THERAPEUTIC APPROACH IN THE TREATMENT OF OBESITY

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ABSTRACT

Obesity is a fast becoming a major public health problem. The exact etiology of obesity still remains obscure. It is mainly caused by a combination of genetic factors, inappropriate eating habits and reduced physical activity. Besides these, dysregulation of many hypothalamic mechanisms controlling energy intake and energy expenditure have been shown in progression of obesity. Drug therapy should be used as an aid to behavioural modification, exercise and diet in the management of obesity.

Key words: Body Mass Index (BMI), Leptin, Neuropeptide Y, appetite suppressants and digestive inhibitor.

INTRODUCTION

Obesity is a common and challenging health problem affecting about 15% of the population [1]. It is not only a problem in itself but also predisposing factor for many other adverse health outcomes like Non-insulin dependent diabetes mellitus (NIDDM), insulin resistance, atherosclerosis etc. and all cause mortality [2].

The World Health Organisation has described obesity as an escalating epidemic and one of the greatest public health problems of our time with an impact on health as great as smoking [3].

It has been measured in various ways percentage of body fat, skin fold thickness, waist to hip circumference ratio and weight adjusted for height. The most commonly used surrogate marker is Body Mass Index (BMI) which is calculated s body weight in kilograms divided by square of the height in metres (Kg/m²) [4]. Table 1 gives the classification of overweight and obesity in adults [5].

Table 1: Classification of overweight and obesity in adults.

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (Kg/m²)</th>
<th>Risk of co-morbidities</th>
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<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>Low</td>
</tr>
<tr>
<td>Normal Range</td>
<td>18.5-24.9</td>
<td>Average</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
<td>Mildly increased</td>
</tr>
<tr>
<td>Obese</td>
<td>&gt; 30.0</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>30.0-34.9</td>
<td>Moderate</td>
</tr>
<tr>
<td>Class II</td>
<td>35.0-39.9</td>
<td>Severe</td>
</tr>
<tr>
<td>Class III</td>
<td>&gt; 40.0</td>
<td>Very Severe</td>
</tr>
</tbody>
</table>

Mortality rises exponentially with increase in body weight. The risk of coronary heart disease is doubled if the BMI is greater than 25 and nearly quadrupled if the index is 29.

The risk of developing diabetes increases with increasing weight and people with BMI greater than 35, have 40 fold higher risk of developing the disease than non-obese people. Respiratory diseases particularly sleep apnea and osteoarthritis are more common in obese people.

Sleep apnea describes episodes of apnea lasting for more than 10 seconds which occurs while sleeping [6]. This may lead to the development of serious cardiac arrhythmias and increased prevalence of heart attacks and cerebrovascular accidents. Two subtypes of sleep apnea have been identified namely, Obstructive (more common) and central (less common). The significance of obesity lies in the greater prevalence of obstructive sleep apnea in obese individuals.

Obesity has been clearly identified as a risk factor for osteoarthritis, particularly involving the knee joints [7]. The correlation between obesity and the risk of osteoarthritis is slightly higher in men. Obesity places excess load on weight bearing joints, accelerate the wear and tear process of these joints, particularly knees, thus increasing the prevalence of osteoarthritis.

The incidence of some malignancies such as cancers of endometrium, breast and colon, may be increased in obese individuals.

Neurotransmitters affecting energy balance

Neurotransmitters that increase food intake generally suppress sympathetic nervous system activity and thus produce thermogenesis, but the reverse is true for neurotransmitter that decreases appetite. Support for the notion that genetic abnormalities contribute to obesity came with identification of the obese gene and its protein product Leptin in 1994 [8]. Leptin is 16K Da peptide hormone synthesized in adipose tissue that acts in the hypothalamus to suppress food intake and increase energy expenditure. When Leptin is administered to rats, neuropeptide Y levels fall, and food intake and energy expenditure are normalized [9]. Leptin concentrations are high in almost all obese people. Decrease in Leptin concentration with weight loss suggests a mechanism that there is some resistance to the central effect of Leptin in obesity. Some of the neurotransmitters affecting energy balance are shown in Table 2.

Table 2: Neurotransmitters affecting energy balance [1].

<table>
<thead>
<tr>
<th>Factors that increase food intake</th>
<th>Factors that inhibit food intake</th>
</tr>
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<tbody>
<tr>
<td>Noradrenaline</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Opioids</td>
<td>Dopamine</td>
</tr>
<tr>
<td>Growth hormone releasing hormone</td>
<td>Cholecystokinin</td>
</tr>
<tr>
<td>Galanin</td>
<td>Neurotensin</td>
</tr>
<tr>
<td>Melanin-concentrating hormone</td>
<td>Glucagon</td>
</tr>
<tr>
<td>Neuropeptide Y</td>
<td></td>
</tr>
</tbody>
</table>

The nerve centre for regulation of energy balance is hypothalamus, which integrates neural, hormonal and nutrient messages from elsewhere in the body and sends signals to higher centres leading to feeling of hunger or satiety. The hypothalamus also controls energy expenditure via., autonomic nervous system and pituitary hormones.

Treatment of obesity

Since obesity is multifactorial problem, various treatment strategies are used in treating the overweight. The importance of treatment strategies depends on several factors.
The BMI value
The presence of central distribution of body fat
The presence of other coronary risk factors like atherosclerosis.

Individual with associated risk factors are considered suitable for treatment when BMI value is 27 Kg/m² or higher. For most people, an initial loss in body weight is relatively easy to achieve, but continuing weight loss and its long term maintenance is more challenging. The average weight reduction with most of the available strategies does not exceed 10%. In fact, more than 90% of people who lose weight initially regain it subsequently. Hence, combined strategies for treatment are recommended and followed on a regular basis which is shown in Table 3.

Table 3: Strategies for treatment of overweight and obesity

<table>
<thead>
<tr>
<th>Behavioural modification</th>
<th>Regular physical exercise</th>
<th>Diet</th>
<th>Drug therapy</th>
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**Behavioural modification**

Behavioural modification is a way of changing eating behaviour and increasing awareness of overeating. This may include:

- Daily recording of food intake
- Adjusting meal frequency
- Adjusting speed of eating
- Removing cues which result in overeating
- Separating eating from other activities

**Exercise**

Exercise is individually adjusted for each patient based on motivation and the extent to which he or she is overweight. The primary purpose of exercise is to increase energy expenditure and improve cardiovascular fitness. It includes walking and cycling at fairly low levels of energy expenditure. Daily, long term, low intensity exercise is as effective as high intensity, short term exercise and decreases the risk of discontinuing the exercise.

**Diet**

Weight reducing diets designed for obese are based on modifying fats, carbohydrates, proteins and fibre intake so as to reduce caloric intake. A deficit of 500-600 Kcal from normal 2000 Kcal/day is both tolerated and safe for most people. It results in a weight loss of about 0.5 Kg/week. Weight reducing diets should provide essential nutrients including vitamins and minerals. Low calorie chemicals substituting for sugars and fats can be helpful in maintaining a diet. Examples include artificial sweeteners and fat substitutes-Olestra.

Artificial sweeteners are low calorie additives in food products and diet drinks. Some of these exceed the sweetness of sucrose by a factor of 30-1000. The most widely used sweeteners are Saccharin sodium (x 400), Cyclamate sodium (x 30) and Aspartame (x 180).

Olestra is a fat substitute approved by FDA. It is a sucrose polyester, which is not absorbed in the GIT. Since olestra may decrease absorption of fat soluble vitamins, olestra containing foods are supplemented with vitamins A, D, E and K. Regular consumption of fat substitutes can produce GI effects such as loose stools and abdominal cramps.

**Drug therapy**

Appetite suppressants and digestive inhibitors are usually used for the treatment of obesity.

Centrally acting adrenergic agents (Benzphetamine, Phenteramine), Serotonergic agents (Fenfluramine), Ardenergic and Serotonergic agents (sibutramine) act as suppressants.

**Adrenergic agents**

Adrenergic agents mimic norepinephrine to enhance catecholamine neurotransmitter leading to increased sympathetic activity and reduced appetite. The first noradrenergic agent introduced was amphetamine, has a high risk of abuse. Phenteramine is similar to Amphetamine in that it modulates noradrenergic neurotransmission to decrease appetite, but has no effect on dopaminergic transmission, thus decreasing potential risk of abuse[11]. Adverse effects include headache, insomnia, nervousness and irritability. Palpitations, tachycardia and elevation in blood pressure occur rarely.

**Serotonergic agents (eg. Fenfluramine)**

They can affect food intake in the following ways

- By reducing snacking , which suggests that the individual has less food seeking behaviour
- By decreasing the amount consumed at a particular meal[12].

It has been reported that these agents increase basal metabolic rate by 100 calories/day[13].

Fenfluramine acts by inhibiting the uptake of Serotonin, releases Serotonin into synaptic cleft, thereby reducing food intake[14].

**Adrenergic and Serotonergic agents (eg. Sibutramine)**

This is a centrally acting agent that is structurally related to amphetamine. It inhibits the reuptake of Serotonin and Noradrenaline (and to a lesser extent dopamine) to increase the concentration of these neurotransmitters in the synaptic cleft.

**Digestive Inhibitors**

Orlistat is a potent and irreversible inhibitor of gastric and pancreatic lipase. It inhibits the digestion of dietary triglycerides, decreasing the absorption of cholesterol and lipid soluble vitamins [15] like A,D, E and K. Hence it decreases the absorption of dietary fat, decreases body weight, reduces plasma cholesterol and can cause steatorrhoea. Adverse effects include abdominal pain, diarrhoea, oily stools, nausea, vomiting and flatulence. It is contraindicated in patients with chronic malabsorption syndrome or cholestasis.

**Conclusion**

Long term treatment of obesity (2-4 years eg. Sibutramine, Orlistat) is required as there is a regain of original weight after discontinuation of drugs. Benefits include significant reduction in health risks, improvement in quality of life, less risk factors like dyslipidemias, insulin resistance and blood pressure etc. Regular physical exercise and diet control can also reduce blood glucose levels. Hence there is a good scope for the effective control and management of obesity.

**References**


