International Journal of Gerontology 12 (2018) 7–11

Contents lists available at ScienceDirect

International Journal of Gerontology

journal homepage: www.ijge-online.com

Review Article

Dyslipidemia Management for Elderly People with Metabolic Syndrome: A Mini-Review

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ARTICLE INFO

Article history:
Received 11 January 2017
Received in revised form
9 July 2017
Accepted 17 July 2017
Available online 23 August 2017

Keywords:
dyslipidemia,
metabolic syndrome,
older adults

SUMMARY

The proportion of people whose age exceeds 65 years is growing rapidly throughout the world and the prevalence of metabolic syndrome (MetS) is increasing among older adults. MetS had a two-fold increased risk for cardiovascular (CV) disease. Most patients with MetS exhibit atherogenic dyslipidemia, which includes elevated triglycerides (TG) and reduced high-density lipoprotein cholesterol (HDL-C). Therefore, physicians are advised to recognize the presence of dyslipidemia in elderly patients with MetS and provide appropriate therapy to reduce CV risk. Lifestyle modification is the initial step for treating dyslipidemia. For older adults with MetS who cannot attain treatment goals by lifestyle modification, pharmacological intervention is usually considered. Treating dyslipidemia in older adults with MetS requires knowledge of the benefits and adverse effects of various pharmacologic agents in the presence of possible multiple comorbidities. The purpose of this article is to review the evidence for recognition and management of atherogenic dyslipidemia in elderly individuals with MetS.

1. Introduction

The proportion of people whose age exceeds 65 years is growing rapidly throughout the world, and the prevalence of metabolic syndrome (MetS) is increasing among older adults. Cardiovascular (CV) and cerebrovascular events occur frequently in elderly patients and carry high morbidity and mortality, including the clustering of several metabolic and CV risk factors termed the metabolic syndrome (MetS). The most prominent components of MetS are abdominal obesity, high blood pressure (BP), impaired glucose tolerance, and dyslipidemia. The prevalence of MetS varies in different countries but, most commonly, is highly age-dependent, and older adults are at higher risk for developing MetS.[1,2] Insulin resistance (IR), which is prevalent in people with MetS, also parallels the increased age and predicted clinical events, including hypertension (HTN), coronary heart disease (CHD), stroke, cancer, and type 2 diabetes mellitus (T2DM).[3] Economic development, medical advances, and changes in socioeconomic status and lifestyles have greatly improved the quality of health in Taiwan, occurring along with rapid growth of the aging population. To face the increase in the number of older adults with MetS in Taiwan, it is essential to understand how to reduce the CV risk associated with MetS.

Atherogenic dyslipidemia is a key metabolic risk factor. Effective lipid management in older adults with MetS may reduce the risk of developing CV disease (CVD) with improvement of quality of life and may also potentially increase longevity. Therefore, this review article focuses on lipid management in older adults with MetS.

2. Prevalence of MetS in older adults in Taiwan

Table 1 summarizes several definitions of MetS provided by different organizations. The International Diabetes Federation (IDF), World Health Organization (WHO) and the National Cholesterol Education Programme (NCEP) have similar definitions of MetS and the corresponding CHD risk.[4] The Framingham Offspring Study[5] observed that MetS is equally associated with CVD using three separate MetS definitions, including those of NECP ATP III, IDF,

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http://dx.doi.org/10.1016/j.ijge.2017.07.001

Table 1
Diagnostic criteria for metabolic syndrome.

	WHO	EGIR	IDF	NCEP ATP III	Taiwan
Criteria	(Insulin re- sistance/Diabetes + >2)	(hyperinsulinemia + >2)	(Obesity + >2)	(≥3)	(≥3)
Central or general obesity	Waist/hip ratio> 0.9 inch males and >0.85 inch females or BMI ≥ 30 kg/m^2	WC for males ≥ 94 cm, females ≥80 cm	BMI ≥ 30 kg/m^2 or ethnic specific group WC cutoffs	WC for males ≥40 inch, females≥35 inch	WC for males ≥ 90 cm, female ≥ 80 cm
TG	TG ≥ 150 mg/dL	TG ≥ 180 mg/dL	TG = 150 mg/dL or treatment of this lipid abnormality	TG = 150 mg/dL or treatment of this lipid abnormality	TG = 150 mg/dL
HDL	HDL<35 mg/dL in males and <40 mg/dL in females	HDL< 40 mg/dL	HDL <40 mg/dL in males and <50 mg/dL in females or specific treatment for this lipid abnormality	HDL<40 mg/dL in males and <50 mg/dL in females or treatment for this lipid abnormality	HDL<40 mg/dL in males and <50 mg/dL in females
BP	≥140/90 mm Hg	≥140/90 mmHg or taking medication for HTN	SBP ≥ 130 or DBP ≥ 85 mm Hg or treatment of previously diagnosed HTN	SBP >130 or DBP >85 mm Hg or taking medication for HTN	SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or taking medication for HTN
Glucose	Insulin resistance required	Insulin resistance required (plasma insulin >75th percentile)	Fasting plasma glucose ≥100 mg/dL or previously diagnosed type 2 diabetes	Fasting glucose ≥100 mg/dL or taking medicine for high glucose	Fasting glucose ≥100 mg/dL, or use of insulin or other hypoglycemic agents
Others	Urine albumin ≥20 μg/min or Albumin/creatinine ratio ≥ 30 mg/g				

Abbreviation: WHO: World Health Organization; EGIR: European Group for the Study of Insulin Resistance; IDF: International Diabetes Federation; NCEP ATP III: National Cholesterol Education Program-Adult Treatment Panel III; BMI: Body Mass Index; WC: waist circumference; SBP: systolic blood pressure, DBP: diastolic blood pressure; BP: blood pressure; HTN: hypertension; TG: triglycerides; HDL: high density lipoprotein.

and European Group for the Study of Insulin Resistance (EGIR). Compared with other MetS definitions, the prognosis and risk management of these three definitions appear to be similar.

The prevalence of MetS increases with aging and varies widely depending on the definition, region, and population. Taiwan provides a typical example. Hwang et al.[6] showed that age-standardized prevalence of MetS was 15.7% using the modified ATP III criteria, 14.3% using the IDF criteria and 16.4% by the MetS -Taiwan criteria, and the prevalence of MetS increased with age in a Taiwanese population. Huang et al.[7] demonstrated that MetS is a common disorder in elderly Taiwanese, and the NCEP defined MetS prevalence in elderly patients to be as high as 21.5% in men and 37.6% in women.

MetS was shown to have a five-fold increase in the risk of T2DM and patients with MetS are at twice the risk of developing CVD over the next five to 10 years after diagnosis as compared to individuals without the syndrome.[8] In a meta-analysis of 21 studies, individuals with MetS had an increased incidence of CVD, CHD and stroke compared to those without MetS.[9] However, few studies have investigated the association between MetS and CV mortality in older adults. In the Health, Aging, and Body Composition (Health ABC) study,[10] subjects over age 70 years with MetS had greater risk of CV events but no significant difference in mortality was observed between older adults with and without MetS. In a study of non-diabetic older adults (age 65−74 years) in Finland,[11] MetS had an increased risk of CHD mortality but was not associated with all-cause mortality. In the Italian Longitudinal Study on Aging,[12] MetS increased risk of stroke and DM, but significantly increased CV mortality occurred only in older men. Older adults with MetS had a higher CVD and all-cause mortality in Taiwan compared to those without MetS.[13] Observations from epidemiological studies suggest associations between age-related increases in the prevalence of MetS and increased risk of CV mortality. Therefore, preventing CV diseases in older adults with MetS has become increasingly important issue.

3. Changes in blood lipids with aging

The prevalence rates of LDL-C ≥160 mg/dL, TG ≥ 200 mg/dL and HDL-C ≤35 mg/dL were 14.8%, 1.2%, 11.0% and 13.6%, 13.4%,12.9%, respectively, in Taiwanese men and women aged over 65 years.[14] Increased TGs, low HDL-C, and the presence of small dense LDL with normal or slightly increased LDL-C in MetS are called the atherogenic triad. Elderly patients with CVD are treated less aggressively and receive less evidence-based care. Clinical recognition and management of older adults with MetS emphasizes the importance of applying adequate treatment to reduce the risk of developing subsequent diseases. The following sections of this article will focus on how to manage dyslipidemia in older adults with MetS.

4. Goals of lipid lowering treatment

Previous studies have reported that high LDL-C, low HDL and high TG were associated with high CV adverse events.[15–17] The Taiwan lipid guidelines recommend the following: 1. For patients with acute coronary syndrome (ACS) and stable CHD, LDL-C < 70 mg/dL is the major target; 2. A LDL-C <55 mg/dL can be considered in ACS patients with DM; 3. For diabetic patients who are ≥40 years old, the LDL-C target should be < 100 mg/dL. After achieving the LDL-C target, combinations of other lipid-lowering agents with statins is reasonable to attain TG < 150 mg/dL and HDL-C >40 in men and >50 mg/dL in women with T2DM.[18] The effects of lipid lowering agents on blood lipid levels are summarized in Table 2.

Table 2
Effects of lipid lowering agents on blood lipid levels.

Agent	LDL-C	HDL-C	TG
HMG-CoA reductase inhibitors (statin)	Decrease	Increase	Modestly decrease
Cholesterol absorption inhibitor (ezetimibe)	Decrease	Very slightly increase	Slightly decrease
Fibric acid (fibrate)	Variable	Increase	Decrease
Nicotinic acid (niacin)	Decrease	Increase	Decrease

Abbreviation as Table 1; LDL: low-density lipoprotein-C.

5. Lifestyle modification

Most guidelines for preventing CV events recommend lifestyle modification as the foremost strategy for blood lipid therapeutic intervention. Few randomized clinical trials (RCTs) have reported clinical endpoints representing the benefits of different interventions and none have targeted older adults directly. A meta-analysis of the effects of exercise on blood lipid profiles among subjects aged over 50 years showed significantly reduced LDL-C by 2.5% and increased HDL-C by 5.6% but only modestly reduced TG by 5.9%.[19] Another study conducted in Europe revealed that adherence to a Mediterranean diet and healthful lifestyle had more than a 50% reduction in mortality among elderly subjects.[20] Replacement of dietary fat with sitostanol-ester margarine reduced LDL-C by 14.1%.[21] Green tea extract, used as an adjunct to low-saturated-fat diet therapy, produced an additional 16.4% reduction in LDL-C.[22] Although these measures can reduce cholesterol values, pharmacological treatment should be considered for those whose risk factors are not adequately reduced with preventive measures such as weight loss, diet, and exercise.[23] Most physicians prefer to prescribe drugs for each component of MetS rather than initiating a long-term strategy to change people's lifestyle, since MetS components respond readily to drug treatments. Thus, physicians should follow current treatment guidelines for treating dyslipidemia, lowering blood pressure and glucose.

6. Benefits and risks from statin trials

In a meta-analysis that included 14 RCTs of statins, a 12% reduction was found in total mortality, 19% reduction in coronary mortality and 17% reduction in fatal or non-fatal stroke per mmol/L reduction of LDL-C.[24] However, very few studies have reported results separately for subjects in the older age group. Two RCTs enrolling older adult subjects in secondary prevention reported results of statin therapy. In the PROSPER trial,[25] subjects aged 70–82 years were randomized to either placebo or 40 mg of pravastatin daily. Those receiving pravastatin had a significant 15% reduction in adverse CV events. In the SAGE trial,[26] intensive versus moderate statin therapy was examined in subjects aged 65–85 years with CHD who had experienced at least one episode of myocardial ischemia. Compared with moderate pravastatin therapy, intensive atorvastatin therapy was associated with fewer major acute CV events and a significantly greater reduction in all-cause death, illustrating the benefits of intensive statin therapy in older adults.[26] Also, a meta-analysis of patients aged ≥60 years enrolled in statin trials on CV prevention reported significant reductions in all-cause mortality by 15%, CHD deaths by 23%, fatal or nonfatal MI by 26%, and fatal or nonfatal stroke by 24%.[27] Another meta-analysis of 9 trials in elderly patients treated with statins estimated that the number needed to treat to save one life was 28.[28] In the T-SPARCLE study,[29] statin use increased the likelihood of achieving LDL-C <100 mg/dL.

Of note, statins are also shown to increase the risk of new-onset diabetes (NOD) among people with MetS.[30] However, in elderly Taiwanese subjects, atorvastatin or rosuvastatin was associated with lower risk of NOD but lovastatin and simvastatin significantly increased NOD.[31] Although myalgia is the most common adverse effect of statin use, no differences were shown in risks of myalgia, myopathy and rhabdomyolysis between treatment and placebo groups in a meta-analysis of statin use among adults aged over 65 years.[32] However, statin use in elderly patients should be done with caution because of age-related decreased muscle mass, frailty, impaired renal and liver function and drug-drug interactions due to polypharmacy, especially drugs that interact with cytochrome p450 enzymes. Statins are not associated with cognitive impairment in a meta-analysis of RCTs.[33]

7. Lipid lowering agents other than statins in older adults

In the ZETELD study,[34] adding ezetimibe to atorvastatin (10 mg) resulted in greater attainment of prespecified LDL-C levels than doubling or quadrupling the atorvastatin dose in patients aged ≥ 65 years old at high risk for CHD. Both treatments were generally well tolerated, with comparable safety profiles.

8. Triglycerides in older adults

In the Asia-Pacific region, TGs are considered an independent predictor of CHD and stroke risk.[35] TG and HDL-C were independent predictors of CHD mortality in elderly women.[36] TG > 200 mg/dL was also reported to be associated with increased CV events in elderly patients.[37] Hypertriglyceridemia therapy has not been fully addressed by guidelines, particularly for older adults.

Among the currently available lipid-lowering therapies, fibrates have the most obvious effect on lowering plasma TG levels. Although new data have appeared in recent statin trials enrolling elderly patients, there is a paucity of data involving other hypolipidemic agents. Meta-analyses of 18 trials demonstrated that fibrate therapy produced a 10% relative risk (RR) reduction for major CV events and a 13% RR reduction for coronary events.[38] In the FIELD study,[39] a subgroup analysis failed to show any benefit in older patients aged ≥ 65 years. Further studies are needed to assess the effects of fibrates on hypertriglyceridemia in older adults with MetS.

9. HDL-C in older adults

Low HDL-C levels were shown to be an inverse predictor of the risk of premature development of atherosclerosis.[40] In the AIM-HIGH trial,[41] ER-niacin + statin increased HDL-C by 25.0%. In a meta-analysis of 18 randomized trials, niacin or cholesteryl ester transfer protein (CETP) inhibitors did not influence CV mortality.[42] The effects of CETP inhibitors on CV outcomes have not yet been confirmed in large outcome trials.

10. Undertreatment of dyslipidemia in older adults

The rate of statin therapy was lower in elderly patients when discharged after ACS.[43] Increasing age was more likely associated with discontinued statins due to associated muscle pain.[44] Factors that influence the undertreatment of dyslipidemia in elderly patients are the presence of renal or liver dysfunction, sarcopenia, impaired cognitive function, reduced life expectancy and polypharmacy.

11. Optimal lipid management in older adults

Fig. 1 summarizes the management of dyslipidemia in older adults with MetS. Older people with MetS exhibited atherogenic

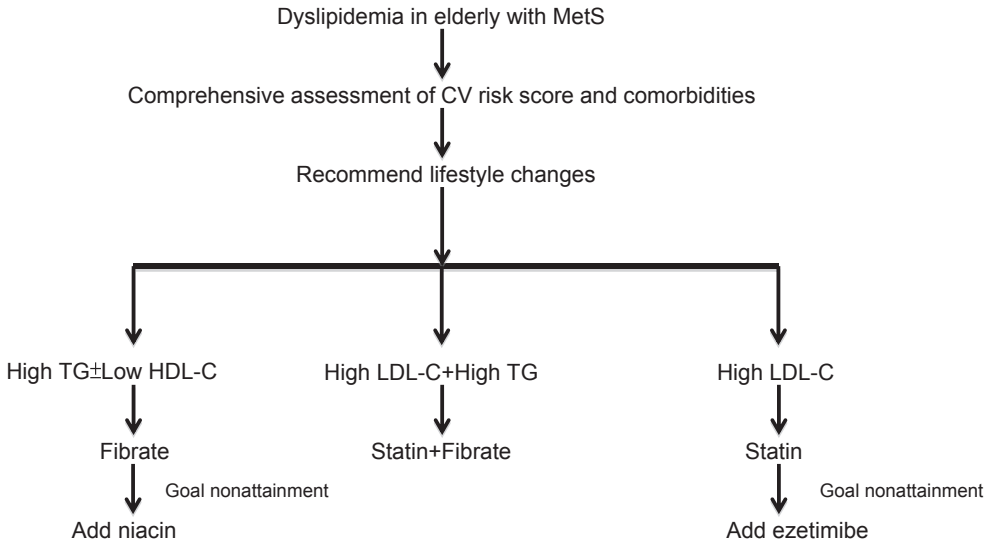

Fig. 1. Illustration summarizes the management of dyslipidemia in elderly with metabolic syndrome. Adjustment of dose is needed to be specially considered in elderly. Abbreviations: Mets: metabolic syndrome; CV: cardiovascular; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

dyslipidemia and had a high risk of CVD. A comprehensive assessment of CV risk scores and comorbidities should be performed in elderly patients prior to initiation of any lipid-lowering therapy. A few statin RCTs conducted in older adults showed similar RR reduction as that found in younger subjects. Ezetimibe can be considered if older persons cannot tolerate statins, and it can be added to low-to-moderate dose statin therapy in order to attain target LDL-C levels. Fibrates are recommended to treat mild to moderate hypertriglyceridemia in the presence of low HDL-C. RCT evidence of adding fibrates or niacin to statin therapy in high-risk patients with MetS is limited. In addition, maintaining optimal nutrition and lifestyle modification are important in elderly patients, and the participation of a dietitian in lipid management is necessary.

12. Conclusion

Older adults with MetS and dyslipidemia are prevalent. Current evidence suggests that aggressive management of dyslipidemia in people with MetS is just as important as treating other individual components of MetS. However, evidence from clinical trials of lipid lowering agents targeting dyslipidemia in older adults with MetS is limited. Further studies are needed to promote aggressive lipid management in elderly patients.

Conflict of interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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