



Review Article

THE GLOBAL PROBLEM: OBESITY AND DYSLIPIDEMIA

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Abstract: Obesity is an excessive accumulation of energy in the form of body fat which impairs health. The main cause of obesity epidemic is clear: overeating, especially that of foods, which are rich in fats, extracted sugars or refined starches. This links to a progressive decline in physical activity results in an imbalance of intake and expenditure of calories, resulting in excess weight and eventually obesity. Co-morbidities commonly associated with obesity include diabetes, cardiovascular and respiratory disease, dyslipidemia, degenerative joint disease, stress incontinence and some form of tumors and other various diseases. Dyslipidemia is a widely accepted risk factor for coronary artery disease and is an important feature of metabolic syndrome. Obesity especially visceral obesity causes insulin resistance and is associated with dyslipidemia, impaired glucose metabolism, and hypertension all of which exacerbate atherosclerosis. The primary dyslipidemia related to obesity is characterized by increased triglycerides, decreased high density lipoprotein levels and abnormal low density lipoprotein composition. Weight loss and exercise can improve this dyslipidemia and thus reduce cardiovascular risk. In addition, obese individuals needed to be targeted for intense lipid lowering therapy, when necessary.

Keywords: Obesity and Dyslipidemia.

Abbreviations: HDL: High density lipoprotein, LDL: low density lipoprotein, TG: Triglycerides, VLDL: Very low density lipoprotein, BMI: Body mass index, MI: Myocardial infarction, ECG: Electrocardiogram, WHR: Waist-to-hip circumference ratio, HDL-C: High density lipoprotein cholesterol, NEFA: Non esterified fatty acids, IL-6: Interleukin-6, PPAR: Peroxisome proliferator activated receptor γ , SREBP-1: Sterol regulatory element binding protein-1, Apo B: apolipoprotein, LDLR: Low density lipoprotein receptor, CETP: cholesterol ester transfer protein, TRLs: Triglyceride-rich lipoproteins, HL: Hepatic Lipase, MTP: Microsomal triglyceride protein.

Introduction

Obesity is a chronic health problem affecting increasing number of people worldwide and is now recognized as a global epidemic. In India, obesity is emerging as an important health problem particularly in urban areas, paradoxically co-existing with under nutrition. Almost 30-65% of adult urban Indians are either overweight or obese or have abdominal obesity¹. The rising prevalence overweight and obesity in India has a direct correlation with the increasing prevalence of obesity-related co-morbidities; hypertension, the metabolic syndrome, dyslipidemia, type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD)²⁻³. There is also a plentiful body of evidence indicating high-fat diet is the major cause of obesity and insulin resistance (1). Obesity is always associated with increases in plasma triglycerides. Dyslipidemia includes hypertriglyceridemia, reduced HDL cholesterol, and increased numbers of small, dense LDL particles⁴. Elevated LDL cholesterol is not a feature of the dyslipidemia seen with abdominal obesity. Other features of the dyslipidemia of abdominal adiposity include elevated very low density lipoproteins (VLDL), and reduced HDL₂, which are the large buoyant antiatherogenic subspecies of total HDL. In some individuals, apo B levels may be elevated, reflecting

an increase in the number of small, dense lipoprotein particles (VLDL and LDL)⁵.

Epidemiology:

The World Health Organization (WHO) Regional Office for the Eastern Mediterranean (EMRO) held a regional consultation on establishing regional guidelines on dyslipidemia, obesity and diabetes, in Beirut, Lebanon, on 31 May–2 June 2004. The objectives were to review national and regional plans for dyslipidemia, obesity and diabetes primary prevention and care and to discuss the establishment of regional guidelines on dyslipidemia, obesity and diabetes primary prevention and care. Dr Hussein A. Gezairy, WHO Regional Director for the Eastern Mediterranean pointed out that there had been a rapid increase in diabetes along with other medical problems such as cardiovascular disorders in obesity, and was concluded as the fourth leading cause of death in the Region; out of a total adult population of 220 million, an estimated 17 million people had diabetes, and studies conducted in different populations of the Region had reported high prevalence rates for diabetes, varying from 7% to 25% in the adult population. In addition, many countries of the Region were reporting the onset of type 2 diabetes at an increasingly

younger age. People were presenting with type 2 diabetes in their 20s and 30s, and in some countries type 2 diabetes was emerging in children⁶. Analysis of the Second National Health and Nutrition Educational Survey (NHANES II) data (1999), which represent a random sample of US adults within a wide range of age and socioeconomic status, also shows an increase in triglyceride levels with increasing obesity in white men and women of all ages⁷. These cross-sectional data are supported by longitudinal data from the Coronary Artery Risk Development in Young Adults (CARDIA) Study, which also show that increasing weight is accompanied by increases in plasma triglycerides⁸.

Co- morbidities, various grade and severity associated with obesity

Obesity is defined as an excessive accumulation of in the body resulting in adverse effects on health of the individual⁹. Simple measures of obesity are widely used in clinical practice; BMI, and waist-to-hip circumference ratio (WHR). The most widely used method to define thinness and fatness is BMI, a ratio of weight in kilograms divided by height in meters squared (kg/m²). It has been correlated to morbidity and mortality risk in various populations¹⁰. Abdominal obesity is defined by easy-to-use parameters with WHR. Though BMI, WHR correlate well with each other, it is also believed that combined use of these parameters of generalized and abdominal obesity may be better in identifying people at risk of CVD than either of them alone¹¹⁻¹³. The currently recommended cut-offs of BMI recommended by World Health Organization include 18.5 - 24.9 kg/m² for normal, 25.0 - 29.9 for overweight and >30 kg/m² for obesity. The currently recommended cut-offs of WC (>102 cm in men and >88 cm in women) are not applicable to all the populations due to heterogeneity in the average levels of measurements and different relationship with cardiovascular risk¹⁴. In a study by Misra et al. WC cut-offs, 72 cm in women (sensitivity: 68.7%, specificity: 71.8%) and 78 cm in men (sensitivity: 74.3%, specificity: 68.0%) were observed to be optimum for identifying those with presence of at least one cardiovascular risk factor. WC cut-offs of ≥ 90 cm in men and ≥ 80 cm in women identified high odds ratio (4.2 & 2.2, respectively) for cardiovascular risk factors and those with a BMI ≥ 25 kg/m². The WC cut-offs of 102 cm and 88 cm in men and women, respectively, were much less sensitive in identifying those with at least one risk factor¹⁵. In the study by Vikram et al. among non-obese (BMI <25 kg/m²) individuals with WC in the range of 70-80 cm, men had significantly high odds for hypertriglyceridemia (3.2), and women had high odds for hypertension (2.5) and hypertriglyceridemia (2.5)¹⁶. In the study by Snehalatha et al. WC cut-offs of 85 and 80 in men and women, respectively, showed optimum sensitivity and specificity in identifying those with increased risk of T2DM. The corresponding WHR cut-offs were 0.88 and 0.81 for men and women, respectively¹⁷. In the study (n= 2350) from South India by Mohan et al. the optimal cut-offs for identifying any two risk factors was 87 cm for men and 82 cm for women¹⁸.

Clinical identification of the metabolic syndrome, according the ATP III definition.

At least three risk factors must be present for a diagnosis to be made (23).

Risk Factor	Defining Level
Waist circumference	≥ 40 inches (102 cm) in men ≥ 35 inches (88 cm) in women
Triglycerides	≥ 150 mg/dL
HDL-C	<40 mg/dL in men <50 mg/dL in women
Blood pressure	$\geq 130/\geq 85$ mmHg
Fasting glucose	≥ 110 mg/dL

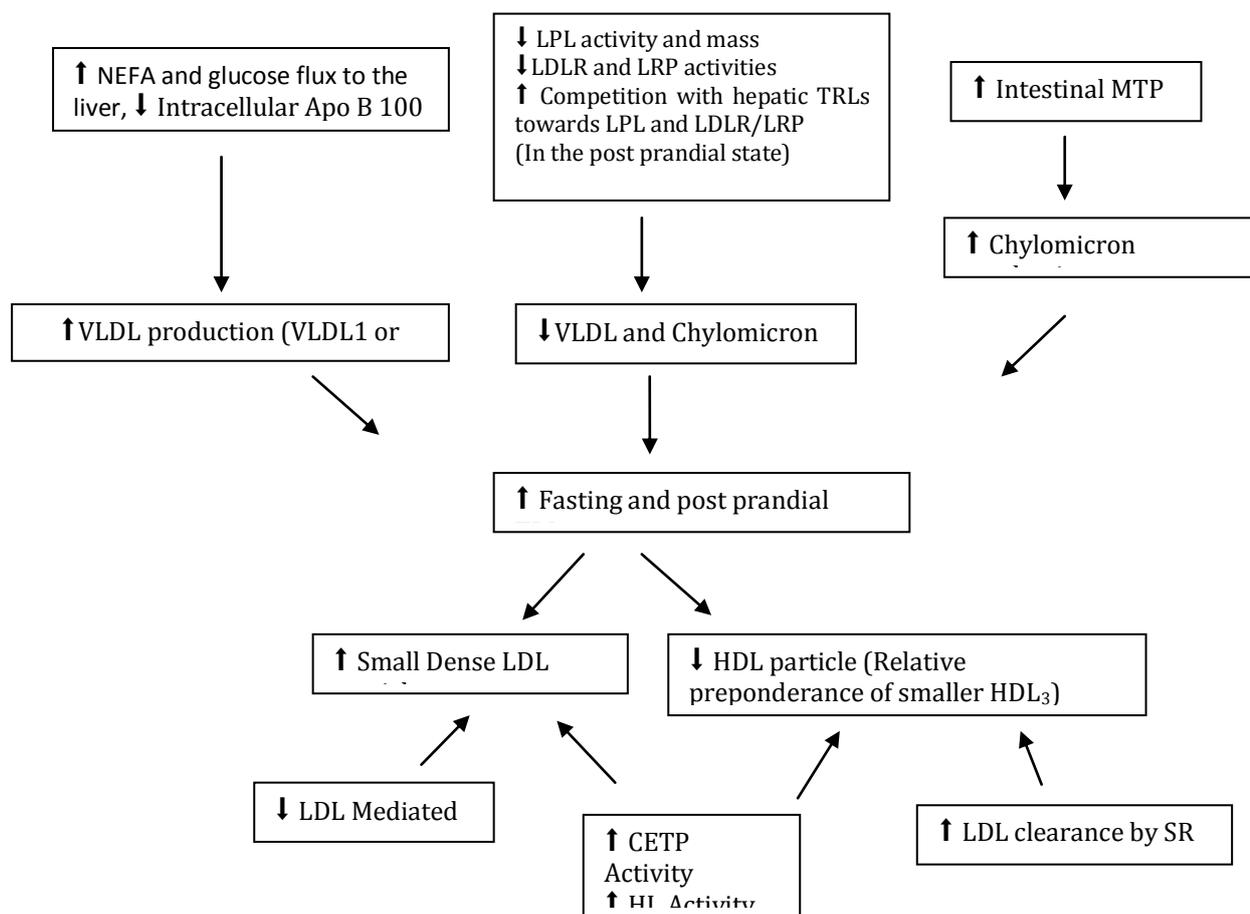
Cut-offs of BMI has been defined against various cardiovascular risk factors by several investigators. In a study in north India by Misra et al., (n= 2000), a BMI cut-off of >21 kg/m² was observed to be optimum in identifying individuals with at least one risk factor (T2DM, hypertension, hypertriglyceridemia and low HDL-c) with a sensitivity and specificity of 63.6% and 65.1%, respectively¹⁹. The cut-offs >23 kg/m² and >25 kg/m² showed higher specificities (79.2% and 90.7%, respectively) but much lower sensitivity (50.8% and 36.0%, respectively). These data have been supported by a study by Snehalatha et al. from South India. Vikram et al. reported that at least one cardiovascular risk factor was present in 66% and 88% non-obese (BMI <25 kg/m²) men and women, respectively²⁰. Non-obese individuals with percentage body fat in the highest quartile had significantly high odds for hypertriglyceridemia (men: 2.8, women: 3.9), hypertension (men: 3.7, women: 3.2) and T2DM (women: 1.3)²¹. Similarly, in patients with T2DM, BMI cut-offs of 22 kg/m² in men and 23 kg/m² in women showed optimum sensitivity and specificity in identifying those with high percentage body fat²². In a study by Mohan et al., the optimal cut-off in identifying any two risk factors was 23 kg/m² in both genders²³.

Dyslipidemia in obesity in relation to biochemical alteration leading various diseases

Dyslipidemia are disorders of lipoprotein metabolism, including lipoprotein overproduction and deficiency which is associated with obesity regardless of ethnic group. They may manifest as one or more of the following: elevated total cholesterol, low-density lipoprotein cholesterol (LDL), and triglyceride levels or as decreased high-density lipoprotein cholesterol (HDL) level with promotion of insulin resistance causing metabolic syndrome in obesity²⁴. Dyslipidemia is a widely accepted risk factor for coronary heart disease. Huges et al. showed that relative risk of MI correlates directly with increased TG and inversely with HDL-c levels in both caucasians and Asians Indians. Kaul et al. have found inverse co relationship between thrombus formation and HDL-c levels, with enhanced platelet-dependent thrombus at low HDL-c levels and vice versa. Bittner et al. have also observed the lower prevalence of Q wave MI on ECG in the subgroups of the patient with high HDL-c (>60mg/dl)²⁵. Hypertriglyceridemia is associated with insulin resistance in type 2 diabetes mellitus. There is a good correlation between insulin resistance and plasma TG

concentration, as TG may influence an early step in insulin action pathway; alternatively, insulin resistance may cause hypertriglyceridemia²⁶. With higher levels of glucose in the blood, more low density cholesterol is glycated. Glycation enhances the affinity of LDL for modified LDL receptors on macrophages, a process that promotes foam cell formation, endothelial cell toxicity and smooth muscle proliferation²⁷. With the growing prevalence of obesity, insulin resistance, and type 2 diabetes in our communities, prevention and management of this dyslipidemic state is critically important for the prevention of coronary artery and macrovascular disease²⁸. Hypertriglyceridemia has also been associated with abnormalities of clotting, the fibrinolytic system, and raised level of C-reactive protein, fibrinogen, plasminogen activator inhibitor (PAI), and IL-6, all of which may play an important role in the pathogenesis of CAD. Another factor that may play a role in atherogenic dyslipidemia and inflammation is peroxisome proliferator activated receptor – a (PPAR-a), a major regulator of intra and extracellular lipid metabolism. In addition, PPARs may play a central role in regulating the interaction between HDL cholesterol and apolipoprotein (apo) B containing lipoproteins²⁹. The hepatic overproduction of VLDL appears to be the primary and crucial defect of the insulin resistant state accompanying obesity and compensatory hyperinsulinemia. Inability to suppress hepatic glucose production, impaired muscle glucose uptake and oxidation, and inability to suppress release of nonesterified fatty acids (NEFA) from adipose tissue are the most important consequences of

insulin resistance in liver, muscle and adipose tissue, respectively. These events give rise to increased NEFA and glucose flux to the liver, an important regulator of hepatic VLDL production³⁰. VLDL particles are mainly cleared from circulation by the LDL receptor (LDLR), also referred to as apo B/E receptor. The transcription of the LDLR gene is regulated by intracellular cholesterol concentration, hormones, and growth factors. Sterol regulatory element binding protein-1 (SREBP-1) is selectively involved in the signal transduction pathway of insulin and insulin-like growth factor-I (IGF-I) leading to LDLR gene activation contributing to the delayed VLDL particle clearance associated with obesity causing insulin resistance³¹. Small, dense LDL concentration and fasting triglyceride levels seems to be more prone to modifications, such as oxidation and glycation (increased in the presence of high glucose levels), which may lead to increased production of antibodies against the modified apoB-100 and formation of immunocomplexes. Further, the reduced diameter of these particles increases the probability of their movement through endothelial fenestrations, thus placing them in the subendothelial space where inflammation, leukocyte ingestion, and transformation into plaque occur³². These modifications may result in a decreased LDLR-mediated clearance of small, dense LDL particles, possibly contributing to their elevated presence in plasma in obese and insulin-resistant individuals³³.



Biochemical alterations of dyslipidemia in obesity

Management of obesity and dyslipidemia:

The management of the obesity and dyslipidemia of the metabolic syndrome is achieved by lowering LDL and apo B and increasing HDL concentration. Statin treatment has been shown to reduce cardiovascular events in persons with low LDL cholesterol levels at baseline³⁴. The percent reduction in LDL cholesterol and apo B by statin medications is similar, but apo B may be a better marker of treatment efficacy in metabolic syndrome patients with normal LDL cholesterol³⁵. The LDL cholesterol has remained the primary target of lipid-lowering therapy, raising HDL levels is now an important secondary target to reduce CAD risk³⁶. Combination lipid-lowering therapy is frequently used to treat the dyslipidemia of the metabolic syndrome (increased triglyceride, reduced HDL, and small, dense LDL particles), if lifestyle changes (weight loss and exercise) are inadequate. Nicotinic acid and fibric acid derivatives both act to reduce triglyceride and increase HDL cholesterol. They are frequently used with statin medications. The fibrate monotherapy lowers plasma triglyceride levels, increasing in LDL levels. Bile acid resin binders lower LDL cholesterol levels, but can increase triglyceride levels in individuals susceptible to hypertriglyceridemia. The niacin is an inexpensive monotherapeutic agent that corrects the dyslipidemia of the metabolic syndrome, but it was found increasing glucose levels in some patients³⁷. Sibutramine has a positive effect on HDL-C with an increase of almost 21%, sibutramine has also been shown to achieve a reduction in Triglycerides of almost 18%. This HDL-C increase is three times greater than what can be achieved with a fibrate alone³⁸. Soluble fiber has been shown to modestly reduce total cholesterol and LDL cholesterol levels. Current dietary guide lines recommend a total daily fibre intake of at least 20 -30 g for adults, with 25% of the fiber being soluble fiber. Higher daily intake of soluble fiber promotes a further modest reduction of cholesterol values³⁹.

Conclusion:

The primary dyslipidemia related to obesity is characterized by increased triglycerides, decreased HDL levels, and abnormal LDL composition. The dyslipidemia associated with obesity no doubt plays a major role in the development of atherosclerosis and CVD, a life threatening diseases in obese individuals. All of the components of the dyslipidemia, including higher triglycerides, decreased HDL levels, and increased small, dense LDL particles, have been shown to be atherogenic. Lifestyle modifications, weight loss and exercise, dietary fibers and with weight loss medications can improve this dyslipidemia reducing CVD risk. In addition, obese individuals should be targeted for intense lipid-lowering therapy, when necessary.

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