# THERAPEUTIC PROCESS FOR THE TREATMENT OF THE METABOLIC SYNDROME AND ASSOCIATED METABOLIC DISORDERS

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a Continuation-in-Part of U.S. patent application Ser. No. 10/635,841 filed Aug. 6, 2003 now abandoned, which claims the benefit of U.S. Provisional Application No. 60/402,231 filed Aug. 9, 2002.

## BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is directed to therapeutic processes for the treatment of obesity and associated metabolic disorders such as the metabolic syndrome, and more particularly to a planned dietary regimen that can treat obesity, metabolic syndrome, prediabetes, and Type 2 diabetes.

2. Brief Description of the Art

The incidence of overweight and obese occurrences in the U.S. and worldwide human population is reaching epidemic proportions. Obesity (commonly defined as a Body Mass Index of >30 kg/m$^2$) is often associated with a variety of pathologic conditions such as hyperinsulinemia, insulin resistance, diabetes, hypertension, and dyslipidemia, and each of these conditions contributes to the risk of cardiovascular disease. Collectively, these pathologies that tend to associate (obesity, insulin resistance, dyslipidemia, and hypertension) have been termed "the metabolic syndrome" and are a major risk factor for cardiovascular disease. More recently, the U.S. National Cholesterol Education Program has classified Metabolic Syndrome as meeting three out of the following five criteria: fasting glucose level of at least 110 mg/dl, plasma triglyceride level of at least 150 mg/dl (hypertriglycerdemia), HDL cholesterol below 40 mg/dl in men or below 50 mg/dl in women, blood pressure at least 130/85 mm Hg (hypertension), and central obesity, with central obesity being defined as abdominal waist circumference greater than 40 inches for men and greater than 35 inches for women. The American Diabetes Association estimates that 1 in every 5 overweight people suffer from Metabolic Syndrome.

According to the guidelines of the American Diabetes Association, to be diagnosed with Type 2 diabetes, an individual must have a fasting plasma glucose level greater than or equal to 126 mg/di or a 2-hour oral glucose tolerance test (OGTT) plasma glucose value of greater than or equal to 200 mg/dl (Diabetes Care, 26:S5-S20, 2003). A related condition called pre-diabetes is defined as having a fasting glucose level of greater than 100 mg/dl but less than 126 mg/dl or a 2-hour OGTT plasma glucose level of greater than 140 mg/dl but less than 200 mg/dl. Mounting evidence suggests that the prediabetes condition may be a risk factor for developing cardiovascular disease (Diabetes Care 26:2910-2914, 2003). Prediabetes, also referred to as impaired glucose tolerance or impaired fasting glucose is a major risk factor for the development of type 2 diabetes mellitus, cardiovascular disease and mortality. Much focus has been given to developing therapeutic interventions that prevent the development of type 2 diabetes by effectively treating prediabetes (Pharmacotherapy, 24:362-71, 2004).

Although pharmaceutical medications exist for the treatment of diabetes, dyslipidemia, obesity, and hypertension, the combined use of such medications for the treatment of the metabolic syndrome suffer many disadvantages. Frequently,



a regimen of medications to treat these pathologies is impractical, unsafe, and only modestly effective in the long term. No singular long-term effective pharmaceutical treatment for the metabolic syndrome currently exists.

A second approach to the treatment of this disorder is nutritional intervention leading to the reduction of excess adiposity (adipose tissue) via a calorie restricting diet. Inasmuch as a reduction of obesity has consistently been demonstrated to improve various pathologies of the metabolic syndrome, prodigious efforts have been made to formulate a nutritional plan that may be effective in the long-term treatment of the syndrome in the general population. The development of an optimal dietary plan to treat the metabolic syndrome has proven an elusive task. There are several reasons for this shortcoming. First, the metabolic rate of calorie-restricted obese individuals quickly decreases to match the reduced energy intake and equilibrium is reached before a reduced ideal body weight is attained. Upon an increase in food consumption following this occurrence, body fat stores cycle often back above pretreatment levels. Secondly, the source of energy in many diets is high carbohydrate/low fat in content, that can exacerbate specific aspects of the syndrome. Thirdly, empirical evidence indicates that calorie restricting dietary plans are difficult to adhere to long-term and most individuals regain weight lost on such diets within 5 years. Most importantly, an enormous body of scientific evidence indicates that the control of metabolism including the development and the reversal of the metabolic syndrome resides within the central nervous system, and is largely independent of the caloric content of the diet.

Studies of vertebrate species in the wild that undergo annual cycles of metabolism oscillating between the metabolic syndrome and normal metabolism indicate that adjustable alterations of neuroendocrine activities regulated by the hypothalamus play major roles in the regulation of metabolism. For example, many vertebrate species will undergo annual cycles of body fat store level without any change in food consumption whatsoever during the year. Moreover, many species are fattest during seasons of greatest energy expenditure, such as during the migratory periods of the year. Therefore, it is not possible to ascribe increased body fat store level in these animals strictly to increased energy input or decreased energy expenditure levels. The change in body composition appears to be a function of changes in metabolic biochemical pathways operative at different seasons. Animals increase or decrease their fat to lean mass ratio by fractionally increasing lipid synthesis or protein turnover, respectively, without necessarily having to alter energy balance.

During the fattening periods of the year, it has been observed that many species develop symptoms of the metabolic syndrome (i.e., hyperinsulinemia, insulin resistance, hyperlipidemia, and glucose intolerance) analogous to the human situation. Research in this area has identified key components of this endogenous mechanism for the regulation of metabolism (Luo, S. et al., NeuroReport vol. 8:3495-3499, 1997; Luo, S. et al., Neuroendocrinology vol. 68:1-10, 1998; Luo, S. et al, NeuroReport vol. 10, 2073-2077, 1999; Cincotta, A. H. et al., Am. J. Physiol. vol. 278:R435-R444, 2000; Boundy, V. A. et al., Am. J. Physiol. 279:R505-R514, 2000; Luo, S. et al., Neuroendocrinology vol 69:160-166, 1999; Bina, K. G. et al., Neuroendocrinology vol. 71:68-78, 2000; Kraszewski, K. Z. et al., Int. J. Molecular Med. vol. 5:349-355, 2000). These include interactions within specific nuclei of the hypothalamus that orchestrate autonomic-neuroendocrine events that in turn interact variably to produce different