

Hyperleptinemia, Insulin Resistance and Metabolic Syndrome in Older Adults

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I. Abstract

Leptin is a product of the ob/ob gene that is associated with obesity, weight loss, cachexia, inflammatory processes, oxidative stress, arterial hypertension, and aging. Elevated serum leptin levels in elderly individuals suggest that aging is associated with a decrease in receptors for leptin and/or resistance to this hormone. Additionally, it has been observed that there is an increase in fat mass and abdominal adiposity during aging as well as an increase in insulin resistance that is frequently associated with high leptin levels and leptin resistance. Leptin directly inhibits insulin secretion from pancreatic β -cells, and elevated serum leptin levels are shown to be associated with elevated fasting insulin, insulin resistance (HOMA-IR), and elevated serum cholesterol, which are core metabolic disturbances of the metabolic syndrome. Furthermore, it has been observed in a recent study that replacement of dietary saturated fat with marine n-3 fat and monounsaturated fat decreases serum leptin levels in hypertriglyceridemic patients. The objectives of the present study are to evaluate the prospective relationships between serum leptin, proinflammatory cytokines (PAI-1, IL-6, TNF α , CRP), and the risk of metabolic syndrome among older adults; to investigate the effects of serum leptin on the prospective associations of n-3 fats with metabolic syndrome and all-cause mortality; and to determine optimal serum leptin levels for the diagnosis of metabolic syndrome and type 2 diabetes. Subjects of the present study are participants in the Health Aging and Body Composition (HABC) study. The Health ABC study has compiled extensive anthropometric measurements, biological measures and food intake data utilizing a food frequency questionnaire (FFQ). Metabolic syndrome is defined in the study by NCEP ATP III guidelines, as the presence of 3 or more of the 5 risk components (waist circumference >102 cm for men and >88 cm for women; triglyceride ≥ 150 mg/dl; high-density lipoprotein cholesterol <40 mg/dl for men and <50 mg/dl for women; blood pressure $\geq 130/85$ mmHg; fasting glucose ≥ 110 mg/dl). Potential confounders include demographic variables (age, gender, race), study site, smoking status, alcohol use, physical activity, and total caloric intake. We anticipate that the results of this study will help in establishing serum leptin as a marker for predicting the risk of developing metabolic syndrome, clarifying relationship between n-3 fatty acids and metabolic syndrome in older adults, and identifying the optimal serum leptin levels for diagnosis of metabolic syndrome. This has obvious benefits for both researchers and clinicians who work with populations at increased risk for metabolic disorders and who would like to diagnose and target those in need of interventions for the prevention of metabolic syndrome.

Specific goals: II. Objectives

- To evaluate the prospective relationships between serum leptin, proinflammatory cytokines (PAI-1, IL-6, TNF α , CRP), and the risk of metabolic syndrome among older adults
- To investigate the effects of serum leptin on the prospective associations of n-3 fatty acids with metabolic syndrome and all-cause mortality

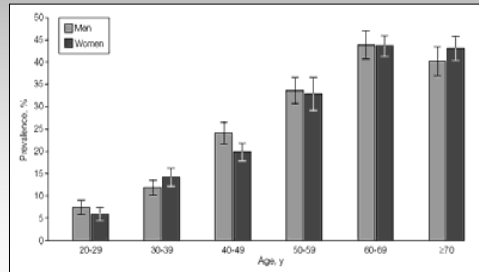
- To determine optimal serum leptin levels for diagnosis of metabolic syndrome or type 2 diabetes.

Long term goal:

- To establish serum leptin as a marker for predicting the risk of developing metabolic syndrome
- To clarify relationship between n-3 fatty acids and metabolic syndrome in older adults
- To identify the optimal serum leptin levels for the diagnosis of metabolic syndrome

III. Background

Age-specific prevalence of metabolic syndrome among US adults, NHANES III, 2002



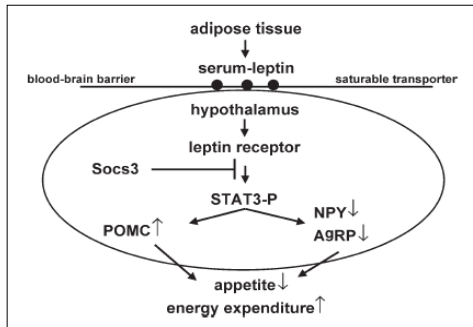
Source: JAMA, January 16, 2002—Vol 287, No. 3.¹

Cost of cardiovascular disease and diabetes in US

Cardiovascular disease, including heart disease and stroke, account for nearly 40% of all annual deaths in the United States with a projected cost of \$431.8 billion in 2007 (CDC, 2007).

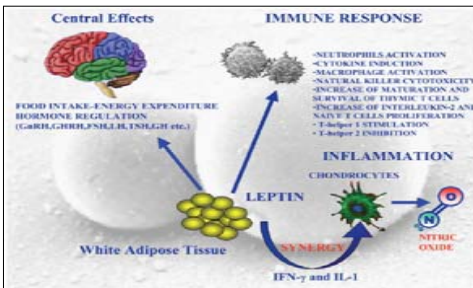
The total direct medical and indirect cost of diabetes in 2007 was \$174 billion. (CDC, 2008)

Leptin action, leptin signal transduction and key players in leptin resistance.



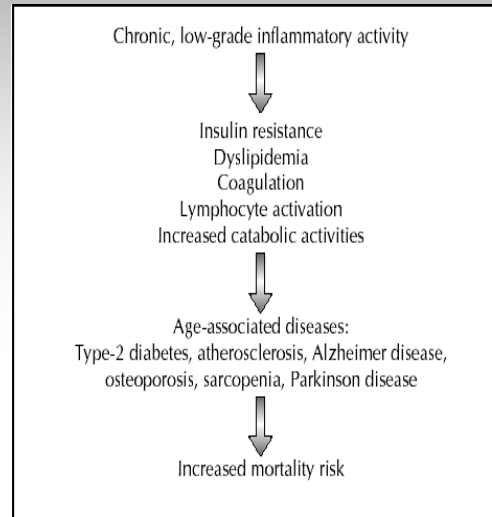
Source: European Journal of Endocrinology (2005) 152, 333-334.²

Effects of leptin at central level and in the periphery with particular attention to the immune system and inflammatory response.



Source: M. Otero et al. / FEBS Letters 579 (2005) 295–301³

Effects of chronic, low grade inflammatory activity in aging



Source: Curr Opin Hematol 2001, 8:131–136.

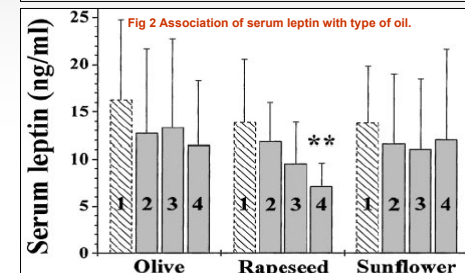
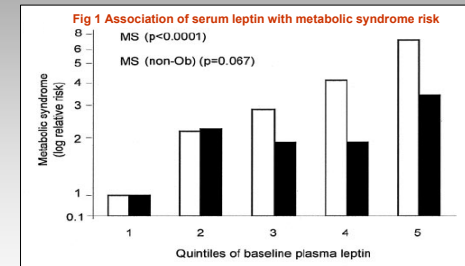
IV. Experimental Design

- Subjects are participants in Health ABC study, which is a longitudinal study on 3075 community dwelling, well functioning black & white men & women aged 70 to 79, recruited in Pittsburgh and Memphis in 1997-98.
- Health ABC assessed socio-demographic, biochemical, health variables and body composition. Food intake was measured with a modified Block FFQ, and the cohort was genotyped for polymorphisms in multiple genes.
- Anthropometric variables in the study include WC, BMI, total abdominal fat, and total percent body fat. Biochemical and clinical variables that will be studied analyzed are BP, Fasting glucose and insulin, Leptin ($\mu\text{g/L}$), CRP (mg/dl), IL-6, TNF- α , PAI-1, HDL-c, and TGL. Dietary variable will include n-3 fats (EPA & DHA).
- Metabolic syndrome will be defined following the NCEP ATPIII definition and IR will be assessed using Homeostasis Model Assessment (HOMA). $(\text{HOMA-IR index}) = (\text{fasting glucose (mmol/l)} \times \text{fasting insulin } (\mu\text{mol/ml}) / 22.5)$.

V. Statistical Analysis

- Multivariate logistic regression models will be used to determine the prospective association between baseline serum leptin and risk of developing metabolic syndrome
- Multivariate logistic regression models will be used to assess the relative risks of developing the metabolic syndrome, for persons in quintiles 2 through 5 of EPA and DHA compared with those in quintile 1, after adjustment for potential confounders.
- Optimal serum leptin concentration for diagnosis of metabolic syndrome and type 2 diabetes will be determined using receiver operator characteristic (ROC) curves.

VI. Expected Results



Data derived from: Fig. 1 Obes Res. 2005;13:1476–1484. Fig. 2 J Clin Endocrinol Metab 87: 5008–5014, 2002.

- Serum leptin is expected to significantly predict the risk for metabolic syndrome. We expect to observe significant effects of cytokines in the above relationship.
- Subjects in quintile 2 through 5 of EPA & DHA are expected to be at greater risk of developing metabolic syndrome as compared to quintile 1. We expect to find significant interaction between leptin and n-3 fats.

VII. Implications

- The findings of this study will help researchers and clinicians who would like to diagnose and target those in need of interventions for preventing the development of metabolic syndrome in a population believed at increased risk for metabolic disorders.
- Provides strong support for the efficacy of leptin sensitivity enhancing drugs.
- Emphasizes the importance of n-3 fatty acids in improving metabolic disorders.

VIII. Limitations

- Results can be applied only to the population of older adults.
- It is not possible, using this methodology to understand the exact cause of elevated leptin levels in older adults

IX. References

- Age-Specific Prevalence of the Metabolic Syndrome among 8814 US Adults Aged at Least 20 Years, by Sex, National Health and Nutrition Examination Survey III, 1988-1994. JAMA (2002); 287:356-359.
- Jorg Dotsch, Wolfgang Rascher and Udo Meiner. New insights into leptin resistance by modifying cytokine receptor signal transduction. European Journal of Endocrinology (2005) 152, 333-334.
- Miguel Otero, Rocio Lago, Francisca Lago, Felipe F. Casanueva, Carlos Dieguez, Juan Jesu's Go'mez-Reino, Oreste Gualillo. Mini review: Leptin, from fat to inflammation: old questions and new insights. FEBS Letters 579 (2005) 295–301.