Aged Garlic Extract

Impacting Cardiovascular Disease & Metabolic Syndrome with Aged Garlic Extract





PHARMACIST CONTINUING EDUCATION

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2 CEUs

Kyolic® Aged Garlic Extract™

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Impacting Cardiovascular Disease & Metabolic Syndrome with Aged Garlic Extract

Rhonda Dorren B.Sc.Pharm.

Learning Objectives

Upon successful completion of this lesson, you should be able to:

1. Discuss the epidemiology and pathophysiology of metabolic syndrome.
2. Discuss risk factors associated with metabolic syndrome and cardiovascular disease.
3. List various pathologies associated with cardiovascular disease and metabolic syndrome that aged garlic extract may have impact on.
4. Discuss the mechanism(s) of action of aged garlic extract in specific pathologies.
5. Recommend aged garlic extract for specific pathologies.

2

CEUs

Contents

Introduction

Metabolic syndrome, also known as “Syndrome X”, may overtake cigarette smoking as the number one risk factor for heart disease.[1] In recent years, evidence has emerged suggesting a number of natural health products can be used for the prevention and treatment of the metabolic syndrome and cardiovascular disease (CVD). This lesson will review the pathophysiology of metabolic syndrome and the potential clinical applications of aged garlic extract in the management of this syndrome.

Aged Garlic Extract (AGE)

More than 580 scientific studies in major universities have been completed on AGE. These studies have focused on aspects such as cholesterol, hypertension, homocysteine levels, inhibiting low density lipid (LDL) oxidation, anti-platelet aggregation and adhesion, stimulating blood circulation, immune stimulation, cognitive effects, liver function and anti-tumor effects. Importantly, investigators at the Research and Education Institute (REI) at Harbor-UCLA Medical Center have presented the evidence that AGE reduces and inhibits plaque formation at a Joint Vascular Conference, at the University of Munich, September 2007.[2]

AGE is a standardized and highly bioavailable supplement produced by prolonged extraction and aging of organic fresh garlic at room temperature. The garlic is sliced, stored in an aqueous ethanol solution in stainless steel tanks and naturally aged, without heating, for up to 20 months. Through this process, harsh and unstable organosulfur compounds, which can cause indigestion and the pungent odour that lingers on the breath and skin, are converted into mild, stable substances. This conversion that eliminates the odour-causing components, results in a truly odourless garlic that contains safe, bioavailable and beneficial compounds.[3]

AGE contains water-soluble allyl amino acid derivatives, which account for most of its organosulfur content, stable lipid-soluble allyl sulfides, flavonoids, saponins and essential macro- and micronutrients. The lipid-soluble volatile organosulfur compound allicin, which is produced enzymatically when garlic is cut or chopped, is absent in AGE. Allicin is an unstable and transient compound, undetectable in blood circulation after garlic ingestion. The aging process converts unstable compounds, such as allicin, to stable substances and produces high levels of water-soluble organosulfur compounds such as S-allylcysteine (SAC), AGE's major component, and S-allylmercaptocysteine, unique to AGE. SAC has a 98% absorption rate into blood circulation (high bioavailability) and is used as the control active for standardizing AGE. Other compounds that are present in AGE include: low amounts of oil-soluble organosulfur compounds, flavonoids, a phenol (allixin), selenium, and saponins.[3]

Scientific evidence has reported conflicting messages and variable results regarding garlic. The negative results obtained in some clinical trials may have resulted from usage of different garlic preparations, unknown active constituents and their bioavailability, inadequate randomization, selection of inappropriate subjects, and short duration of trials.[4]

Garlic supplements that are commercially available fall into one of four categories: dehydrated (dried) garlic (Kwai®), powder, (Garlicin®) garlic oil,/ garlic oil macerate (Super Garlic Oil, Jamieson®) and AGE. When considering a garlic preparation, importance lies in the bioactive components including their identity, bioavailability and metabolism. The preparations must be standardized if clinical outcomes are expected. Scientific evidence such as randomized controlled trials are important requiring correct methodology, providing data on morbidity and mortality, biochemical markers, dosages and timelines.[5]

Metabolic Syndrome and Cardiovascular Disease

The key components of Metabolic Syndrome are dyslipidemia, dysglycemia, and hypertension, which are all major risk factors for cardiovascular disease. Other factors may include: hyperinsulinemia and/or insulin resistance, abdominal obesity, hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, elevated fasting glucose, hypertension, increases in proinflammatory (e.g. C-reactive protein (CRP), interleukin-6 (IL-6), etc.) and prothrombotic (e.g. fibrinogen, etc.) markers.[1]

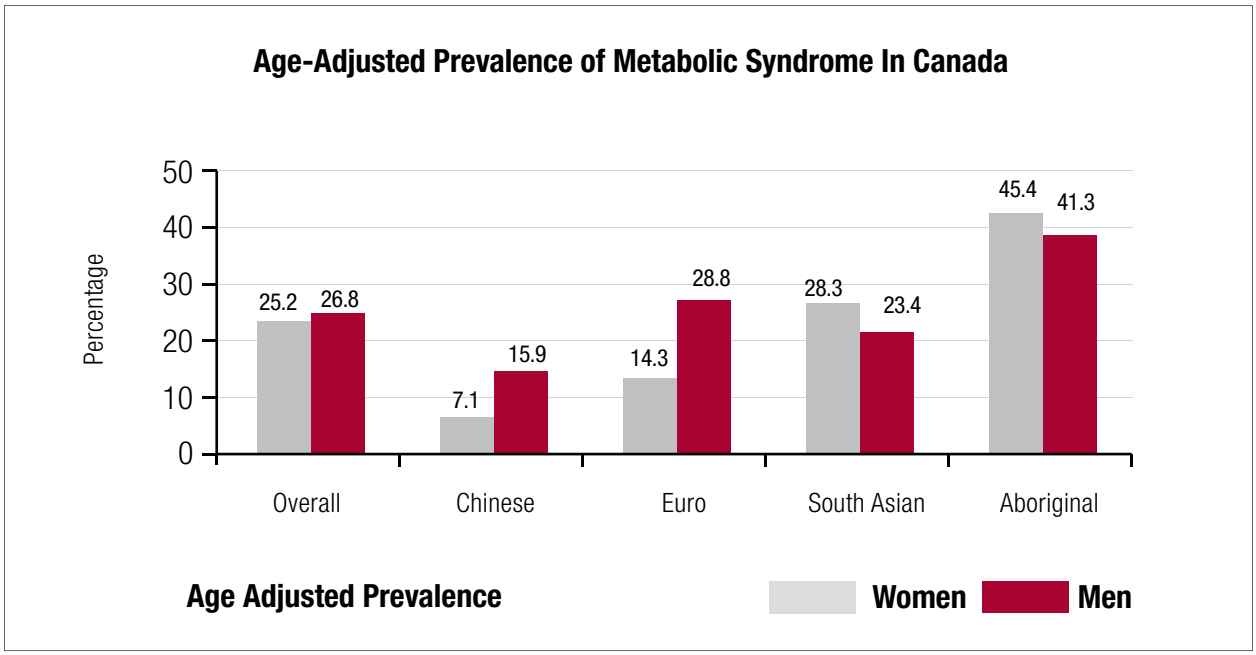
The composite coronary risk factors associated with metabolic syndrome are hypothesized to occur as a consequence of various factors such as lifestyle.[6] In the presence of metabolic syndrome, the relative risk for death from coronary heart disease (CHD) increases 3.7-fold and the relative risk for death from all causes increases 2.4-fold.[7]

Metabolic syndrome is complex requiring health care providers to investigate for numerous risk factors, and it encourages behavioral therapy rather than just pharmacological treatment of the risk factors.

Prevalence of Metabolic Syndrome

Metabolic syndrome has become a common condition, no longer are there a small number of individuals with metabolic syndrome, currently a significant percentage of society has metabolic syndrome. The INTERHEART study, conducted in 52 countries reported a global presence of metabolic syndrome of 26% of the people.[8] The National Health and Nutrition Examination Survey (NHANES) data in the United States (US), of individuals 20 years of age and older, reported 25% of the population have metabolic syndrome with prevalence of more than 3 risk factors (described below), and 71% of have 1 risk factor.[9] A randomized controlled trial (RCT) examining randomly sampled Canadians (n=1276) reported the prevalence of metabolic syndrome in Canada as 25.8% (95% CI, 23.5 to 28.2) (Chart 1).[10]

Chart 1



Source: Anand S, et al. Circulation. 2003 jul 29;108(4):420-5

Etiology of Metabolic Syndrome

The pathophysiology of metabolic syndrome is extremely complex. The syndrome is progressive, beginning with borderline (straddling the dividing line between two categories) risk factors that eventually progress to categorical (definitely relating to a specific category) risk factors. The constellations of risk factors that are associated with metabolic syndrome are of metabolic origin, and are accompanied by increased risk for CVD and type 2 diabetes.[11]

While the adverse clustering of cardiovascular risk factors includes hypertension, glucose intolerance, high triglycerides, low HDL concentrations, atherogenic dyslipidemia, prothrombotic state, and proinflammatory state; several other metabolic abnormalities are also associated with this syndrome, including obesity, microalbuminuria, and abnormalities in fibrinolysis and coagulation. Insulin-resistance is often a common denominator of metabolic syndrome which is associated with obesity, type 2 diabetes, and in many cases with hypertension, hypertriglyceridemia and low levels of HDL.[6] However, individuals with metabolic syndrome may not present with insulin resistance. Exacerbating factors of metabolic syndrome are physical inactivity, advancing age, and endocrine and genetic factors (Table 1).[11]

Primary treatment of metabolic syndrome is lifestyle therapy such as weight loss, increased physical activity, and diet modifications. A diet that includes greater fruits, vegetables, whole grains, monounsaturated fats, and low-fat dairy products may benefit most patients with metabolic syndrome. Explicit dietary changes considered appropriate for addressing the different aspects of metabolic syndrome are often suggested: reducing saturated fat intake to lower insulin resistance, reducing sodium intake to lower blood pressure, and reducing high-glycemic-index carbohydrate intake to lower triglyceride levels. Five symptoms common to most definitions of metabolic syndrome are those that may be reliably improved by carbohydrate restriction. A carbohydrate restricted diet, whether fat or protein or a combination of both is substituted for calorie requirements, may: have a lowering effect on triglycerides (TC), result in raising HDL, improve TC/HDL ratios, increase insulin sensitivity and glycemic control, and cause a reduction in blood pressure and weight. These potential positive impacts on the risk markers of metabolic syndrome are promising, especially with recent data that suggests that even without weight loss, such improvements to the various risk factors are seen when carbohydrate restriction is followed.[12] However, as the condition progresses, intervention therapies directed toward the individual risk factors might be required.[11,13]

Table 1

Possible Risk Factors of Metabolic Syndrome	
Atherogenic dyslipidemia	Elevations of lipoproteins, apolipoprotein B, elevated triglycerides, increased small particles of LDL, and low levels of high-density lipoproteins (HDL)
Elevated plasma glucose	Pre-diabetes or diabetes
Prothrombotic state	Anomalies in procoagulant factors (e.g. increases in fibrinogen and factor VII), anti-fibrinolytic factors (e.g. increases in plasminogen activator inhibitor-1), platelet aberrations, and endothelial dysfunction
Proinflammatory state	Elevations of circulating cytokines and acute phase reactants (e.g. C-reactive protein)
Source: Grundy. JACC. 2006;47(6):1093-1100.	

Pathophysiology of Metabolic Syndrome

The pathogenesis of metabolic syndrome is multifactorial. Obesity and insulin resistance are major underlying risk factors. Risk associated with obesity is best identified by increased waist circumference (abdominal obesity). Insulin resistance can be secondary to obesity but not always and insulin resistance can have genetic components as well. Several other factors exacerbate metabolic syndrome: physical inactivity, advancing age, endocrine dysfunction, and genetic aberrations affecting individual risk factors.[14-18] The risk factors of metabolic syndrome are of metabolic origin and consist of atherogenic dyslipidemia, elevated blood pressure, elevated plasma glucose, a prothrombotic state, and a proinflammatory state.[11,18]

Research from various clinical trials indicates that the risk of CVD and diabetes, accompanying a diagnosis of metabolic syndrome, is greater than the sum of the risk of the individual risk factors.[11] Metabolic syndrome risk is very difficult to assess and a number of different diagnostic criteria have been proposed. In Canada, metabolic syndrome is defined as having three or more of the risk factors: abdominal obesity, insulin resistance, elevated fasting glucose, elevated plasma triglyceride levels, low HDL levels and high blood pressure (Table 2).[19] The US NCEP/ATP III (National Cholesterol Education Program/Adult Treatment Panel) Guidelines, International Diabetes Federation (IDF), World Health Organization (WHO), and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) have unique and in some cases have adopted the same guidelines for identifying metabolic syndrome (Appendix 1).[20-23] In all cases, a fundamental behavioral intervention is recommended to reduce obesity and increase physical activity.

Table 2

Clinical identification of metabolic syndrome in Canada*	
Risk Factor	**Defining Level**
Abdominal obesity	
Men	Waist circumference >102cm
Women	Waist circumference >88cm
Triglyceride level	>1.7mmol/L
HDL-C level	
Men	<1.0 mmol/L
Women	<1.3 mmol/L
Blood pressure	> 130/85 mm Hg
Fasting glucose level	6.2-7.0 mmol/L
*Criteria 3 or more of the risk factors	
Source:Genest et al., CMAJ 2003;168(9):921-4	

Insulin Resistance, Impaired Glucose Tolerance (IGT) and Diabetes

Insulin resistance is a state in which a given concentration of insulin produces a less-than-expected biological effect, arbitrarily defined as the requirement of 200 or more units of insulin per day, to attain glycemic control and to prevent ketosis. The mechanisms responsible for insulin resistance syndrome include genetic or primary target cell defects, autoantibodies to insulin, and accelerated insulin degradation. While adiposity and insulin resistance are related, they are not necessarily synonymous, and each may make independent and different contributions to increasing the risk of CVD.[24,25]

When pancreatic beta cells fail to adapt adequately to insulin secretion, high insulin levels occur resulting in impaired fasting glucose (IFG) levels, impaired glucose tolerance (IGT), and type 2 diabetes (Table 3). Insulin resistance can play a major pathogenic role in the development of metabolic syndrome. The compensatory hyperinsulinemia that accompanies insulin resistance is one of the factors associated with increased risk of CVD. Individuals with insulin resistance present with endothelial dysfunction and a 40-50% decrease in nitric oxide (NO)-mediated vasodilation which also contributes to CVD.[24,25]

Table 3

Plasma Glucose Levels for Diagnosis of Impaired Fasting Glucose (IFG) Impaired Glucose Tolerance (IGT) and Diabetes.

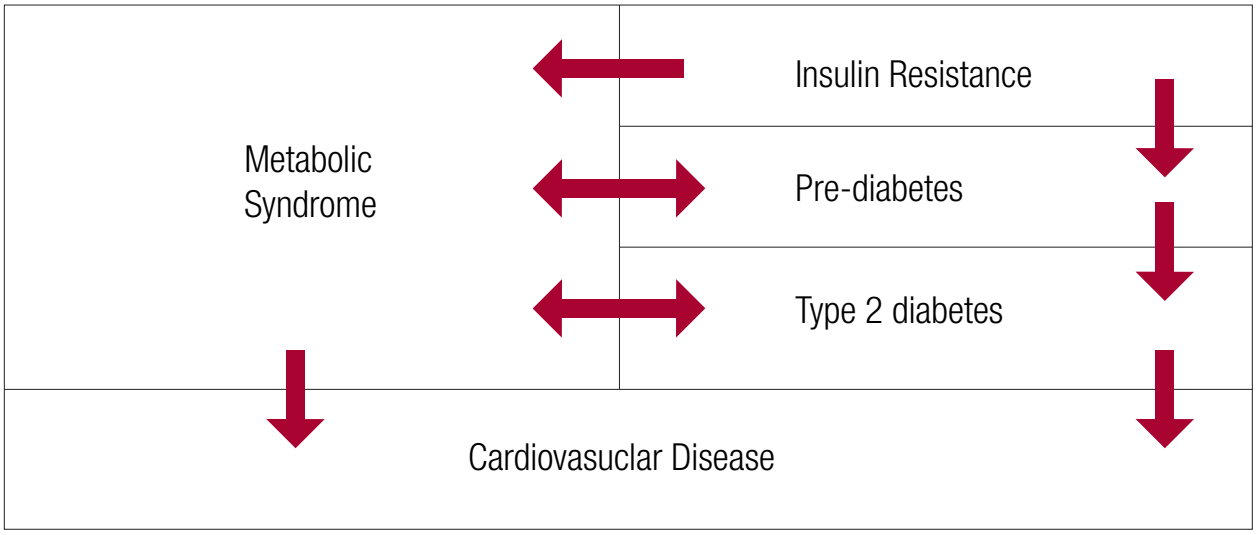
	FPG (mmol/L)		2hPG in the 75-g OGTT (mmol/L)
IFG	6.1–6.9		NA
IFG (isolated)	6.1–6.9	and	<7.8
IGT (isolated)	6.1	and	7.8–11.0
IFG and IGT	6.1–6.9	and	7.8–11.0
Diabetes	≥7.0	or	≥11.1

2hPG = 2-hour plasma glucose
FPG = fasting plasma glucose
IFG = impaired fasting glucose
IGT = impaired glucose tolerance
NA = not applicable
OGTT = oral glucose tolerance test

Source: Canadian Diabetes Association. Clinical Practice Guidelines 2003 [26]

Insulin resistance, IGT and IFG are not necessarily part of metabolic syndrome. However, people with IGT, particularly as a contributor to a diagnosis of metabolic syndrome, are at significant risk for the development of CVD. Indeed, some studies suggest that their vascular risk is almost as high as individuals with type 2 diabetes.[27] Type 2 diabetic patients pass through a phase of IGT to IFG known as, prediabetic state (Chart 2). The prediabetic state may form a part of metabolic syndrome, with other components such as obesity, hypertension, dyslipidemia, hyperinsulinemia and insulin resistance.[28] The transition from the early metabolic abnormalities that precede diabetes, IFG and IGT, to diabetes may take many years. Individuals over 50 years of age with diabetes, have an extremely high prevalence of the metabolic syndrome (86%).[29]

Chart 2



Source: JACC. 2006;47(6):1093-1100.[11]

Although the biochemical steps linking insulin resistance with metabolic syndrome have not been completely clarified, mounting experimental and clinical evidence indicates oxidative stress plays a central pathogenic role. Metabolic syndrome patients present with increased delivery of reactive oxygen species, decreased antioxidant protection and increased lipid peroxidation. Common associations supporting oxidative stress as a common event in a unifying pathogenic view are:

- Increased abdominal fat storage
- Liver steatosis
- Systemic oxidative stress
- Diminished concentration of NO derivatives and antioxidant vitamins
- Endothelial oxidative damages

Moreover, it has been observed that oxidative stress regulates the expression of genes governing lipid and glucose metabolism through activation or inhibition of intracellular sensors. Metabolic syndrome patients may express different disease features and extents, according to the different pathways activated by oxidative stress-modulated effectors.[30]

Obesity, Visceral Obesity and Waist Circumference

Metabolic syndrome is associated with dysregulated adipose tissue. Adipose tissue, previously believed to be a mere energy depot, is now considered a major endocrine organ regulating whole-body metabolism, as well as inflammatory and immune responses. These actions are mediated by a number of molecules collectively known as adipokines that are secreted by adipocytes, and act in an autocrine, paracrine, or endocrine fashion, adapting metabolic fluxes to the amount of stored energy. The discovery of such endocrine functions of the adipose tissue has prompted the hypothesis that a genetic dysregulation of the adipokine network may contribute to the pathogenesis of insulin resistance and related disorders such as type 2 diabetes and CVD. The proinflammatory state in the adipose tissue also leads to a local insulin resistance including an impaired inhibitory effect of insulin on free fatty acid (FFA) release and then insulin resistance further supports the proinflammatory state.[31-35]

Visceral obesity refers to the distribution of adipose tissue in the abdominal region. The accumulation of central fat plays a key role in the pathophysiology of metabolic disorders. Abdominal obesity, measured either by waist circumference or waist-to-hip ratio, is associated with insulin-resistance and the development of type 2 diabetes. Furthermore, abdominal obesity predicts subsequent coronary artery disease (CAD) better than body mass index (BMI).[36] Central fat accumulation and the presence of insulin-resistance have both been associated with a cluster of dyslipidemic features: elevated plasma triglyceride levels, an increase in very low density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL), presence of small dense LDL particles, and a decrease in HDL.[37]

Being overweight after menopause, results in worsening insulin resistance and elevations in adipocytokine levels.[38]

Cardiovascular Disease (CVD)

CVD is a disease of societal change that has led to altered lifestyles. Sparked by an obesity epidemic, the rising incidence of metabolic syndrome and type 2 diabetes have led to an upsurge of cardiovascular risk. Global increases in CVD are also attributed to factors such as a decrease in childhood and infectious disease leading to a greater aging population, increased tobacco use and urbanization (e.g. more automation, less physical activity, increased energy consumption, increased fat consumption and increased psychological stress).[39]

Metabolic syndrome confers cardiovascular risk beyond that which is associated with its component risk factors.[40] Individuals with metabolic syndrome only, have a 2.0-2.5 (women, men) increase risk of CVD. For women with diabetes and metabolic syndrome the increased risk of CVD is 8.2 and for men 3.1.[41] Metabolic syndrome is similar to a major risk factor for CVD like hypertension and smoking, and almost to the same magnitude as a CHD risk equivalent.

Atherosclerosis and Inflammation

Inflammation plays a major role in the development and progression of atherosclerosis. In atherosclerosis, an initial injury damages the endothelial cells lining the blood vessels. Injuries are caused by various factors: increased levels of oxidized low density lipoproteins (oxLDL), free radicals (e.g. as formed by cigarette smoking), infectious agents, or shearing stress placed on endothelial cells due to hypertension.[42] The endothelial cell wall injury triggers a cascade of events and the secretion of mediators that modulate the inflammatory response.[43]

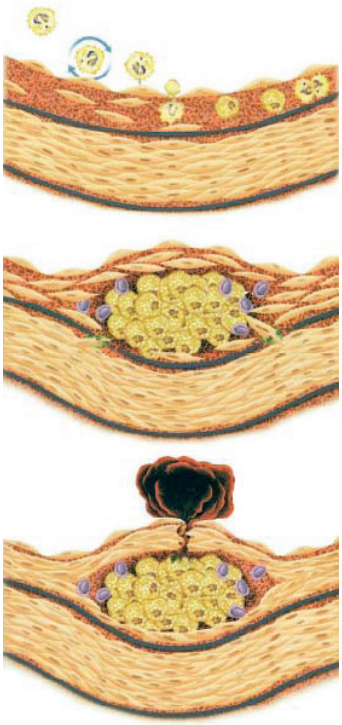
Calcium deposition occurs in the walls of coronary arteries as an active process, rather than a simple mineral precipitation in the atheromatous plaque. Calcification has been shown to be an early feature of atherosclerotic plaque formation, beginning with fatty-streak formation. The homeostatic properties of the surface of the endothelial cell become procoagulant allowing leukocytes and platelets to adhere. Nuclear factor kappa beta is released from monocyte/macrophages, smooth muscles cells, endothelial cells, and T cells. It initiates the transcription of cytokines involved in inflammation including tumor necrosis factor-alpha (TNF-alpha), chemokines such as monocyte chemoattractant protein-1 (MCP-1) and the vascular cell adhesion molecule-1 (VCAM-1). MCP-1 attracts circulating monocytes to the site of injury, and through binding to VCAM-1, monocytes adhere to the endothelial cell wall. The monocytes are then able to migrate across the endothelial barrier into the intima layer and differentiate into macrophages. They phagocytosize the increased amount of lipoproteins from the LDLs and transform into foam cells.[43]

Foam cells secrete pro-inflammatory molecules such as interleukin-1 (IL-1), IL-6, and TNF-alpha, which can contribute to additional leukocyte accumulation and induce smooth muscle proliferation, and migration from the medial layer into the intima. As more LDLs are taken up by macrophages, the arterial wall begins to thicken and an atheroma (core of lipids and necrotic cellular debris resulting from dying foam cells) is formed. The smooth muscle cells produce collagen which forms a fibrous cap over the atheroma. In order to compensate for the growth of the atheroma, the vessel dilates and allows for continuous blood flow.[43]

Eventually, the size of the atherosclerotic plague encroaches on the lumen of the blood vessel causing a reduction in blood flow. Plaque develops most commonly in areas of increased turbulence where direction of blood flow changes at branches and bifurcations. The continuous elaboration of the proteolytic enzyme, matrix-metalloproteinases (MMP), by the macrophages under the fibrous cap initiates a breakdown of the collagen. As a result, the cap weakens and eventually ruptures. The atheroma and its thrombotic material are exposed and leads to the formation of a thrombus and ensuing emboli. This is the event that can lead to a myocardial infarction (Schematic 1).[43]

Schematic 1

Events of atherothrombosis



Early Stage: Endothelial Dysfunction

- Impaired vasomotion
- Endothelial activation

➡ Leukocyte recruitment & invasion

Early Atherosclerotic Plaque: Fatty Streak

- Differentiation & proliferation of macrophages
- Lipid accumulation & foam cell formation

Advance Lesion

- Apoptosis of cells & further lipid accumulation

➡ Formation of necrotic core

- Immigration & proliferation of smooth muscle cells, production of extracellular matrix

➡ Formation of fibrous cap

Plaque Rupture

- Inhibition of collagen synthesis & expression of collagenases

➡ Prothrombic situation, platelet thrombus

Source: Weiss N. Vascular Symposium. Munich, Germany 2007.

C-Reactive Protein (CRP)

In addition to being a marker of inflammation, CRP plays an integral part in the inflammatory process of atherosclerosis. High concentrations of CRP mRNA have been demonstrated to be present in atherosclerotic plaques.[44] CRP activates macrophages to secrete the powerful procoagulant, tissue factor and may play a role in the decreased expression of NO in endothelial cells.[45] NO inhibits platelet aggregation, decreases vasoconstriction and the proliferation of smooth muscle cells.[46]

CRP has been shown to possess some proatherogenic properties that may influence the progression of atherosclerosis and has a direct pro-inflammatory effect on endothelial cells. CRP stimulates other cells including endothelial cells to develop chemokines (MCP-1), pro-inflammatory cytokines (IL-1, IL-6, TNF-alpha), and adhesion molecules such as intercellular adhesion molecule (ICAM-1) and VCAM-1 that will attract monocytes to the site of injury.[47,48] Macrophages are then able to adhere more readily to the endothelial cells.[43]

CRP present in atherosclerotic plaques binds to oxLDL and enhances the ability of macrophages to phagocytize LDL and form foam cells (through the CRP receptor CD32).[43]

High-sensitivity CRP (hs-CRP) testing has been shown to be a much better predictor of risk for CVD than traditional risk markers such as the cholesterol/HDL ratio.[49] The third National Health and Nutrition Examination Survey (NHANES III) reports, 24% of the population in the US has at least 3 of the components of metabolic syndrome and hs-CRP levels increase with the number of metabolic syndrome conditions.[9] Similar results linking high levels of hs-CRP to metabolic syndrome were seen in the Women's Health Study (WHS) study and the Insulin Resistance Atherosclerosis Study.[15,50] In the WHS, there was an increase in the rate of future CVD as the hs-CRP levels increased in subjects with metabolic syndrome. Determination of hs-CRP levels can aid in the diagnosis of metabolic syndrome and provide important risk information.[43]

Tumour Necrosis Factor Alpha (TNF-alpha)

Endothelial dysfunction occurring in metabolic syndrome is affected by the inflammatory cytokine TNF-alpha and subsequent production of the highly toxic free radical superoxide (O_2^-).[51] TNF-alpha upregulates expression of arginase in endothelial cells, which leads to O_2^- production and induces endothelial dysfunction in ischemia-reperfusion injury.[52]

Lipids

Atherogenic dyslipidemia in metabolic syndrome comprises hypertriglyceridemia, low levels of HDL and a preponderance of small dense LDL particles.[53]

High LDL and the presence of metabolic syndrome are established risk factors for CVD. The risk of coronary artery calcification (CAC) in asymptomatic individuals with moderate or high LDL is magnified in persons with metabolic syndrome. The relative risk for the presence of CAC with metabolic syndrome compared with that of moderate or high LDL cholesterol was evaluated in asymptomatic men (n=440, mean age 46 +/- 7 years, range 29 to 65). CAC was observed in 40% of the participants. Prevalence was lowest in participants without metabolic syndrome, and the highest in metabolic syndrome positive men.[54]

Given the increasing prevalence of metabolic syndrome with age, the reality that the proportion of the population aged 60 years or more is growing faster than any other age group, and the fact that the vast majority of cardiovascular events occur in older individuals, new solutions are required to reduce their risk.[55]

Oxidized LDL (oxLDL)

A real culprit is oxLDL. When LDL is oxidized, it acquires numerous new properties which are absent in the native or unoxidized LDL including new antigenic properties and new biologic activities. OxLDL induces accumulation of lipids in the arterial wall and promotes vascular dysfunction. It exerts direct cytotoxicity toward endothelial cells, increases chemotactic properties for monocytes, transforms macrophages to foam cells via scavenger-receptors and enhances the proliferation of various cell types, (e.g. endothelial cells, monocytes and smooth muscle cells). All of these events are recognized as contributing to atherogenesis. OxLDL therefore, increases the risk of atherosclerosis, cardiovascular, and cerebrovascular disease.[56,57]

Circulating oxLDL is a prognostic marker of CVD. Metabolic syndrome is associated with a higher fraction of oxLDL and higher levels of circulating oxLDL, making affected individuals a high-risk group for developing CHD. The oxidation of LDL is a potential contributing mechanism for the increased risk for myocardial infarction (MI) among those with the metabolic syndrome.[58]

Apolipoprotein (apo) B and apo A-I

Apo B and apo A-I are lipid-transporting apolipoproteins. ApoB transports all potentially atherogenic VLD, IDL and LDL particles. ApoA-I transports and acts as the major antiatherogenic protein in the HDL particles. The ratio of apoB/apoA-I is a simple, accurate and new risk factor for CV disease; the lower the apoB/apoA-I ratio, the lower is the risk.[59,60] Apo B concentrations, which reflect the number of small, dense LDL particles in plasma, are a significant predictor of cardiometabolic risk among adults with a high prevalence of metabolic syndrome, independent of waist circumference and CRP.[61]

Endothelial Dysfunction, Nitric Oxide and Hyperhomocysteinemia

Endothelial dysfunction manifests as an imbalance between normal vasodilatory and vasoconstrictory mediators, anti-coagulatory factors shifting to a more coagulatory environment, and proinflammatory mediators overcoming anti-inflammatory mediators leading to promotion of vascular cell growth. Functionally intact endothelium exerts potent anti-atherothrombotic effects whereas endothelial dysfunction plays a crucial role in the pathogenesis and progression of atherothrombotic vascular disease.[62,63]

Elevated plasma levels of homocysteine increase the risk for atherosclerosis, stroke, myocardial infarction, possibly Alzheimer's disease, cognitive impairment in the elderly, birth defects in pregnant women, and all-cause mortality.[64] Observational studies have demonstrated that lower homocysteine levels are associated with lower rates of CHD and stroke, and that folic acid, vitamins B6 and B12, lower homocysteine levels. Evidence is inconclusive as to the ability of supplements combining folic acid and vitamins B6 and B12 to reduce the risk of major cardiovascular events in patients with vascular disease or diabetes with or without consideration of homocysteine levels. Hyperhomocysteinemia is a risk factor for CVD independent of cholesterol and is related to a deficiency of folate, B6 & B12. Severe hyperhomocysteinemia could result from hereditary homocystinuria (e.g. homozygosity for defects in cystathionine beta-synthase, 5,10-methylenetetrahydrofolate reductase, or other enzymes of methionine metabolism).[65,66] The pathobiological mechanisms that lead to the atherogenic propensity associated with hyperhomocysteinemia are elevated homocysteine levels in the vascular endothelium, where it produces endothelial dysfunction and structural endothelial injury.[67]

Mildly elevated plasma homocysteine concentrations (12 mmol/L), are frequently found in Western populations. A meta-analysis of prospective clinical studies conducted in 2002, reported the presence of mild hyperhomocysteinemia is associated with a relative risk of 1.49 (95% CI 1.31–1.70) for CHD and a relative risk of 1.37 (95% CI 0.99–1.91) for cerebrovascular disease (CD).[68] Mild hyperhomocysteinemia has also been associated with peripheral arterial occlusive disease and venous thromboembolism.[69,70] Several arguments weigh in favor of hyperhomocysteinemia as a causative CV risk factor.[71,72] Homocysteine levels are increased in patients with metabolic syndrome; suggesting that this risk factors might be taken into consideration in addition to known risk factors during the evaluation of patients with metabolic syndrome.[73]

A key component of endothelial dysfunction is an impairment of the endothelium-dependent regulation of vascular tone, which is indicative of a reduction in the bioavailability of the endothelium-derived signaling molecule NO.[74] Besides regulating vascular tone, endothelium derived NO is able to mediate most of the other anti-atherothrombotic functions of the endothelium.[75] Therefore, a reduction in the bioavailability of NO constitutes an important step in the pathobiology of atherosclerotic vascular disease. Furthermore, the cellular antioxidant system of glutathione and glutathione peroxidase in regulating endothelial function system is crucial for maintaining normal endothelial function.[70, 76]

Smoking

Smoking is not included in the definition of the metabolic syndrome however smoking (1-5 cigarettes per day) increases the risk of the metabolic syndrome 1.5 fold which is thought to be a greater (stronger) risk factor than CRP.[77,78]

Traditional Prevention of Coronary Artery Disease (CAD)

Although lifestyle modifications, including improved diet and increased exercise levels benefit general health, metabolic syndrome and insulin resistance in particular, most people continue to resist changes in their daily routines. Thus, physicians must continue to educate their patients regarding an optimal balance of drug therapy and personal behavior. Treatment beyond LDL is still required since despite statin use in patients, 62-75% experience cardiovascular events. Correcting LDL only partially normalizes the risk of cardiovascular events.[79]

While pharmacologic treatments with the statin class of drugs have reduced cholesterol levels and lowered mortality rates, numerous large controlled clinical trials, including the Scandinavian Simvastatin Survival Study,[80] the Cholesterol and Recurrent Events trial,[81] the Air Force/Texas Coronary Atherosclerosis Prevention studies,[82] and Long-term Intervention with Pravastatin in Ischemic Disease study,[83] have indicated that cardiovascular events continue to occur in two thirds of all patients. Follow-up studies, such as the Heart Protection Study[84] and the Pravastatin or Atorvastatin Evaluation and Infection Therapy/Thrombolysis In Myocardial Infarction-22 Trials,[85] reinforced these earlier results. Although therapy with gemfibrozil, showed reduced occurrence of cardiovascular events in the Helsinki Heart Study[86] and the Veterans Affairs HDL Intervention Trial,[87] results of other studies, such as the Bezafibrate Intervention Program[88] and the Diabetes Atherosclerosis Intervention study,[89] showed less encouraging results.[79]

When patients are treated for hypercholesterolemia with statins, atherosclerosis is slowed by approximately 15% per year.[90] Many such events take place in patients presenting with type 2 diabetes and metabolic syndrome. There is new focus on combined atherogenic dyslipidemia which typically presents in patients with type 2 diabetes and metabolic syndrome. This mixed dyslipidemia (or “lipid quartet”) characterized by hypertriglyceridemia, low HDL, a preponderance of small, dense LDL particles and an accumulation of cholesterol-rich remnant particles (e.g. high levels of apolipoprotein B) has emerged as the greatest “competitor” of LDL among lipid risk factors for CVD. Pharmacologic therapy now considers various combination therapies of fibrates, niacin, ezetimibe and statins, since each regulate serum lipids by different mechanisms. Selection is made on the basis of their safety and effectiveness offering specific benefits in patients with combined hyperlipidemia as compared with statins monotherapy.[91]

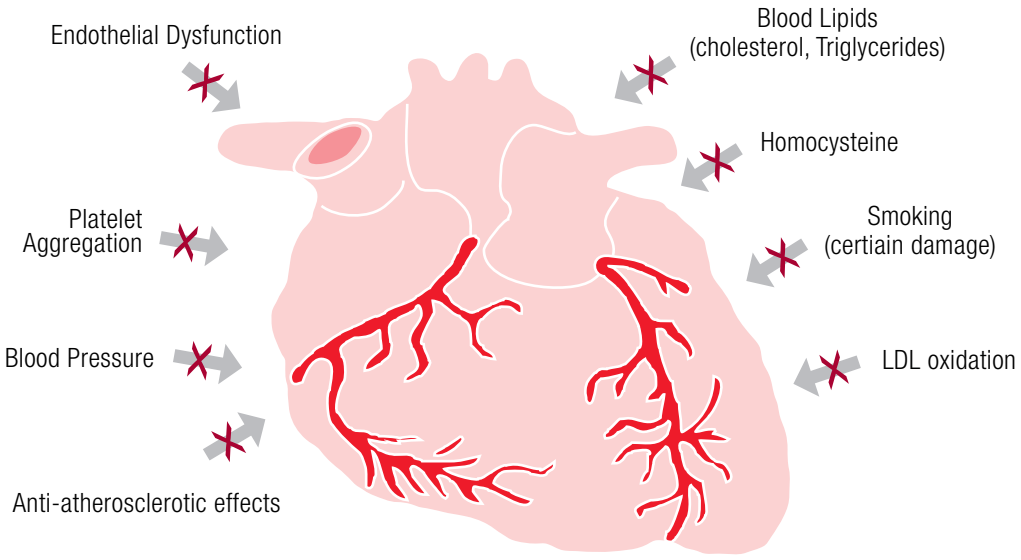
Patients with atherosclerotic disease treated with combination therapies such as antiplatelet therapy, statins, lipid lowering therapy, angiotensin converting enzyme (ACE) inhibitors, and beta blocking therapy still present with a 12-15% incidence of MI, stroke or death from cardiovascular disease.[92]

Aged Garlic Extract (AGE) and Cardiovascular Disease (CVD)

AGE has been shown to modulate cardiovascular risk factors in laboratory and human studies (Schematic 2) demonstrating cardioprotective effects listed as percentages of improvement (Table 4).

Schematic 2

Aged Garlic Extract Reduces Multiple Risk Factors in Cardiovascular Disease



Source: Budoff M. Associate Prof of Medicine. Div of Cardiology. Harbor-UCLA Medical Center. 2007.

Table 4

Cardioprotective Effects Found In Various Age Clinical Studies

	Improvement %
Platelet Adhesion[1,15]	34-58
Platelet Aggregation[1,15]	10-25
LDL Cholesterol[2,3,6,7]	5-12
Total Serum Cholesterol[3,4,6,7]	6-31+
Tryglycerides[4-6]	10-19
Blood Pressure[3,6]	6-8
Homocysteine[8,9]	24-35
LDL Oxidation[10,16]	35-51
Smoking Caused Oxidative Damage[11]	29-37
Microcirculation[12,13,14]	67
Plaque Progression[16]	67

Source:

1. Steiner, et al, 1994. J Amer Coll Nutr. 13(5): 524
2. Yeh, et al, 1995. J Amer Coll Nutr. 13: 545
3. Steiner, et al., 1996. Am J Clin Nutr. 64: 866-870
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AGE Cardioprotective Effects

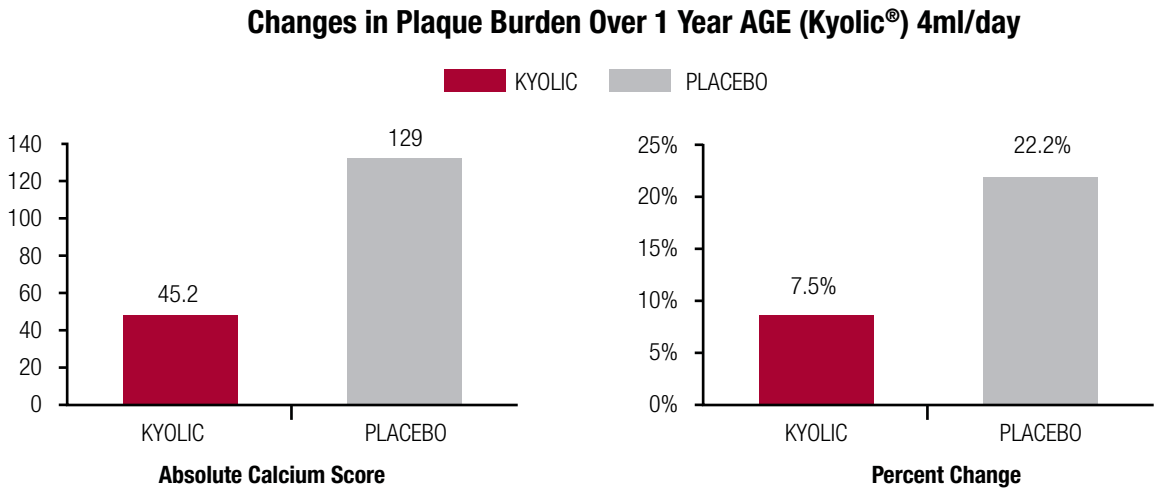
AGE has been shown in an intervention trial to impart cardiovascular benefits through multiple mechanisms by reducing numerous cardiovascular risk factors including blood pressure, cholesterol, platelet aggregation and adhesion, while stimulating NO generation in endothelial cells.[93] Moreover, laboratory investigations of AGE have been shown to improve endothelial function, inhibit endothelial cell damage, and transform smooth muscle cells through inhibition of smooth muscle phenotypic change and proliferation, and on lipid accumulation in the artery wall and into the macrophage.[94,95] Studies have also demonstrated positive clinical outcomes with AGE for HDL, LDL, reducing total cholesterol, LDL oxidation, smoking-caused oxidative damages and suppressing atherosclerosis.[96-99] Efficacy of AGE has been demonstrated in laboratory and human trials for controlling arterial function through inhibition of the damage of inducible nitric oxide synthase (iNOS) and modulating the formation of early atherosclerotic lesions, making it a useful intervention to help prevent atherosclerotic vascular diseases.[100,101]

AGE Inhibits Plaque Formation in the Coronary Artery

The total amount of coronary calcium (usually expressed as the 'Agatston score') predicts coronary disease events beyond standard risk factors, assessable by CT angiography using Multi-detector Tomography (MDT) or electron beam tomography (EBT).[102]

A placebo-controlled, double-blind, randomized study demonstrated a significant difference in the rate of atherosclerotic plaque formation as detected by EBT, demonstrating the potential ability of AGE to inhibit the rate of progression of coronary calcification over 1 year. Participants (n=23, mean age 59.9 6 +/- 10.5yr) all with known CAD were given 4 ml (1200mg) of AGE (Kyolic®) or placebo equivalent for one year. All patients were taking a stable dose of statin and aspirin throughout the study. The mean change of the calcium score (volumetric method) for the AGE group (n = 9) was 7.5% (+/- 9.4%) over 1 year. The placebo group (n = 10) demonstrated an average increase in calcium scores of 22.2% (+/- 18.5%), significantly greater than the treated cohort (P = 0.046). The study showed that patients on placebo (with statin baseline therapy) progressed at a rate of 22.2% per year, while the addition of AGE reduced progression to 7.5% (Chart 3).There were no significant differences in individual cholesterol parameters or CRP levels between the groups. Lipid peroxidation significantly decreased at follow-up period in both groups. Although the homocysteine changes did not achieve significance in this small study, there was a favorable trend toward reducing homocysteine for the treatment group. This study demonstrated the potential ability of AGE to inhibit the rate of progression of coronary calcification, as compared to placebo over 1 year.[103-105]

Chart 3



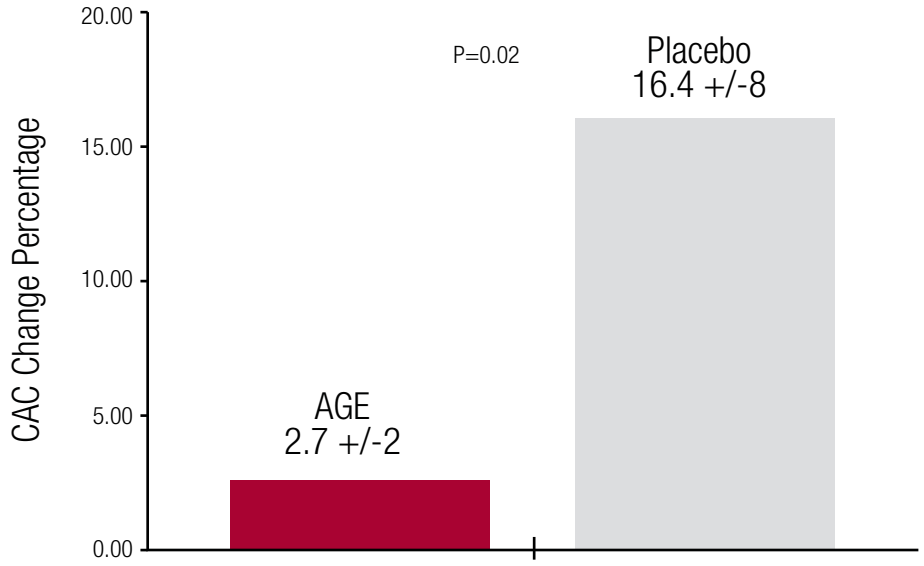
Source: Budoff et al. Prev Med. 2004 Nov;39(5):985-91

It is important to note that AGE is not recommended as an alternative, but rather in addition to statin drugs.[104] Individuals taking statin therapy or statin plus additional medications to reduce cholesterol, or who are at high risk for heart attack, may benefit from taking AGE. Dr. Matthew Budoff, lead researcher at Research and Education Institute (REI) at Harbor-UCLA Medical Center reported "AGE inhibited the rate of progression of coronary plaque formation, as compared to placebo over one year; AGE may be a useful and beneficial dietary addition for the people who have high cardiovascular risk or who have undergone heart surgery."[106] The value of these investigations for individuals on statin therapy is encouraging.[103,104] Statin treated patients still have great residual risk as seen particularly in diabetics since statin therapy fails to normalize lipid levels in these patients.[107]

This study was followed with a placebo-controlled, double-blind, randomized trial to determine whether AGE with a combination of folate, vitamin B6 and B12, and L-Arginine can change the rate of atherosclerotic plaque burden detected by electron beam tomography (EBT) as compared to placebo.[108] The outcome data was presented at the Vascular Symposium, Munich, Germany in September 2007. Intermediate risk patients (n=65) currently on statin therapy were enrolled and 58 patients (mean age 60 +/- 9 years, 79% participants male) completed the study protocol. Four capsules of AGE (250 mg), with Vitamin B12 (100mcg), Folic Acid (300 mcg), Vitamin B6 (12.5mg) and L-Arginine (100mg) in a capsule form or placebo was given to subjects for the duration of one year. The patients were well matched at baseline. Patients' cholesterol profiles and biomarkers of atherosclerosis including CRP, homocysteine and endothelial function were measured throughout the study. The preliminary conclusions reported the AGE group had less CAC progression (22 +/- 18 Agatston units) than placebo group (62 +/- 43) over 1 year (Chart 4). AGE significantly slowed the atherosclerosis process (Coronary Calcium) when added to statin and aspirin therapy. The AGE group demonstrated a change to lower total cholesterol, LDL, and homocysteine than placebo group and the AGE group had a significant increase in HDL as compared to placebo (Chart 5). There were no significant differences in individuals' triglyceride or CRP between the groups. In conclusion, the AGE group showed trends toward benefit for: HDL Cholesterol, LDL Cholesterol, Homocysteine, and Cholesterol:HDL Ratios. This study indicates the potential ability of AGE product including B-vitamins, L-Arginine and folate to retard progression of coronary artery calcification, and biomarkers of atherosclerosis including homocysteine independent of age, gender and conventional risk factors.[108]

Chart 4

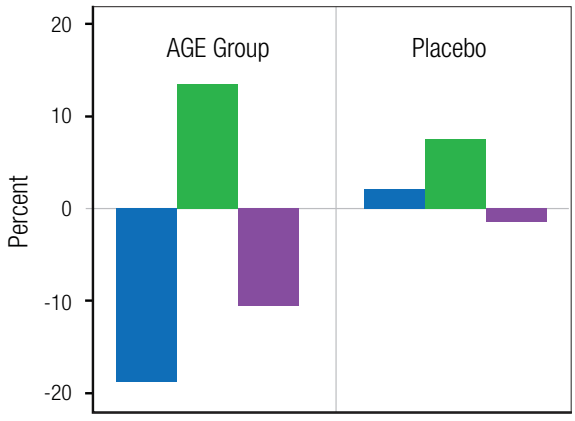
Calcium Score Changes in 1 Year Follow Up

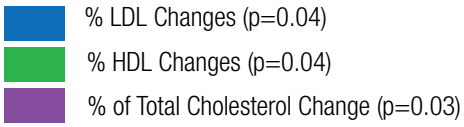


Source: Budoff. 2007 Vascular Symposium Munich, Germany[108]

Chart 5

AGE plus B-vitamins, L-Arginine and Folate Effects on Cholesterol Reduction





Absolute Changes in Values over One Year Follow Up

Variable	AGE Group	Placebo	P Value
Total Cholesterol	-16 +/-20	0.5 +/-25	0.03
HDL	7.25 +/- 6.7	3 +/- 7.2	0.03
LDL	-14.2 +/-22	1.5 +/-26.7	0.03

Cholesterol Changes in 1 year Follow Up

Source: Budoff. 2007 Vascular Symposium Munich, Germany[108]

AGE Mechanism of Action to Inhibit Atherosclerosis

AGE exhibits direct antiatherogenic effects through inhibition of smooth muscle phenotypic change and proliferation (the growth of smooth muscle cells over accumulated scar tissue in blood vessels), and impacts lipid accumulation in the artery wall and into the macrophage.[96] In general, intimal-cell hyperplasias followed by fatty streaks develop before arterial calcification.[101] Furthermore, by inhibiting damage of the endothelial cells and transforming smooth muscle cells as shown in the several studies using AGE, it may have an effect of controlling arterial function and improving endothelial function through inhibiting the damage of nitric oxide synthase (NOS). This mechanism is via increased NO production by activating constitutive NOS (cNOS), but not inducible NOS (iNOS).[109]

Toxic peroxynitrite, a powerful oxidant, is produced by the reaction of NO with superoxide and AGE protects erythrocytes from membrane damage induced by peroxynitrite. An increase in NO derived from cNOS and protection against peroxynitrite are important factors in the prevention of CVD.[109] Data suggests AGE may also increase glutathione levels and protection of endothelial cells by reducing oxidant stress, especially LDL oxidation.[104]

The possible mechanisms by which AGE may inhibit coronary plaque formation are listed in Table 5.

Table 5

Possible mechanisms by which garlic may inhibit atherosclerosis
• Inhibition of stenosis caused by damage induced by balloon catheterization (in vivo)
• Inhibition of cell transformation and cell growth in the smooth muscle cells (in vitro)
• Inhibition of lipid accumulation into macrophage (foam cells) (in vitro)
• Inhibition of LDL oxidation-caused endothelial cell damage in artery (in vitro)
• Inhibition of LDL oxidation-induced free radical generation from damaged endothelial cells in artery (in vitro)
• Inhibition of glutathione depletion from the endothelial cells (in vitro)
• Activation of cNOS (in vitro)
• Increase of Nitrous Oxide metabolites; cNOS activation (in vivo)
• Lowering of cholesterol, raising of HDL cholesterol (in vivo)
• Lowering blood pressure (in vivo)
• Reduction of homocysteine (in vitro)
• Improvement of endothelium function (in vivo)
Source: Budoff. J. Nutr. 2006;36:741S–744S.

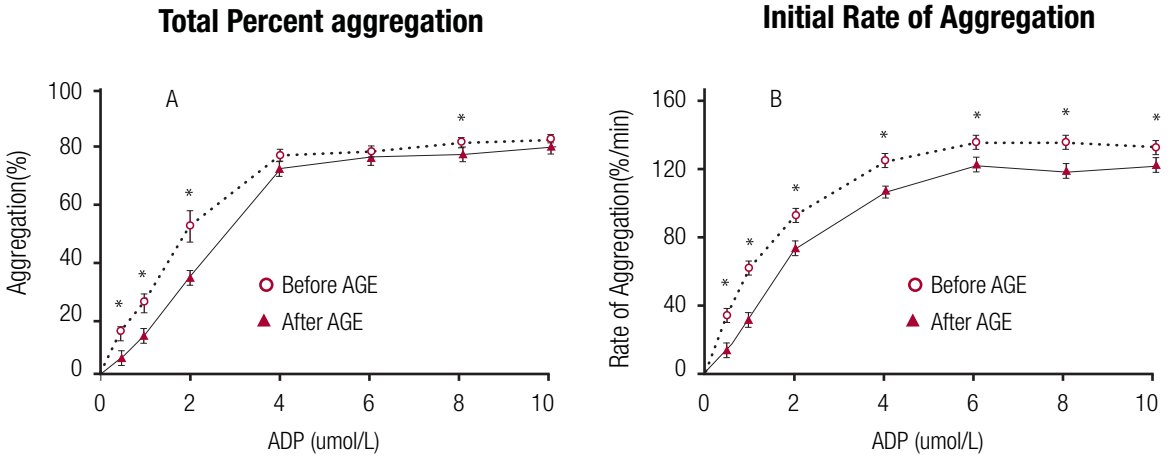
AGE - Circulation and Platelet Aggregation

Supplementation with AGE may significantly inhibit both the total percentage and initial rate of platelet aggregation.

In a 10-month placebo controlled study comparing the effect of AGE (7.2 g/day) with placebo, on the lipid profiles of moderately hypercholesterolemic men, AGE improved blood flow by reducing platelet aggregation. After three months, subjects taking AGE showed 33% less platelet aggregation and after six months showed 43% less aggregation than the placebo group. Furthermore, platelet adhesion to fibrinogen was reduced by approximately 30% in subjects taking AGE compared to placebo.[110] In a 44 week double-blind, crossover trial of normal individuals (n=28), AGE (or placebo) was given at a dosage of 3 capsules/day (each 800 mg) for 6 weeks, 6 capsules/day for 6 weeks, and 9 capsules/day for 6 weeks. This intervention period was followed by a 2-week washout and subjects were switched. A final 2-week washout period concluded the study. AGE demonstrated selective inhibition on platelet aggregation and adhesion. Platelet functions are important for the development of cardiovascular events such as myocardial infarction and ischemic stroke.[97]

In human subjects with normal cholesterol levels, AGE significantly inhibited both the total percentage and initial rate of platelet aggregation induced by adenosine diphosphate (ADP) (Chart 6). This 13 week RCT demonstrated both the rate of clotting and the amount of clotting were significantly inhibited in patients taking AGE in the first stage of platelet aggregation. The normolipidemic participants (n=23, 12 men, 11 women, age range 22-45) ingested 5 mL (=1500 mg) of AGE (Kyolic®) per day. Thus AGE, when taken as a dietary supplement by normolipidemic subjects, may be beneficial in protecting against CVD as a result of inhibiting platelet aggregation.[98]

Chart 6



N=23; platelet aggregation studies before and after 13 weeks of ingestion of AGE

Source: Rahman et al. J. Nutr. 2000;130:2662–2665.

Mechanism of Action

AGE acts in a synergistic manner in its inhibitory effect on platelet aggregation. The mechanisms involved appear to be multiple in nature and may involve membrane fluidity changes, inhibition of phospholipase C, inhibition of calcium mobilization, increase in NO and cAMP production, and inhibition of ThromboxaneA2 (TXA2), all of which may lead to an inhibition of platelet aggregation.[111]

AGE - Cholesterol Reduction

Studies have shown that AGE has an ability to reduce cholesterol.[93,112,113] A double-blind crossover study comparing the effect of AGE with a placebo on blood lipids was performed in a group of 41 moderately high hypercholesterolemic men. The participants were advised to adhere to a National Cholesterol Education Program Step I diet. AGE (7.2 g/day) or placebo was administered as a dietary supplement for a period of 6 months, then switched to the other supplement for an additional 4 months. Major findings were a maximal reduction in total serum cholesterol of 6.1% or 7.0% in comparison with the average concentration during the placebo administration or baseline evaluation period, respectively. LDL was also decreased 4% by AGE when compared with average baseline values and 4.6% in comparison with placebo period concentrations.[112]

In a five-month, double-blind, randomized, placebo-controlled intervention study of free-living hypercholesterolemic men, AGE was found to reduce total plasma and LDL-cholesterol by 7% and 10%, respectively. The cholesterol-lowering effects demonstrated in this study could not be attributed to dietary modification but rather to the daily supplementation of the garlic extract since no change in the participants' diet was included. Plasma concentrations of HDL cholesterol and triacylglycerol remained constant throughout the study in the subjects regardless of the treatment.[113]

A clinical trial investigated LDL concentration in a parallel-design of adults (n=192) with moderate levels of LDL (130-190 mg/dL or 3.36-4.91 mmol/L). Participants were randomly assigned to one of the following four treatment arms: raw garlic, powdered garlic supplement, AGE supplement, or placebo. Garlic product doses equivalent to an average-sized garlic clove were consumed 6 days per week for 6 months. Fasting plasma lipid concentrations were assessed monthly. None of the forms of garlic used in this study, including raw garlic, when given at an approximate dose of a 4-g clove per day, 6 days per week for 6 months, had statistically or clinically significant effects on LDL or other plasma lipid concentrations in adults with moderate hypercholesterolemia.[114] Differences in the outcomes of this study may be attributed to the inadequacy of the study's plan for compliance measurement; investigators failed to measure the blood concentration of active compounds and therefore had no reliable method to prove people took what they were supposed to. Checking compliance markers in blood is very important to prove reliable results. Also, the LDL range of the test group who participated in the study was in a fairly normal range and in the case of AGE, it is known to work well with relatively high LDL levels. Thus for this study to be more meaningful, solid compliance measurements and a longer test period, given the participants relatively normal LDL levels to start with, would be required.

Mechanism of Action

The mechanism of hypocholesterolemic action of AGE is postulated as stemming in part from inhibition of hepatic cholesterol synthesis, specifically inhibition of squalene monooxygenase and beta-hydroxy-beta-methylglutaryl-CoA (HMG-CoA) reductase. The water-soluble organosulfur compounds, especially SAC, are inhibitors of cholesterol synthesis, and hence may be the major principles of AGE responsible for the reduction of plasma cholesterol level.[113]

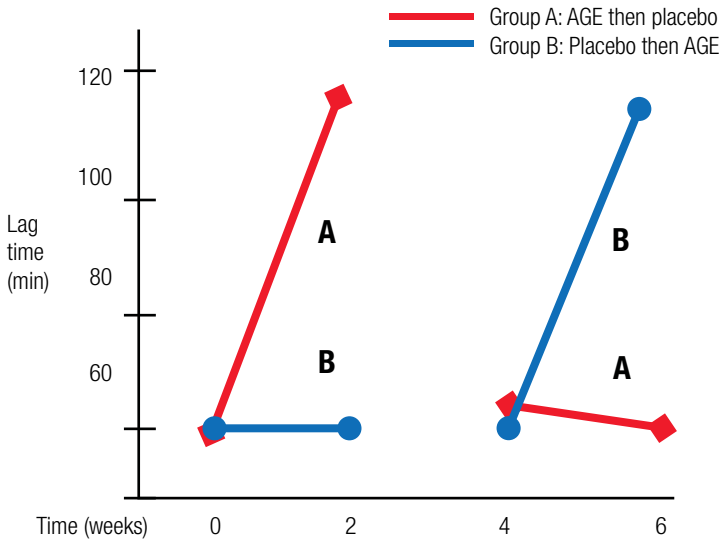
AGE - Reduction of Oxidized LDL (oxLDL)

The real culprit in CVD is oxLDL. Suppression of LDL oxidation may be one of the most powerful mechanisms accounting for the beneficial effects of AGE. Oxidized LDL damages blood vessels by directly damaging cells lining the vessels and transforming immune cells into foam cells which are more likely to adhere to and cause damage to the lining of vessels. The difference between LDL and oxLDL is similar to the difference between a marble and a burr going though the veins. AGE and its constituents have been shown to not only prevent the oxidation of LDL, but also to prevent oxidized LDL from damaging membranes, oxidizing lipids (fats) and damaging or killing cells.[115-117]

Early research demonstrated AGE's ability to enhance resistance to LDL oxidation. Participants were supplemented daily with one of: 6 g raw garlic; 2.4 g AGE; or 0.8 g DL-alpha-tocopherol acetate for 7 days to determine the effect on the susceptibility of LDL particles to Cu2+-mediated oxidation. LDL isolated from subjects given either alpha-tocopherol or AGE, but not raw garlic, was significantly more resistant to oxidation than LDL isolated from subjects receiving no supplements. These results suggest that if antioxidants are proven to be antiatherogenic, AGE may be useful in preventing atherosclerotic disease.[118]

A double-blind, placebo-controlled, crossover study involving 20 subjects (10 men and 10 women; mean age 64) demonstrated an increase in the resistance of plasma LDL to oxidation. Subjects (n=10) took 1.2 g AGE 3 times a day for 2 weeks, then 2 weeks of no garlic (washout period), followed by 2 weeks of placebo. The other subjects (n=10) took a placebo for the first 2 weeks, followed by 2 weeks of washout, and 2 weeks of 1.2 g AGE 3 times a day The oral ingestion of AGE was found to significantly increase the resistance of plasma LDL to oxidation (Chart 7).[119]

Chart 7



Lag times of LDL oxidation in subjects who consumed AGE and placebos, the garlic supplement significantly increased the lag time of LDL oxidation (P=0.05) indicating its ability to increase the resistance of plasma LDL to oxidation.

Source: Lau. J. Nutr. 2006;136:765S–768S.

Mechanism of Action

S-allylcysteine (SAC), one of the major compounds in AGE, inhibits LDL oxidation and minimizes oxidized LDL-induced cell injury.[120] SAC can protect endothelial cells from oxidized LDL-induced injury by removing peroxides and preventing the intracellular glutathione (GSH) depletion suggesting this compound may be useful for the prevention of atherosclerosis.[121]

AGE - Homocysteine and Endothelial Dysfunction

Another cardiovascular protective factor of AGE is homocysteine-lowering action, Aged Garlic Extract (Kyolic®) is patented by the U.S. government for its ability to reduce homocysteine.[122] Folate deficiency contributes to hyperhomocysteinemia. Laboratory investigations reported homocysteine lowering potential of AGE in rats rendered folic acid deficient with a diet devoid of folic acid creating hyperhomocysteinemia. Supplementation of AGE to the deficient diet reduced plasma protein-bound, free, and total homocysteine by 28% to 33%.[123]

A placebo-controlled, blinded, crossover trial demonstrated AGE reduces macro- and microvascular endothelial dysfunction during acute hyperhomocysteinemia, induced by an oral methionine challenge in healthy subjects (n=11).[124] Subjects received placebo or AGE (4 mL/d) for a 6 week intervention period, followed by a 6 week washout phase and crossed over. Flow mediated vasodilation of brachial artery using vascular ultrasound in macro- and skin perfusion by laser-doppler flowmetry in microcirculation were used. Acute hyperhomocysteinemia lead to a significant decrease in both micro- and macro-endothelial function, but pretreatment with AGE significantly diminished the adverse effects of acute hyperhomocysteinemia in both vascular territories ($p<0.005$). AGE may at least partly prevent a decrease in bioavailable NO and endothelium-derived hyperpolarizing factor during acute hyperhomocysteinemia. AGE may maintain healthy arteries through reduction of multiple cardiovascular risk factors.[75,124]

Another trial has shown that AGE may help improve endothelial function in men with CAD. This randomized, placebo controlled, cross-over design study investigated men (n=30) with angiographically proven CAD, and receiving aspirin and statin therapy for improvement in endothelial function with AGE treatment. When supplemented with AGE, brachial artery flow mediated endothelium-dependent dilation (FMD) significantly increased (44%, $p=0.04$) from the baseline, and mostly in men with lower baseline FMD. At the end of AGE treatment, FMD levels were significantly higher ($p=0.03$) when compared with the placebo treatment.[125]

Mechanism of Action

It is postulated that the hypohomocysteinemic action of AGE stems in part from inhibition of methylenetetrahydrofolate reductase (MTHFR) and stimulation of cystathionine beta-synthase. A decrease in the activity of MTHFR, an increase in the activity of cystathionine beta-synthase and a reduction of S- adenosylhomocysteine (SAH) concentration resulting in relieving the activation of S-adenosylhomocysteine hydrolase may decrease plasma homocysteine.[126] AGE contains water- and oil-soluble sulfur compounds that modify the intracellular thiol and redox state, minimize intracellular oxidant stress, and stimulate NO generation in endothelial cells. AGE may partly prevent a decrease in bioavailable NO and endothelium-derived hyperpolarizing factor.[75,124]

AGE - Antioxidant Effects and Smokers

AGE has been shown to be useful in reducing oxidative stress in smokers and non-smokers. Participants were given 5ml (1500mg) AGE daily for 14 days. Plasma and urine concentrations of 8-iso-PGF2 , a marker of lipid peroxidation, or oxidative damage, were reduced by 29% and 37% in nonsmokers and by 35% and 48% in smokers. Two weeks after cessation of dietary supplementation, plasma and urine concentrations returned to normal.[127]

Mechanism of Action

AGE exerts antioxidant action by scavenging reactive oxygen species (ROS), enhancing the cellular antioxidant enzymes superoxide dismutase, catalase and glutathione peroxidase, and increasing glutathione in the cells.[128]

AGE - Blood Pressure (BP) / Vascular Tone

In Canada, the medical community declares BP should be less than 140/90 mmHg and in individuals with diabetes or chronic kidney disease, less than 130/80 mmHg. One in five adult Canadians has high normal blood pressure (130-139/85-89 mmHg) and up to 60% of these people will develop hypertension within 4 years. Over 90% of hypertensive Canadians have other cardiovascular risks.[129]

The presence of insulin resistance, can predict the development of hypertension.[130] Metabolic syndrome can be found in approximately one third of patients who do not have diabetes but have primary hypertension.[131] More than 50% of hypertensive patients are found to be insulin resistant, primarily because of the consequences of insulin resistance that occur at a cellular level. The body attempts to compensate for insulin resistance by hypersecretion of insulin, resulting in higher circulating levels. This hyperinsulinemia results in the following precursors of hypertension:[132]

- Increased levels of catecholamines with resulting sympathetic nervous system stimulation
- Renal sodium retention
- Vascular smooth-muscle hypertrophy due to the effects of hyperinsulinemia on the mitogenic insulin-signaling pathway
- Endothelial dysfunction and decreased production of NO
- Modification of ion transport across the cell membrane and increase of cytosolic calcium
- Augmentation of the pressor and aldosterone response to angiotensin II.

The metabolic syndrome for cardiovascular risk stratification in hypertensive patients, in the ICEBERG study (n=4039), illuminated the value of investigating metabolic syndrome components in patients with high-normal or high blood pressure in order to identify individuals with high added risk of CVD.[133]

In vitro trials have demonstrated the positive effect of AGE on BP based on improvement in the blood circulatory system, such as the maintenance of the blood vessel flexibility and the improvement of erythrocyte deformability. It has been shown that AGE and its components improve the peripheral circulation system.[134]

Clinical investigations demonstrate that protection and maintenance of the flexibility in the blood vessel may be one mechanism for the systolic blood pressure (SBP) lowering effect of AGE. Other laboratory investigations demonstrated that the antihypertensive and renoprotective effects of SAC and AGE are associated with their antioxidant properties and that they may be used to ameliorate hypertension and to delay the progression of renal damage.[135]

AGE - Peripheral Blood Circulation

AGE improves microcirculation and rheological (ability to flow) blood properties and preserves the structure and function of erythrocytes not only through an antioxidant process but also via the glycolysis pathway and membrane stabilization of erythrocytes. Moreover, these results demonstrate AGE might be a useful substance to prevent several peripheral vascular diseases (e.g. sickle cell anemia, arteriosclerosis and hyperlipidemia).[136]

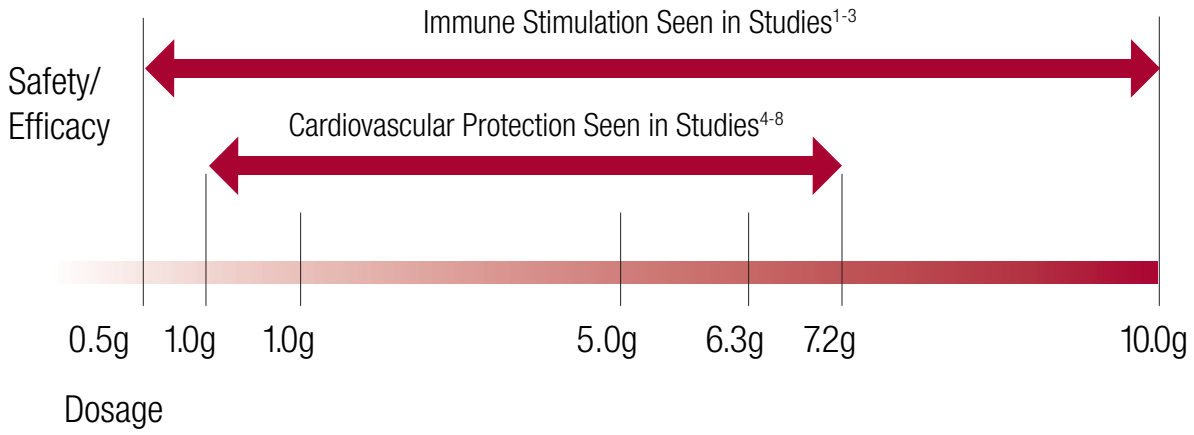
Recommended Dosage of AGE

The majority of the clinical studies conducted utilized approximately 4 ml of the liquid AGE, roughly equivalent to 1,200 mg of the powder; however, a range of doses was utilized (Chart 8).

As a dietary supplement, the manufacturer's recommended dosage of aged garlic extract (Kyolic®) is one 600mg caplet daily. However, higher dosages such as one 600mg caplet twice daily or, ¼-½ teaspoon (300-600mg), or 30-60 drops aged garlic extract liquid (Kyolic®) with a meal, twice daily, are suggested to help maintain healthy cholesterol levels, enhance circulation, support immune function, help fight stress and fatigue, and maintain healthy function of the liver and nerves.[137]

Chart 8

Range of Dosage of AGE on Safety and Efficacy



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8. Budoff et al. Prev. Med. 2003

Safety of AGE

The safety of AGE has been demonstrated in toxicological tests and in clinical studies with more than 1000 subjects. High quality control in AGE production (Kyolic®) and standardization by its stable key compound S-allylcysteine (SAC), provides assurance that AGE in capsule, tablet or liquid form, always contains a standard amount of stable beneficial ingredients, as labelled.[138] AGE (Kyolic®) received the stamp of approval from ConsumberLab when tested for all claims, purity standards, and dose per capsule.[137]

Patients on oral anticoagulation (warfarin) therapy demonstrate no increase in incidence of hemorrhage with the use of AGE. AGE is safe and poses no serious hemorrhagic risk for closely monitored patients on warfarin oral anticoagulation therapy.[139]

As there are other garlic products on the market, there is often confusion over allicin, since some garlic powder manufacturers advertise allicin as a measure of the product's activity and benefits (Kwai®, Garlicin®). Allicin is a volatile and reactive oxidant that is not bioavailable and not a component of AGE.[140,141]

Side Effects of AGE

AGE is truly the only odorless garlic supplement. No severe side effects were noted in the more than forty clinical studies using AGE confirming the safety of such preparations. The preparations were generally well tolerated, even at high dosages. Minor side effects, noted in only a few clinical studies, were few in number and were noted in less than 10% of the subjects. Main complaints included stomach discomfort, nausea, flatulence, diarrhea, or odor.[3]

Contraindications of AGE

There are no known contraindications. The product is not for use by pregnant or breast feeding women, patients with pemphigus or prior to surgery. [104,139,142]

Drug Interactions with AGE

There are no known interactions with AGE and any prescribed medications or natural supplements.[104,139,142]

Roll of the Pharmacist

Patients that present to pharmacists with 3 of the 5 criteria for metabolic syndrome may benefit from additional counseling regarding their increased risk of CVD. Patients on statin and hypertension medications that present with increased abdominal obesity may have metabolic syndrome. Their status can be investigated via discussions with them, or their attending physician, regarding applicable blood test values (e.g. HDL, fasting glucose, triglyceride levels), and measurement of waist circumference. If the findings of their status reveal metabolic syndrome, then referral to their physician for confirmation is suggested. Educating patients about impacting metabolic syndrome includes discussions about helpful lifestyle modifications including diet and exercise. AGE taken at a dose of 1200mg to 1500mg daily for one year may help improve clinical outcomes.

Similarly, patients presenting with high cardiovascular risk, such as known arteriosclerosis or CAD that may or may not be currently taking a stable dose of statin and/or aspirin, may benefit from AGE taken at a dose of 1200mg to 1500mg daily for one year. Patient education as to the possible benefit would be to explain that taking AGE may result in less platelet aggregation (stickiness and formation of clots) and may inhibit the rate of progression of coronary calcification (hardening of the blood vessels in the heart with calcium deposits) over the year they are taking AGE. Educating these patients about the importance of diet and exercise is also suggested and in applicable cases (e.g. evidence of risk factors) about metabolic syndrome.

Smokers, patients with relatively high triglyceride and low HCL levels or those with hyperhomocysteinemia may be good candidates for education about metabolic syndrome. While smoking and homocysteine levels are not specifically indicated in the clinical guidelines for Canada, both have been shown to contribute to metabolic syndrome and cardiovascular disease. Education regarding diet and lifestyle modifications, as well as supplementing with AGE for one year (1200-1500mg/day), may help improve health outcomes.

For best results, it is valuable to emphasize taking AGE for at least one year, when seeking to impact specific clinical outcomes. The majority of evidence presented in the lesson, prescribes that AGE be taken for one year to help improve clinical outcomes, at a dose of 1200mg to 1500mg daily.

Conclusion

The main therapeutic goal in the management of patients with the metabolic syndrome is to reduce risk for clinical cardiovascular events and to prevent type 2 diabetes. In particular, for individuals with established diabetes, risk factor management must be intensified to reduce their higher cardiovascular risk. Lifestyle changes have a critical role in the clinical management of the risk factors predisposing to metabolic syndrome, such as overweight/obesity, and physical inactivity.[143] In diabetes patients and the majority of insulin-resistant nondiabetic patients, statins are probably an excellent baseline or first-line therapy for lipid reduction, but in many cases they're not adequate (see relevant guidelines).[144]. To further reduce risk, it is recognized that use of a second type of intervention or drug that modifies the lipid profile and cardiac risks, is warranted to augment the benefits of statins in terms of reducing risk.

AGE may help reduce the risk of these various diseases and risk factors. AGE scavenges oxidants, increases superoxide dismutase, catalase, glutathione peroxidase, and glutathione levels, and inhibits lipid peroxidation and inflammatory prostaglandins. AGE reduces cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase and is additive with statins in its action. The inhibition of cholesterol, LDL oxidation, and platelet aggregation by AGE, may inhibit arterial plaque formation; AGE may decrease homocysteine, lower blood pressure, and increase microcirculation, which is important in diabetes, where microvascular changes increase heart disease and dementia risks.[128]

With the increasing prevalence of metabolic syndrome and the scientific evidence supporting the use of AGE to modulate associated risk factors for CVD, pharmacists should consider recommending AGE for appropriate patients.

Appendix 1

Criteria for Metabolic Syndrome National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment [ATP] Panel III) Adopted by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI)*

Central obesity - measured by waist circumference	Men ≥ 40 inches
	Women ≥ 35 inches
Fasting blood triglycerides	≥ 150mg/dL
Blood HDL cholesterol	Men ≤40 mg/dL
	Women ≤ 50 mg/dL
Blood pressure	≥ 130/85 mmHg
Fasting glucose	≥ 100 mg/dL
*According to the ATP III criteria, the metabolic syndrome is identified by the presence of three or more of these components	

Source: American Heart Association criteria for Metabolic Syndrome[145]

Criteria for Metabolic Syndrome World Health Organization Diagnostic *

Abdominal obesity – measured by waist circumference	Men 102cm (>40 inches)
	Women >88cm (>35 inches)
High levels of triglycerides	At least 150mg/dL
Low HDL cholesterol	Men <40mg/dL
	Women <50mg/dL
High blood pressure	At least 130/>85mmHG
High fasting glucose	At least 110mg/dL
*At least 3 of 5 criteria must be met to diagnose metabolic syndrome	

Source: WHO Metabolic Syndrome Guidelines [146]

Source: IDF consensus worldwide definition of the Metabolic Syndrome[147]

Definition of Metabolic Syndrome International Diabetes Federation (IDF) *

Central Obesity** defined as waist circumference ***	
Raised triglycerides	≥ 150mg/dL (1.7mmol/L) or specific treatment for this lipid abnormality
Reduced HDL cholesterol	Men <40mg/dL (1.03mmol/L) or specific treatment for this lipid abnormality
	Women <50mg/dL (1.29mmol/L) or specific treatment for this lipid abnormality
Raised blood pressure	Systolic BP ≥130 or diastolic BP ≥85mmHg or treatment of previously diagnosed hypertension
Raised fasting plasma glucose	(FPG) ≥100mg/dL (5.6mmol/L), or previously diagnosed type 2 diabetes
	If above 5.6mmol/L or 100mg/dL OGTT is strongly recommended but is not necessary to define presences of the syndrome
*IDF definition states an individual must have central obesity plus any two of the other four factors	
** Central obesity see chart below	
*** If BMI is >30kg/m2 central obesity can be assumed and waist circumference does not need to be measured.	

Source: IDF consensus worldwide definition of the Metabolic Syndrome[147]

**** International Diabetes Federation (IDF) definition of Central Obesity**

Country/Ethnic Group		Waist circumference
Euroids* In the USA, the ATP III values (102cm male; 88cm female are likely to continue to be used for clinical purposes)	Male	≥94cm
	Female	≥80cm
South Asians	Male	≥90cm
Based on a Chinese, Malay and Asian-Indian population	Female	≥80cm
Chinese	Male	≥90cm
	Female	≥80 cm
Japanese**	Male	≥90cm
	Female	≥80cm
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available	
*In future epidemiological studies of populations of Europid origin, prevalence should be given using both European and North American cut-points to allow better comparisons.		
**Originally different values were proposed for Japanese people but new data support the use of the values shown above.		

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Self Assessment Questions

Instructions

1. After carefully reading this lesson, study each question and select the one answer you believe to be correct. Circle the appropriate letter on the attached reply form.
2. To pass this lesson, a grade of 70% (21 out of 30) is required.
3. Fax the printed answer card to 519-853-4447 or scan and email to robb@puritylife.com. Your reply card will be marked and you will be advised of your results within 6 weeks with a letter.

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1. Aged garlic extract contains water soluble allyl amino acid derivatives except:

a. S-allylcysteine (SAC)
b. Allicin
c. S-allylmercaptocysteine
d. Allixin

2. Aged garlic extract is standardized to which constituent:

a. S-allylcysteine (SAC)
b. Selenium
c. Organosulfur contents
d. S-allylmercaptocysteine

3. Which factor is not important when considering the bioactive components of a garlic preparation?

a. Identity
b. Metabolism
c. Bioavailability
d. Critical mass

4. Metabolic syndrome is a major risk factor for:

a. Arthritis
b. Lupus erythematosus
c. Coronary heart disease
d. Crohn's Disease

5. Risk factors associated with metabolic syndrome congregate randomly.

a. True
b. False

6. Prevalence of metabolic syndrome in Canada is:

a. Significantly greater than US prevalence
b. Similar to global prevalence
c. Significantly less than global prevalence
d. Significantly less than US prevalence

7. The clustering of cardiovascular risk factors in metabolic syndrome includes all of the following except:

a. Elevated liver enzymes
b. Hypertension
c. Dyslipidemia
d. Glucose intolerance

8. Patient R.B. is a 50 year old female, diagnosed with metabolic syndrome. Which of the following factors may exacerbate her condition?

a. Advancing age
b. Level of physical activity
c. Endocrine dysfunction
d. All of the above
e. A and B

9. Patient P.T. presents with waist circumference of 115cm, triglycerides of 2.1mmol/L, HDL-C of 0.9 mmol/L, blood pressure of 120/ 75 mm HG and fasting glucose of 5.5 mmpl/L. Patient P.T. has metabolic syndrome. True or False?

a. True

b. False

10. Why is insulin resistance postulated to be pathogenically related to metabolic syndrome?

a. Decreased delivery of reactive oxygen species

b. Increased oxidative stress

c. Decreased lipid peroxidation

d. Increased glucose tolerance

11. Which statement is least correct about visceral obesity?

a. Refers to distribution of adipose tissue in the abdominal region

b. Measured by waist-to-hip ratio

c. Is not associated with dyslipidemic features

d. Predicts coronary artery disease better than body mass index (BMI)

12. Patient W.T. presents as a 55 year old post menopausal female, who is over weight with a waist circumference of 120cm. What risk factors for metabolic syndrome may occur?

a. Worsening insulin resistance

b. Down regulated adipose tissue

c. Elevations in adipocytokine levels

d. All of the above

e. A and C

13. Which is most correct regarding the risk factor of cardiovascular disease?

a. Metabolic syndrome only in women 3.0

b. Metabolic syndrome only in men 3.5

c. Metabolic syndrome and diabetes in women 8.2

d. Metabolic syndrome and diabetes in men 5.0

14. Which statement is most correct regarding C-reactive protein (CRP)?

a. High-sensitivity CRP testing is a better predictor of CVD than cholesterol/HDL ratio

b. CRP deactivates macrophages

c. Increases nitric oxide expression

d. Posses antiatherogenic properties

15. Which of following is least correct regarding the mechanism by which aged garlic extract is imparts cardiovascular benefits?

a. Inhibit endothelial cell damage

b. Modulating the formation of early atherosclerotic lesions

c. Stimulating nitric oxide generation in endothelial cells

d. Down regulating liver function

16. Patient Y.R. has atherosclerosis diagnosed from EBT testing and is currently on standard statin and aspirin therapy. Which answer is most correct regarding the potential change in calcium scores with supplementation of aged garlic extract?

a. Decrease by up to 7.5%

b. Increase by up to 32.2%

c. Decrease by up to 17.5%

d. Decrease by up to 22.2%

17. A suggested recommendation for Y.R. is to:

a. Discontinue aspirin therapy

b. Discontinue statin therapy

c. Add AGE to current pharmaceutical therapy for 1 year

d. All of the above

18. Y.R.'s physician supports the suggestion for AGE supplement and asks you to explain how AGE will slow the rate of his atherosclerosis. Which of the following is the best answer?

a. AGE exhibits direct atherogenic effects

b. Inhibition of smooth muscle phenotypic change and proliferation

c. Positively impacts lipid accumulation in the artery wall

d. All of the above

e. B and C

19. AGE may improve blood flow by reducing platelet aggregation by what percentage less aggregation than the placebo group?.

a. 23%

b. 43%

c. 73%

d. 34%

20. Patient Q.R. presents as a hypercholesterolemic man aged 50 years who is challenged to follow a diet helpful for his condition. Supplementation with aged garlic extract may help reduce Q.R.'s cholesterol regardless of diet. True or false?

a. True

b. False

21. AGE's ability to enhance resistance to LDL oxidation is significantly better than which of the following:

a. Raw garlic

b. Alpha-tocopherol

c. Milk thistle

d. All of the above

e. B and C

22. Patient C.T. presents as a 30 year old healthy women who smokes 7 cigarettes per day. What is the benefit of AGE supplementation in this patient?

a. Reduces cellular antioxidant enzymes

b. Reduces oxidative stress of smoking

c. Reduces the associated weight gain with smoking cessation

d. Reduces the craving for nicotine

23. What is the proposed mechanism by which AGE may help to improve blood pressure?

a. Lowers systolic blood pressure

b. Maintenance of the blood vessel flexibility

c. Protection of blood vessel flexibility

d. All of the above

e. A and C

24. Patient M.F. is currently taking standard statin, aspirin therapy and warfarin as prescribed by his physician for his atherosclerosis. AGE is not safe to add to his current prescribed regime. True or False?

a. True

b. False

25. Age helps to reduce cholesterol levels by:

a. Reduction in the action of statins

b. Stimulating the action of statins

c. Inhibition of HMG-CoA reductase

d. Enhancing HMG-CoA reductase

26. The action of aged garlic extract is particularly important for patients with diabetes because AGE:

a. Increases microcirculation

b. Inhibits cholesterol synthesis

c. Increases homocysteine

d. Increases CRP

27. Dr. N.W. asks you to explain how aged garlic extract helps to improve the health of patients with mild hyperhomocysteinemia? In cases of hyperhomocysteinemia AGE:

a. Reduces vitamin B12

b. Enhances the activity of folic acid

c. Reduces macro- and microvascular endothelial dysfunction

d. Reduces brachial artery flow

28. For the pathologies below, which one might aged garlic extract demonstrate the greatest percentage of improvement on?

a. Total serum cholesterol

b. Plaque reduction

c. LDL cholesterol

d. Blood Pressure

29. What is the maximum daily dose that has been seen in studies on aged garlic extract?

a. 600mg

b. 5.0 g

c. 7.2

d. 10 g

30. The manufacturer's recommended maintenance dose of aged garlic extract (Kyolic®) is:

a. 60 mg

b. 1500 mg

c. 600 mg

d. 6000 mg

Anwser Sheet

Contact Information: **Fax this Anwser Sheet to 519-853-4447 or scan and email to robb@puritylife.com**

Pharmacist Name: _____ Email Address: _____

Store Name: _____

License Number: _____ Store Number: _____

Address: _____

City: _____ Province: _____ Postal Code: _____

How do you prefer your results? ☐ Traditional Mail ☐ Email

Question Anwsers:

Question # 1
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__ d

Question # 2
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Question # 3
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Question # 4
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Question # 27
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Question # 28
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Question # 29
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Question # 30
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__ c
__ d

Program Evaluation:

1. As a result of completing this lesson, do you now have a better understanding of impacting cardiovascular disease and metabolic syndrome with aged garlic extract	__Yes __No
2. Was the information in this lesson relevant to your practice?	__Yes __No
3. Will you be able to incorporate the information from this lesson into your practice?	__Yes __No
4. How satisfied are you with our program?	__ Very __ Somewhat __ Not at all

Notes: