. This 'weight cycling' may in itself be deleterious, given that some recent population-based observational epidemiological studies suggest that the weight fluctuation itself may be associated with increased mortality. His own recently published epidemiological study in overweight white American women found that if they were intentionally losing weight, then mortality was reduced; however, this finding only applied if they already had obesity-related co-morbidities. Therefore, although recent evidence suggests that modest (approximately 10%) intentional weight loss decreases mortality in obese people with associated problems, this may not apply in those with moderate obesity and no co-morbidities.

Jensen and Quaade from the Obesity Clinic in Copenhagen explored the reasons for reducing the body

mass index of younger women with a moderate gynoid diffuse overweight. They concluded that among women seeking medical help for weight loss, only 7% are pre-menopausal and have a moderate degree of so-called 'cosmetic overweight'. They are significantly affected by the psychosocial consequences of being overweight, more so than the women with marked obesity. The relatively few moderately overweight women who seek professional help for their condition are probably entitled to medical advice for the purpose of weight loss.

A study from Leeds (**Hill and Franklin**) investigated the transmission of weight control via mothers and daughters. Forty young girls were selected on the basis of their dietary restraint for 2 years. The group of higher-restraint girls were significantly heavier than the lower-restraint girls, and wanted to be thinner. They also had a lower body- and self-esteem. Their mothers reported more between-meal snacking and fasting behaviour. In addition they rated their daughters' attractiveness significantly lower than the other mothers.

The search for an ideal anti-obesity drug was also highlighted at the ECO Congress during a satellite symposium. Drug therapy for obesity is indicated if the BMI is above 30 kg/m^2 in patients with a central distribution of body fat and who also have metabolic or haemodynamic risk factors, as well as in those in whom there has been failure of non-drug therapy. Sibutramine is a serotonin and noradrenaline reuptake inhibitor that also induces thermogenesis by stimulation of the beta-3 receptor in brown adipose tissue. Studies have shown an average 10% of weight loss in a third of patients treated with sibutramine, with a concomitant reduction in cardiovascular risk factors.

The benchmark medical therapy for obesity for the last few years has been dexfenfluramine, and it still is. Work presented here confirmed its efficacy in seasonal affective disorder, premenstrual tension and binge eating, as well as in snacking and simple obesity. **Guy-Grand** (France), who was involved with the earlier studies looking at 3 months' treatment with dexfenfluramine, reviewed more recent studies showing that a year of continuous dexfenfluramine maintained a 10 - 15% weight loss with improved metabolic parameters throughout this period. He emphasised that drugs for obesity should be prescribed as an adjunct to dieting and energy expenditure, and are indicated in moderate obesity, as well as in those patients with metabolic risk factors and those with anthropometric measurements that indicate increased visceral fat mass.

Despite major strides in the field of obesity, the maintenance of weight loss remains a major problem and appears to depend largely on behaviour modification therapy, aimed at altering eating patterns of obese individuals. While these efforts continue, clinicians and patients can take solace in the fact that even modest degrees of weight loss result in significant improvement in metabolic and cardiovascular risk factors, and still remain a worthwhile long-term objective.

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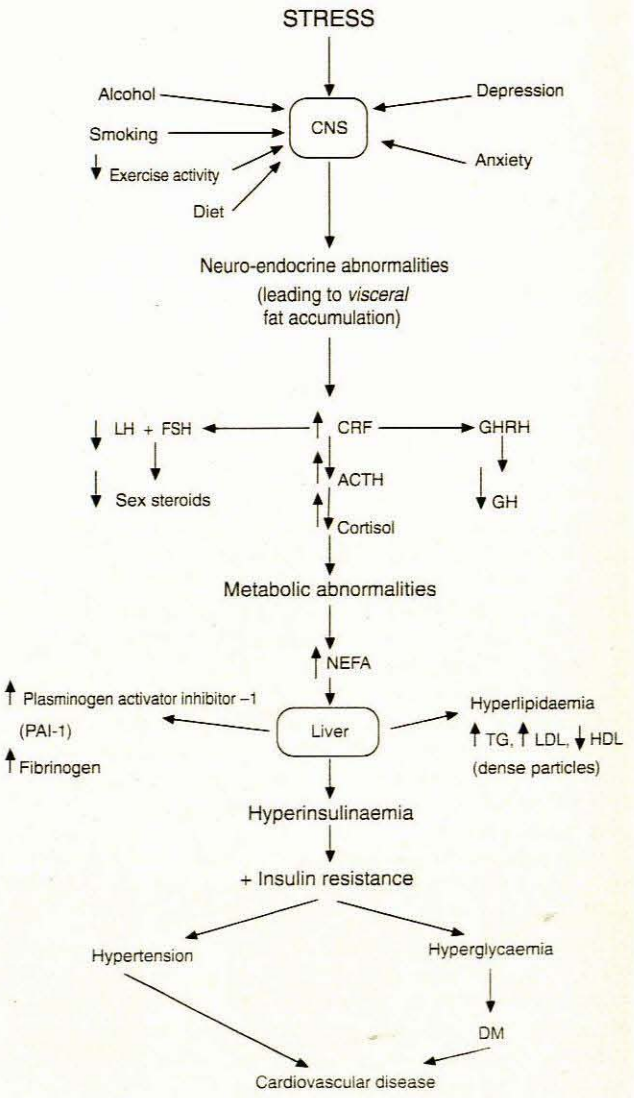

Cascade of central obesity and its complications.