Obesity, Adiposity, and Dyslipidemia: A Consensus Statement from the National Lipid Association

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Obesity, Adiposity, and Dyslipidemia: A Consensus Statement from the National Lipid Association

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PROCESS:

NLA Consensus Conference On September 16, 2012, with presentations of specific topics assigned to opinion-leaders in adiposity and dyslipidemia:

- Researchers
- Academicians
- Physiologists
- Medical journal editor
- Clinicians
- Clinical trialists
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PROCESS:

- Submission of documents based upon face-to-face presentation and feedback from the Consensus Conference
- Peer review of all documents with subsequent revisions
- Consolidation of all documents
- Editorial review of all documents with subsequent revisions
- Publication in Journal of Clinical Lipidology
- Consensus Statement
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PROCESS:

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- The project content had no input from industry
- The authors received no payment for their contributions
Definitions

• (1) Diabetes mellitus = diagnosed and previously undiagnosed type 1 or type 2 diabetes mellitus

• (2) Hypertension = administration of antihypertensive medication or systolic blood pressure $\geq 140$ mm Hg or diastolic blood pressure $\geq 90$ mm Hg

• (3) Dyslipidemia = any of the following: total cholesterol $\geq 240$ mg/dL, triglycerides $\geq 200$ mg/dL, low-density lipoprotein cholesterol $\geq 160$ mg/dL, or high-density lipoprotein cholesterol $< 40$ mg/dL
BMI and Prevalence of Metabolic Disease
NHANES 1999-2002

Body Mass Index (BMI) vs. % of Patients

- Diabetes Mellitus
- Hypertension
- Dyslipidemia

BMI Among Patients With Metabolic Disease NHANES 1999-2002

Body Mass Index (BMI)

- <18.5: Lean
- 18.5-24.9: Normal
- 25-26.9: Overweight
- 27-29.9: Normal
- 30-34.9: Overweight
- 35-39.9: Obese
- ≥40: Obese

Adiposopathy: Definition

Adiposopathy is defined as pathogenic adipose tissue:

• Promoted by positive caloric balance and sedentary lifestyle in genetically and environmentally susceptible patients

• Anatomically manifested by adipocyte hypertrophy, visceral adipose tissue accumulation (adiposity), growth of adipose tissue beyond its vascular supply, as well as ectopic fat (triglyceride) deposition in peripheral organs such as liver, muscle, and pancreas

• Physiologically manifested by adverse metabolic and immune consequences leading to metabolic disease
<table>
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<td>Pathogenic adipose tissue immune responses</td>
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<td>(e.g., increased pro-inflammatory responses through increased TNF-α and decreased anti-inflammatory responses through decreased adiponectin)</td>
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Clinical manifestations of adiposopathy

- Hyperglycemia
- High blood pressure
- Elevated VLDL triglycerides and apoB (small dense LDL)
- Low HDL-C
- Metabolic syndrome
- Atherosclerosis
- Fatty liver
- Hyperandrogenemia in women
- Hypoandrogenemia in men
- Cancer
Abnormalities in glucose metabolism
- Insulin resistance in skeletal muscle
- Insulin resistance in liver
- Increased hepatic glucose production
- Decreased pancreatic insulin release

Hypertension
- Increased mineralocorticoid activity
- Increased catecholamine activity

Dyslipidemia
- Hypertriglyceridemia
- Low HDL cholesterol levels
- Abnormalities in lipoprotein particle size and subclass distribution
- Hypercholesterolemia

Atherosclerosis and vascular damage

Atherosclerotic plaque

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Executive Summary – Key Points

• Adiposity is an important contributor to the dyslipidemia epidemic and other metabolic disease epidemics such as T2DM, high blood pressure, and CVD.
• Adipose tissue is a body organ that is integral to essential endocrine and immune functions affecting lipid levels.
• An increase in caloric balance among genetically and environmentally susceptible patients causes adipocyte and adipose tissue dysfunction (adiposopathy), which may promote dyslipidemia.
• “Adiposopathic dyslipidemia” is characterized by elevated TG, reduced HDL-C, increased small dense LDL, and increased lipoprotein remnant lipoprotein levels, and often occurs in overweight patients with visceral adiposity and fatty liver.
Executive Summary – Insulin Resistance

• The development of insulin resistance in adiposity is closely associated with ectopic lipid accumulation, specifically DAG.
• In skeletal muscle DAG mediated activation of PKCθ impairs insulin stimulated muscle glucose transport.
• In the liver, DAG mediated activation of PKCε diminishes the ability of insulin to promote glycogen synthesis and inhibit gluconeogenesis.
• Therapies that decrease ectopic lipid accumulation may improve insulin resistance and potentially valuable in treating metabolic syndrome and T2DM.
Executive Summary – Metabolic Syndrome

- A large number of non-obese individuals, particularly from racial minority groups, are not recognized as having the metabolic syndrome and elevated risk for T2DM and CVD because of current focus on adipose tissue mass alone.

- Adipose tissue ENPP1 is involved in the regulation of adipocyte maturation. Lack of appropriate ENPP1 down-regulation in adipose tissue during weight gain associates with adipose tissue dysfunction, increased plasma free fatty acid, systemic insulin resistance, and other components of the metabolic syndrome.

ENPP1 = Ectonucleotide pyrophosphatase/phosphodiesterase 1
Executive Summary - Triglycerides

- Adiposity is often accompanied by a complex interaction of insulin resistance, genetics, diet, energy balance, and other factors leading to disordered metabolism of TG rich lipoproteins.
- Adiposity and insulin resistance are common “second hits” in genetically and environmentally susceptible individuals potentially leading to severe hypertriglyceridemic dyslipidemias.
- Modest hypertriglyceridemia in the setting of adiposity is often associated with increased concentrations of small dense atherogenic LDL particles and TG rich remnant lipoproteins, and is associated with heightened risk for atherosclerotic disease.
Executive Summary - Triglycerides

- T2DM, CVD, and steatohepatitis are common outcomes in adiposity complicated by hypertriglyceridemia.
- Adiposity with hypertriglyceridemia is common, frequently occurring in the setting of the metabolic syndrome. Identifying the lipoproteins in excess and severity of TG elevation is best accomplished by measurement of serum TG and apo B levels.
- Very high TG levels, >500 and more typically >1000 mg/dL, are associated with an increased risk of pancreatitis, usually due to inability to clear chylomicrons from serum, severe elevations in VLDL levels, or both.
- Moderately elevated TG levels are frequently associated with risk for vascular disease secondary to increased levels of atherogenic apo B containing lipoproteins.
- T2DM, NAFLD, deterioration of vascular mechanics, and an increase in all-cause mortality are late consequences of chronic insulin resistance and hypertriglyceridemia.
Executive Summary – HDL-C

- HDL-C is a highly validated predictor of CV risk and reductions in serum levels of this lipoprotein are a defining feature of the metabolic syndrome/insulin resistance.
- A low HDL-C in a background of insulin resistance is associated with greater CV risk than a low HDL-C in individuals who have normal insulin sensitivity.
- Insulin resistance and heightened systemic inflammation stemming from increased adiposity are associated with adverse changes in the HDL proteome and HDL metabolism, yielding reduced biosynthesis and increased catabolism.
- Renal function significantly impacts serum HDL-C; the glomerular hyperfiltration that can be observed among patients with adiposity, IR, or DM may exacerbate hypoalphalipoproteinemia.
Executive Summary – HDL-C

- The reduction in serum levels of HDL may exacerbate hyperglycemia and insulin deficiency since islet cells appear to require exposure to HDL in order to synthesize and secrete insulin.
- No adequate outcomes data exist with which to recommend pharmacologic intervention for low HDL-C in the setting of adiposity and IR.
- Exercise, weight loss, and smoking cessation are associated with significant elevations in serum HDL-C and should always be encouraged and likely constitute the best approach toward raising HDL-C in obese patients with or without IR.
Executive Summary – LDL-C

• LDL-C plasma concentrations tend to increase with increasing body weight in those <30 years of age, even among those who are not significantly overweight. LDL-C increases in middle aged patients with a BMI of up to about 28 kg/m2. A rise in fasting TG levels is a consistent finding in overweight and obese persons.

• The cholesterol content of LDL particles often falls with weight gain. But a concomitant increase in the number of LDL particles results in little change in the observed LDL-C. LDL particles and apo B increase far more when TG exceeds 150 mg/dL, but measured LDL-C tends not to increase.
Executive Summary – LDL-C

• HDL-C and HDL particle number tend to decrease with weight gain.
• Weight loss in obese individuals produced by diet, drugs, or bariatric surgery reduces TG and increases HDL-C concentrations but produces minimal change in LDL-C levels. The total number of LDL (apo B containing) particles usually falls with weight loss and the cholesterol content per particle rises. The HDL particles and their cholesterol content tend to increase. A fall in plasma TG rich lipoproteins appears to drive these changes through reduced CETP activity.
• From a lipid standpoint, the risk of vascular disease events correlates best with an increase in LDL particle or apo B concentration.
Executive Summary – Clinical Management

• Adipose tissue is biologically active, and contributes to metabolic homeostasis.
• Adipose tissue anatomical changes, and the development of dysfunction due to accumulation of regional fat mass, constitute adiposopathy.
• Adiposopathy is etiological in the development of metabolic derangements that are established cardiovascular risk factors.
• The use of BMI alone to stratify metabolic risk has limited clinical application.
• Measurements of intra-abdominal or visceral fat mass are good clinical markers of adiposopathy.
• The dyslipidemia of adiposopathy is best managed with interventions that along with total fat reduction, also result in intra-abdominal fat mass reduction.
Executive Summary - Nutrition

• TG levels are among the lipid parameters most like to respond to nutritional intervention. Higher baseline TG levels typically having the potential for greatest reduction with nutrition-derived weight loss in overweight patients.
• The type of nutritional intervention also is of significance, in that weight loss achieved in overweight patients by lower carbohydrate diets would be expected to lower TG more than weight loss achieved by higher carbohydrate diets.
• During weight loss, LDL-C typically decreases followed by: 1) some increase compared to baseline levels; 2) return to baseline levels, or 3) a sustained reduction. These varied responses may be related to the type of nutritional content consumed after weight loss, and/or weight loss maintenance or weight regain after weight loss.
• HDL-C is affected by weight loss and the composition of the weight loss diet. Higher carbohydrate/low fat diets decrease HDL-C whereas higher protein/lower carbohydrate diets maintain or increase HDL-C.
Executive Summary – Physical Activity

- Exercise training of sufficient quantity can reduce adiposity with or without weight loss.
- Although not always true, in general, fat weight reduction is required for exercise generated total cholesterol and LDL-C reduction.
- Exercise intervention provides potential advantages to dietary-only intervention. Exercise induces greater insulin action and insulin sensitivity particularly when matched for energy equivalent dietary restriction. Sufficient physical activity also prevents the decrease in RMR typically associated with weight loss by energy restriction alone. Additionally, when exercise training is added to dietary weight loss there is a preferential reduction in subcutaneous abdominal adipocyte size, and intramuscular TG and visceral adipose tissue.
- Overweight and obese adults should progress to a minimum of 150 min of moderate intensity exercise per week and, when possible, progress to >200 min of moderate intensity exercise per week.
Executive Summary – Weight Management Drug Therapy

- Weight management drug therapy may not only improve the weight of patients, but may also improve the health of patients, including patient lipid levels.
- The lipid parameter most consistently susceptible to improvement with weight loss is the reduction in TG levels, which is the lipid parameter most associated with adiposopathic dyslipidemia. Greater weight loss is often required to reduce LDL-C levels.
- Given that the effectiveness of TG-lowering agents is greatest among patients with the highest baseline levels, studies of weight management agents in patients with hypertriglyceridemia are needed.
- At the very least, post-hoc analyses of existing trials in patients with higher and lower baseline TG levels (such as tertile analyses) would be helpful to lipidologists and clinicians who manage overweight hypertriglyceridemic patients.
Executive Summary – Weight Management Drug Therapy

• In overweight patients, a loss of about 5% of body weight can improve adipocyte and adipose tissue function in patients with adiposopathy, with a consequence that a loss of only about 5 – 10% of body weight can improve metabolic diseases such as dyslipidemia.

• Weight loss drug therapies do not typically result in substantial changes in HDL-C levels, which is similar to responses to modest exercise alone.
Executive Summary – Bariatric Surgery

- Bariatric surgery is becoming a more frequently used treatment for adiposity. This is occurring not only to reach BMI targets, but also to improve metabolic parameters such as lipid fractions, plasma lipoprotein levels, reduce inflammatory markers, as well as improve insulin sensitivity.
- Roux-en-Y gastric bypass (RNYGB), laparoscopic adjustable banding (LAGB), and LSG are the most commonly performed procedures, each of which has different anatomic and physiologic properties.
- The most evidence thus far supports surgical procedures that by-pass the stomach (e.g., RNYGB) as superior for achieving loss of excess body weight as well as improvement in lipid profile, which are likely due a combination of reduction in body fat, as well as due to alterations in gut and other hormones and inflammatory factors.
- The more recent procedures such as LAGB and LSG have favorable metabolic and lipid consequences as well due to gastric restriction, a change in gut hormone levels, and reduction in inflammatory markers.
Overview

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