IL-18 in Morbid Obesity: Relation to Insulin Resistance

Thesis

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INTRODUCTION

Most attention in recent years has been devoted to the concept that obesity elicits a chronic low-grade systemic inflammatory response that results from a combination of increased insulin resistance and an increased production of inflammatory mediators by the expanding pool of adipocytes **(Rensen et al., 2009).**

Numerous evidences suggest that fat tissue is viewed as an active endocrine organ with high metabolic activity **(Kershaw et al., 2004).** Adipocytes produce and release several bioactive substances that act as true hormones responsible for the regulation of energy intake and expenditure **(Bastard et al., 2006).** The dysregulation in the production of these hormones (called adipocytokines) can contribute to the proinflammatory environment associated with obesity **(Vendrell et al., 2004)**.

Following the observation that serum concentration of the number of inflammatory makers including high sensitivity-CRP, TNFá-, and interleukin-6 are elevated in over weight and obese individuals, obesity is now viewed as a low grade inflammatory disease **(Fantuzzi, 2005).**

Several studies in different population indicate that inflammation may be the link between obesity and insulin resistance **(Doumatey et al., 2010)**.

Taken these data in consideration one could argue for a role of the adipose tissue as a new member of the innate immune system **(Anderson et al., 2007).**

Interleukin-18 is found to be associated with obesity, cardiovascular diseases and changes in insulin resistance and its level reduced after weight loss **(Thorand et al., 2005).** IL-18 is a fundamental proinflammatory cytokine, which its levels are increased in obese subjects. It acts as mediator in the inflammatory response and may have systemic effects, influencing the metabolism and action of insulin, that is associated with insulin resistance in non-morbidly and morbidly obese patients **(M. Civera et al., 2010).** Adipose tissue expression of IL-18 is increased in obesity but not affected by weight loss, indicating that changes in plasma IL-18 are related to insulin resistance rather than changes in obesity per se **(Bruun et al.,2007).** Therefore determination of the plasma IL-18 levels may be important for understanding onsets of metabolic diseases such as type 2diabetes in obesity.

AIM OF THE WORK

The aim of the present study is to determine serum concentrations of IL-18 in morbidly obese patients in comparison to normal weight controls. It is also designed to detect the correlation between IL-18 on one side and the insulin resistance and inflammation on the other side in the group of patients.

OBESITY

Obesity is a global epidemic health problem affecting all age groups, not only in developed countries but also in developing countries **(Kim et al., 2011).**

The "World Health Organization (WHO)'' modern obesity definition states that obesity is a disease of excess body fat which accumulates in adipose tissue to the extent that impairs health. This definition is important for two reasons, first it unequivocally characterizes the condition as a disease, not a character defect, cosmetic aberration, or personality disorder, and second it associates the disease with body fat, not body weight, desirable weight, or size **(Kushner and Robert**, **2007).**

There is a consensus between international organization and world experts that obesity is a disease of epidemic proportions that impairs the normal function and health. The degree of health impairment is determined by multiple factors as the amount of fat, the distribution of fat, and the presence of other risk factors **(Campbell and Haslam, 2005).**

Obesity is usually defined using the body mass index (BMI) which is equal weight (in Kg) divided by height square (in m^2). Generally speaking , a BMI $\geq$ 30 kg/m2 defines a state of obesity while BMI $\geq$ 35kg/m2 is defined as sever or morbid obesity **(Sturm, 2007).** There is a strong linear relation between BMI and relative body fat mass. The current practical definition of obesity is based on the relationship between BMI and health outcome rather than BMI and body composition **(Andrea, 2011).**

Several factors influence BMI-related health risk. For example, obese persons with excess abdominal fat named visceral obesity are at increased risk for diabetes, hypertension, dyslipidemia, and ischemic heart disease than obese persons whose fat is located predominantly in the lower body portion **(Iloh et al., 2011).**

Table (1): The International classification of overweight and obesity by BMI and associated disease risk.

	Obesity class	**BMI(kg/ m2)**	**Risk**
Normal	-	18.5-24.9	Normal
Overweight	-	25-29.9	Increased
Obesity	I	30-34.9	High
Obesity	II	35-39.9	Very high
Obesity	III	>40	Extremely high

(Hill et al., 2005).

There is a strong relationship between BMI and mortality. Obese persons have higher risk for adverse health consequences than those who are overweight **(Bays et al; 2006).**

Epidemiology of obesity:

Obesity is a leading preventable cause of death worldwide. It is the most prevalent nutritional disorder all over the world. Before the 20th century, obesity was rare; in 1997 the WHO formally recognized obesity as a global epidemic. In 2008

the WHO estimated that at least 500 million adults (10%) are obese, with higher rates among women than men and the rate of obesity was also increased with age at least up to 50 or 60 years old. Severe obesity in the United States, Australia, and Canada was increasing faster than the overall rate of obesity in the other world countries **(WHO, 2011).**

Obesity rates are rising worldwide and affect both the developed and developing world. These increases have been felt most dramatically in urban settings. The only remaining region of the world where obesity is not common is sub-Saharan Africa **(Tsigosa et al., 2008).** If obesity was solely a cosmetic problem, it would have little to fear, however with increasing prevalence of obesity a dramatic increase in obesity-related disease has occurred. We are therefore faced with an epidemic disease with hugely significant implications for individuals, health services and national economics **(Johansson et al., 2009)**.

There are multiple factors that influence the occurrence of obesity. These factors are age, gender, smoking, socioeconomic and cultural status as well as physical activity **(Choi et al., 2001).**

Factors influencing occurrence of obesity:

Age:

The Second National Health and Nutrition Examination Survey conducted in years 1999 and 2000 suggested that the prevalence of overweight is doubled among children with age between 6 and 11 years of age and tripled among those with age between 12 and 17 years of age **(Benson et al ., 2009).**

In ***Egypt, the Nutrition Institute in 2004*** reported that in adults the lowest proportion of overweight and obesity was among the age between 20 and 30 years. Both overweight and obesity gradually increased as the age progressed to reach the peak at ages between 50 and 60 years as the metabolic rate slows down with the progression of age and fewer calories are required to maintain the weight **(William, 2004).**

Gender:

Obesity is more prevalent in women than in men. Men have a more central distribution of fat, whereas women have a more gluteal/femoral pattern of fat distribution **(Mayes and Watson, 2004).** It was found that gluteal-femoral fat in women might eventually lead to a more favorable lipid profile (lower triglyceride and increased high density lipoprotein (HDL)-cholesterol levels) leading to some cardioprotection **(Lemieux, 2004).**

Socioeconomic status:

In most countries, obesity is more common in families with low social class. Obesity is more associated with poverty because of the lower cost of foods that are rich with energy such as the refined grains which may be reinforced by the high palatability of sugar and fat. In contrast, high socio-economic classes can afford getting diets based on meat, fish, fresh vegetables and fruits that are less energy foods (**McLaren, 2007**). However other studies manifested that the prevalence of obesity is very high in developed countries with high socioeconomic standards **(Wang, 2001).**

Physical activity:

Lack of physical activity is a significant contributing factor for overweight and obesity. Normal regulation of body weight occurs when energy intake equals energy expenditure, so weight gain may result when there is inadequate physical activity to balance our food consumption **(Lau et al., 2006).**

Active individuals require more calories than less active ones. Physical activity tends to diminish appetite while increasing the body's ability to metabolize fat as an energy source (**Nammi et al., 2004**).

A sedentary lifestyle plays a significant role in obesity. Worldwide there has been a large shift towards less physically demanding work, and currently at least 60% of the world's population gets insufficient exercise. This is primarily due to increasing use of mechanized transportation and a greater prevalence of labor-saving technology in the home. In children, there is decline in levels of physical activity due to less walking and physical education (**WHO, 2009**).

Smoking:

Smoking and smoking cessation are associated with weight changes. Smoking increases caloric requirements by increasing resting metabolic rate which promotes weight loss, while smoking cessation with maintaining constant food intake and exercise, will lead to increase body weight between 5% and 10% (**Demosthenes et al., 2006**).

Etiology of Obesity:

Obesity is a chronic condition that develops as a result of a complex interaction between a person's genes and the environment. At its simplest, obesity is characterized by an excess of energy intake in relation to energy expenditure. Any excess energy intake above an individual's daily requirement will result in that energy being stored **(Lau et al., 2006).**

Energy is stored as fat, and deposited subcutaneously and viscerally. Large increases in body fat can result from even minor but chronic differences between energy intake and energy expenditure. In one year, the ingestion of only 5% more calories than expended can promote the gain of approximately 5 kg in adipose tissue. Over 30 years, the ingestion of only 8 kcal per day more than expended can increase body weight by 10 kg **(Olsen and Heitmann, 2009).**

However, weight regulation appears to be much more complex than a simple problem of energy in versus energy out. It was estimated that as much as 70% of a predisposition to obesity is genetic, however, those implicated genes might not necessarily convey an inevitability of future weight gain. Our

genes are switched on or switched off by environmental, neurological and psychogenic influences, all of which could have an effect on an individual's predisposition and ultimate development of obesity **(Campbell and Haslam, 2005).**

1. Genetic and familial factors:

Obesity is a polygenic disease; the genes involved may result in increase or decrease food intake**.** Obesity definitely runs in families. It is generally believed that this similarity between twins is genetically controlled. Studies have shown that children born to overweight mothers had a significantly lower energy expenditure and more rapid weight gain than children from normal weight mothers **(Haworth et al., 2008).**

The genes can direct the degree of feeding with several routes. These include genetic abnormality of feeding center to set the level of nutrient storage high or low **(Evans et al., 2002).** Abnormal hereditary psychic factor that either decrease the appetite or cause the person to eat as a release mechanism **(Rodin, 2007)** and reduction of enzyme lipase in the adipose tissue, causing prevention of the release of fat from the adipose tissue **(Flier et al ., 2004).**

In April 2007, British scientists discovered a link between obesity and a gene known as FTO (fat-mass and obesity associated) which is located in chromosome region 16q12.2. They reported that people who carry two copies of a particular version of the FTO gene, an estimated 16 percent of UK population, are on average three kilograms heavier than people who do not have the variant, while those who carry just one copy of the gene variant, an estimated 50 percent of UK population are around 1.6 kg heavier **(Calton and Vaisse, 2009).**

Twenty chromosomes containing genes which are thought to be responsible for obesity have been identified. However the disease of morbid obesity has a genetic landscape which is acted on by medical, lifestyle and psychological factors which interact to decide the final obesity phenotype **(Ramachandrappa and Farooqi , 2011).**

Also, mutation of certain genes can lead to obesity. One of these genes is the ***Leptin gene (ob. gene)*.** The discovery of "ob" gene, which was mapped to chromosome 7, has led to a renewed interest in understanding the patho-biological bases of genetic predisposition in obesity. It is expressed only in adipocytes and it is responsible for production of Leptin hormone that seems to provide information to the hypothalamus about the energy status of the body through special receptors **(Gautron and Elmquist, 2011).** Any mutation of "ob" gene leads to improper coding of leptin, which further results in obesity. The effects of ob gene are mediated through effects on both energy intake and energy expenditure. Mutation of leptin receptor, leads also to obesity **(Williams et al., 2009).**

Other studied genes include ***Genes of Beta-3-adrenergic receptors***, ***Tumor necrosis factor and lipoprotein lipase***. B3 adrenergic receptors are responsible for regional distribution of fat in obese subjects. They are more frequent in visceral adipose tissue and concern with lipolysis **(Emilio et al., 2010).**

2-Diet:

Diet plays a significant role both in development and control of obesity. Over eating plays an important role in obesity **(Marantz et al., 2008).** Intake of excess dietary fat and carbohydrates has been implicated as a major cause of obesity for decades **(Modak and Mukhopadhaya, 2011).**

Fat provides more energy than proteins and carbohydrate per unit weight and contribute to obesity. It can also influence food intake, energy metabolism and substrate oxidation. High fat foods are also preferentially selected by individuals because of their high palatability and a weak satiety effect**.** Extra carbohydrates consumption as sweetened beverage is also implicated as a main cause of obesity **(Coslen and Heitmann, 2009).**

As societies become increasingly reliant on energy-dense and fast food meals, the association between fast food consumption and obesity becomes more obvious **(Rosenheck, 2008).** For many people, even when caloric intake is not above the recommended level, the number of calories expended in physical activity is insufficient to consumption. This will lead a person to be obese **(James, 2008).**

3- Environmental Factors:

The environmental factors include race, social environment and more important the physical environment. According to **WHO (1997)**, the fundamental causes of the obesity epidemic are sedentary life styles and high fat-energy dense diets **(Hill et al., 2005).**

4- Endocrinal Factors:

Endocrine glands disturbance represents an important factor for obesity as growth hormone deficiency is associated with increased body fat. Cushing syndrome is the endocrine disease most often associated with obesity. Also, the syndrome of polycystic ovaries may be a combination of hypothalamic and endocrine obesity**.** Hypothyroidism is also closely associated with obesity **(Keljman and Frohman, 2006)**.

5- Psychogenic Factors:

Psychological disorders may result in overeating in response to emotional tension; it seems that eating is often a mean of release from tension **(Chiles and Van, 2010).** On the other hand, some individuals under similar conditions may develop anorexia leading to thinness. It is presumed that this difference in response reflects basic personality differences (**Rodin, 2007**).

6- Hypothalamic Factors:

Hypothalamic obesity is a rare syndrome in humans. Trauma, malignancy and inflammatory diseases involving the ventro-medial hypothalamus may produce it .The ventro-medial region of hypothalamus is responsible for integrating information of energy stores. When this region is damaged, hyperphagia develops and obesity follows **(Campbell and Haslam, 2005).** The secretion of insulin associated with the change in hypothalamic function may be one pathogenic link in its development. Treatment of the syndrome requires treating the underlying disease and giving appropriate endocrine support **(Campbell and Haslam, 2005).**

7- Childhood Over nutrition:

The rate of formation of new fat cells is especially rapid in the first few years of life, which results in a greater rate of fat storage. In obese children the number of fat cells is often as much as three times that in normal children. However, after adolescence, the number of fat cells remains almost identically the same throughout the remainder of life. Therefore, it has been suggested that overfeeding children, especially in infancy and to lesser extent during the older years of childhood, can lead to lifetime obesity **(Vohra et al., 2011).**

8- Drugs:

There are drugs that may increase the body weight either by improving the appetite or by altering the metabolism. These include contraceptive pills, antidepressants, phenothiazines, steroids and antiepileptics **(Schwartz et al., 2004).**

Pathogenesis of Obesity:

Fat accounts for 21% to 37% of weight of middle-aged men and women. At sometime in life the obese individuals take more calories than what they expend and this simply will lead to obesity **(Campbell and Haslam, 2005).**

Mechanisms controlling fat cell size and numbers are still poorly understood, however, there are several factors that are known to share in the pathogenesis of obesity **(Stanley et al., 2005).**

Lipoprotein lipase enzyme (LPL):

Normally, the enzyme lipoprotein lipase is produced by the adipose tissue and permits fat cells to take up fatty acids from circulating chylomicrons (dietary fat) and very low-density lipoprotein. LPL plays a homeostatic function to facilitate lipid clearance and promote adipose tissue storage **(Pulnilkunnil and Rodrigues, 2006).** Well-fed fat cells can grow to maximum of 1 ug. Storage of more fat requires an increase in adipocytes number by differentiation of preadipocytes **(Flier et al., 2004).** It was found that LPL is increased in obesity. Much evidence suggests that the insulin response to hyperglycemia is an important part of the response of LPL in adipose tissue as insulin is stimulant to release of