Alexandria Journal of Medicine xxx (2017) xxx–xxx

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Contents lists available at ScienceDirect

Alexandria Journal of Medicine

journal homepage: http://www.elsevier.com/locate/ajme

Is sdLDL a valuable screening tool for cardiovascular disease in patients with metabolic syndrome?

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ARTICLE INFO

Article history:
Received 1 July 2016
Revised 29 October 2016
Accepted 9 January 2017
Available online xxxx

Keywords:
Small dense low density lipoprotein
Metabolic syndrome
Cardiovascular disease
Prevention
Atherogenic
Screening

ABSTRACT

Many patients with cardiovascular disease have their low density lipoprotein cholesterol within normal range. This raises the question about the most important lipoprotein to use as a marker of atherogenecity. In fact, small dense low density lipoprotein has recently been suggested as a strong predictor of cardiovascular disease. Among high risk patients, those with metabolic syndrome represent an important target population.

Different methods of small dense low density lipoprotein measurement were developed. Accordingly, two phenotypes of low density lipoprotein are recognized: Phenotype A (predominance of large buoyant low density lipoprotein) & phenotype B (predominance of small dense low density lipoprotein). However, none of the methods has been yet considered as a gold standard one. A lot of studies confirmed the role of small dense low density lipoprotein in the development of cardiovascular disease through atherogenic properties & clinical trials. However, others failed to do so. These discrepancies may be due to different sample sizes, different populations, different age groups, different methods of measurement & other possible confounding factors.

The aim of this review is to discuss the role of small dense low density lipoprotein as a valuable screening/preventive tool of cardiovascular disease in patients with metabolic syndrome.

Contents

Abbreviations: AAA, abdominal aortic aneurysm; AACE, American Association of Clinical Endocrinologists; ACS, acute coronary syndrome; AIS, acute ischemic stroke; ALP, atherogenic lipid profile; ARIC, atherosclerosis risk in communities; BMI, body mass index; CAD, coronary artery disease; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular diseases; DGU, Density Gradient Ultracentrifugation; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; GGE, gradient gel electrophoresis; GH, growth hormone; HDL, high density lipoprotein; HIV, human immunodeficiency virus; HT, hypertension; IDF, International Diabetes Federation; IMT, intima media thickness; IR, insulin resistance; KHGS, Korean Health and Genome Study; LDL, low density lipoprotein; LDL-C, Low Density Lipoprotein Cholesterol; LDL I, large buoyant LDL; LDL II, intermediate density LDL; LDL III, smaller dense LDL; MetS/MS, metabolic syndrome; NCEP:ATP III, National Cholesterol Education Program Adult Treatment Panel III; NMR, Nuclear Magnetic Resonance Spectroscopy; PCOS, polycystic ovary syndrome; PVD, peripheral vascular disease; RCTs, randomized controlled trials; SCORE, Systematic Coronary Risk Evaluation; sdLDL, small dense low density lipoprotein; sd-LDL-C, small density LDL-cholesterol; T2DM, type 2 diabetes mellitus; VAP, Vertical Auto Profile; VLDL, very low density lipoprotein; WHO, World Health Organization; WHR, waist–hip ratio.

Peer review under responsibility of Alexandria University Faculty of Medicine.

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http://dx.doi.org/10.1016/j.ajme.2017.01.002
2090-5068/

1. Introduction

1.1. Cardiovascular diseases: Definition and epidemiological studies

Cardiovascular diseases (CVD) include any medical conditions concerning the heart and blood vessels**;** such as coronary heart disease (CHD), strokes, peripheral vascular disease (PVD), and abdominal aortic aneurysm (AAA). Cardiovascular diseases are the main cause of morbidity and mortality worldwide. About 17.5 million people died from CVD in 2005. Among them, 7.6 million deaths were due to CHD and 5.7 million were due to stroke. We should be careful as regards progression of CVD, because about 20 million CVD deaths were estimated in 2015.[1] Many studies suggest that metabolic syndrome (MetS/MS) cases are more liable for future development of CHD and type 2 diabetes mellitus (T2DM).[2]

1.2. Definition of metabolic syndrome

Different definitions of MetS were established. According to National Cholesterol Education Program: Adult Treatment Panel III (NCEP: ATP III), MetS is defined by three or more of the following: waist circumference <_102 cm in men (or >_88 cm in women), triglycerides >_150 mg, high density lipoprotein (HDL) <40 mg/dl in men (or <50 mg/dl in women), fasting plasma glucose >_110 mg/dl, blood pressure >_130/85 mmHg.[3,4] According to the World Health Organization (WHO): Metabolic syndrome is defined by insulin resistance (identified by 1 of the following: T2DM, impaired fasting glucose, impaired glucose tolerance or for those with normal fasting glucose levels (<110 mg/dl), glucose uptake lower than the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions) plus any two of the following parameters: body mass index (BMI) > 30 kg/m^2, waist–hip ratio (WHR) > 0.9 in men (or >0.85 in women), triglycerides >_150 mg/dl, low HDL (<35 mg/dl in men or <39 mg/dl in women), blood pressure >_140/90 mmHg or antihypertensive medication, urinary albumin excretion rate >_20 μg/min or albumin:creatinine ratio >_30 mg/g.[5] Metabolic syndrome can be defined (according to the International Diabetes Federation (IDF)) by obesity, given as waist circumference <_94 cm in men (or <_80 cm in women) for Europeans, plus at least two of the following parameters: triglycerides <_150 mg/dl or treatment for hypertriglyceridemia, HDL < 40 mg/dl in men (or <50 in women) or treatment for this lipid abnormality, fasting plasma glucose (mg/dl) > 100 or diagnosis of diabetes mellitus, blood pressure <_130/85 mmHg or treatment for hypertension.[3] It should be noted that a lot of cases of metabolic syndrome are asymptomatic. They only present lately by symptoms of diabetes.[6]

1.3. Low density lipoprotein subclasses, phenotypes, reference values and methods of measurement

Some studies have shown that the use of hypolipidemic agents reduces CVD risk through the modification of Low density lipoprotein (LDL) particle size; however, the use of statins was associated with reduction rates of CVD less than 30%. To get better reduction rates, we should concentrate on the "**beyond cholesterol**" concept.

Low density lipoprotein particles include three subclasses (LDL I–III), LDL I (large buoyant LDL), LDL II (intermediate density LDL), and LDL III (smaller dense LDL). Different laboratory procedures can be used to separate LDL subclasses. Among them ultracentrifugation and electrophoresis have been mostly used for determining LDL subclasses**.** However, none of these methods has been established as a "gold standard" one.[7,8]

In fact, Gradient Gel electrophoresis (GGE) was considered as an important criteria of CHD risk. However, there is inadequate evidence that LDL subclassification by GGE improves outcomes in patients with CV disease.

Besides, as regards Density Gradient Ultracentrifugation (DGU), the Vertical Auto Profile (VAP) test measures the relative distribution of cholesterol within various lipoprotein subfractions, quantifying the cholesterol content in the VLDL, IDL, LDL, lipoprotein(a) and HDL subclasses. It includes LDL density and other components (i.e.pattern A versus pattern B).[9]

Concerning Nuclear Magnetic Resonance Spectroscopy (NMR), FDA clearance of NMR does not mean the test has clinical importance.[9] However, according to Mehta et al., measuring sdLDL by NMR were shown to be a strong predictor of CV events.[10]

In addition, the Ion-Mobility Analysis measures both the size and concentration of lipoprotein particle subclasses on the basis of gas-phase differential electric mobility.[9]

According to LDL particle size and density, the human lipid profile can be classified into two phenotypes: pattern A and pattern B. Pattern A is characterized by predominance of large buoyant LDL (LDL > 25.5 nm) and pattern B is characterized by predominance of small dense LDL (LDL $\leq$ 25.5 nm).[1,11,12]

Small dense low density lipoprotein (sdLDL) phenotype is expressed in adulthood as a result of genetic and environmental factors. Dyslipidemia, obesity and insulin resistance lead to expression of phenotype B.[4,12] For a given triglyceride level, women were found to have less sdLDL than men. On the other side, Korean males have a greater tendancy to develop a sdLDL phenotype than their Western counterparts.[13]

2. Atherogenic properties of small dense low density lipoprotein

Many experimental studies have explained the atherogenic properties of sd-LDL particles. Small dense low density lipoprotein particles have small size which enables them to penetrate easily into the arterial wall. They have also a high affinity for proteoglycans in the arterial wall, leading to prolonged residency in the subendothelial space.[4,8,14,15] Besides, the affinity of sd-LDL for LDL receptors is lower than larger LDL particles and its clearance from plasma is delayed.[4,14–17] Small dense low density lipoprotein particles are deficient in vitamin E and are highly susceptible to oxidization.[4,7,8,14,15] All these features explain the increased atherogenicity of small LDL subclasses.[1,7,8,13,18–20]

Please cite this article in press as: Zaki Khalil R.M.A., et al.. Alex J Med (2017), http://dx.doi.org/10.1016/j.ajme.2017.01.002